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Standardised Treatment And Monitoring Protocol to assess safety and tolerability of bacteriophage therapy for adult and paediatric patients (STAMP study)

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Keywords:	PAEDIATRICS, INFECTIOUS DISEASES, MICROBIOLOGY, GENERAL MEDICINE (see Internal Medicine), THERAPEUTICS

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Title: Standardised Treatment And Monitoring Protocol to assess safety and tolerability of bacteriophage therapy for adult and paediatric patients (STAMP study)

Abbreviated title: Standardised Treatment and Monitoring of Phage therapy (STAMP)

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Keywords

Bacteriophage; child; adult; clinical trial; therapeutic monitoring

Word count: 4028

Trial registration details

Prospectively registered on ANZCTR 10 November 2021: ACTRN12621001526864. (https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=382817&isReview=true).

WHO Universal Trial Number: U1111-1269-6000

Trial registration data set

Data category	Informationv
Primary registry and trial identifying number	ANZCTR (anzctr.org.au) ACTRN12621001526864
Date of registration in primary registry	10 November 2021
Secondary identifying numbers	U1111-1269-6000
Source(s) of monetary or material support	Medical Research Future Fund (Australia) National Health and Medical Research Council (Australia)
Primary sponsor	Western Sydney Local Health District, Australia

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Data category	Informationv
Secondary sponsor(s)	Not applicable
Contact for public queries	Ameneh Khatami (ameneh.khatami@gmail.com)
Contact for scientific queries	Ameneh Khatami (ameneh.khatami@gmail.com)
Public title	Safety and tolerability of Standardised Treatment and Monitoring of Phage therapy (STAMP) in adults and children
Scientific title	Safety and tolerability of a standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy
Countries of recruitment	Australia
Health condition(s) or problem(s) studied	Bacterial infections
Intervention(s)	A standardised treatment and monitoring protocol for bacteriophage therapy.
Key inclusion and exclusion criteria	Ages eligible for study: all ages Sexes eligible for study: both Accepts healthy volunteers: no
	Inclusion criteria: 1) Patient for whom at least two suitably qualified clinical specialists have agreed phage therapy should be used 2)S uitable phage(s) available and compliant with all relevant regulatory requirements for therapeutic administration
	Exclusion criteria: Participant, parent or guardian or person responsible has not provided informed consent
Study type	Interventional
	Single arm, non-randomised, uncontrolled, open trial
	Primary purpose: treatment
	Phase: Not applicable
Date of first enrolment	April 2022
Target sample size	50
Recruitment status	Recruiting
Primary outcome(s)	Safety; as defined by the absence of serious adverse events attributable to study material (phage) occurring from day 1, until 15

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Data category	Informationv
	days after completion of therapy.
Key secondary outcomes	1) Additional safety outcomes: Any adverse event attributable to phage therapy occurring up to 6 months after completion of phage therapy. 2) Feasibility of a standardised treatment and monitoring protocol, assessed as the proportion of participants with >80% of minimum data requirements available for analysis; time-frame: 15 days after completion of phage therapy. 3) Clinical response to phage therapy defined as cure, with or without persisting disability; partial response; or no response. Good clinical response is defined as all participants assessed as "cured" or with "partial response" at least 15 days after completion of phage therapy. 4) Quality-of-life indicators assessed using EQ-5D-5L/EQ-5D-Y at baseline, day 29, and 3, 6 and 12 months after starting phage therapy. 5) Microbiological clearance of target pathogen(s) defined as the proportion of participants with sustained microbiological clearance (at least 2 consecutive negative cultures) by the end of the intervention period (including up to day 29); and time to clearance among participants with sustained clearance.

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Abstract

Introduction

There has been renewed interest in the therapeutic use of bacteriophages (phages); however, standardised therapeutic protocols are lacking, and there is a paucity of rigorous clinical trial data assessing efficacy. The purpose of this study is to standardise therapeutic management and data collection for assessing the overall safety and tolerability of phage therapy in children and adults, and to assess the feasibility of a standardised national protocol.

Methods and Analysis

We propose an open-label, single-arm trial investigating a standardised treatment and monitoring protocol for phage therapy. Patients included will have exhausted other therapeutic options for control of their infection and phage therapy will be administered under Australia's Therapeutic Goods Administration Special Access Scheme. A phage product with high *in vitro* activity against the targeted pathogen(s) must be available in line with relevant regulatory requirements. We aim to recruit 50-100 patients over five years. The standardised protocol will specify clinical assessments and biologic sampling at scheduled time points. Safety will be assessed by the frequency of adverse events, and will be overseen by an independent Data Safety Monitoring Board (DSMB). Feasibility will be measured as the proportion of participants with >80% of minimum data available for analysis. Additional endpoints will be assessed, including clinical response, patient/guardian reported quality of life measures, phage pharmacokinetics, human host immune responses, and microbiome analysis. All trial outcomes will be summarised and presented using standard descriptive statistics.

Ethics and dissemination

The trial protocol was approved by the Sydney Children's Hospitals Network Human Research Ethics Committee in December 2021 (Reference 2021/ETH11861) . In addition to publication in a peer-reviewed scientific journal, a lay summary of study outcomes will be made available for participants and the public on the Phage Australia website (https://criticalinfection.com/phage-australia/).

Trial registration

Registered on ANZCTR 10 November 2021: ACTRN12621001526864. (https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=382817&isReview=true).

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Article Summary

A nationally standardised clinical trial protocol for administering and monitoring bacteriophage (phage) therapy in adults and children is presented.

Strengths and Limitations

- **Strength:** This protocol builds on an existing phage therapy program, expanding it to a national scale, co-designed with key stakeholders including government and the public.
- **Strength:** The trial has been endorsed by adult and paediatric infectious diseases specialists throughout Australia; optimising potential for participant recruitment.
- **Strength:** The trial is designed to be embedded into routine clinical practice and is both pragmatic and inclusive.
- **Strength:** The protocol promotes standardisation of therapy and outcome assessment, enabling credible inference about risks and benefits.
- **Limitation:** Heterogeneity in disease syndromes and phage products used will limit inference about any particular syndromes or products.

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Introduction

There has been renewed interest in the therapeutic use of bacteriophages (phages), driven by emerging challenges in the medical landscape (1). Growing antimicrobial resistance (AMR) has fuelled a crisis in medicine, contributing to a significant rise in mortality, morbidity and associated healthcare costs (2). Without novel solutions, AMR infections are predicted to be the leading cause of death by 2050, to cost US$30 billion annually in lost productivity, and to threaten many advances in medicine (2). Similarly, there is an unmet need for new strategies to manage complex infections in individuals with chronic conditions, including cystic fibrosis, and infections that respond poorly to antibiotics, such as prosthetic device-related infections (1). Phage therapy (PT) has the potential to meet these needs.

Phages are viruses that selectively kill bacteria (3). PT uses this characteristic to provide a novel, non-antibiotic approach to treating infections (3), with effectiveness independent of antimicrobial susceptibility (3). PT has a proven safety record (4-10) and can be used as monotherapy or in conjunction with antibiotics (3). PT can also alter the bacterial antimicrobial susceptibility profile. Bacterial reversion to susceptible phenotypes has been observed with PT, restoring the efficacy of antibiotics to pathogens that were previously testing non-susceptible (11, 12).

PT has several other potential advantages over standard care. Phages are highly selective, targeting a narrow range of bacteria. This specificity reduces their impact on the microbiome and sidesteps the associated risk of the emergence of AMR and *Clostridioides difficile* infection (13). Biofilm formation is increasingly recognised to play a role in a broad range of conditions beyond the traditionally recognised prosthetic device-related infections (14). Biofilms protect bacteria from the immune response and reduce antibiotic efficacy (14). Due to their mechanism of action, phages remain effective in killing bacteria present in biofilms (14, 15).

There are increasing reports underlining the value of PT in severe sepsis, bladder infections and osteomyelitis (5, 6, 8-10). Despite these potential benefits, PT is not routinely used currently. Numerous barriers to widespread adoption remain. Experience with PT is restricted to a handful of centres worldwide. Standardised therapeutic protocols are lacking, and there is a paucity of rigorous clinical trial data assessing efficacy. Furthermore, due to limitations in production, sufficiently purified phages are generally not readily available (16).

Since 2007, a program for compassionate access to PT for adults and children has been in operation at Westmead Hospital and Sydney Children's Hospitals Network. This protocol aims to enable a national expansion of this program to both adults and children, providing a standardised treatment and monitoring protocol linked to a national database to ensure systematic data collection. This protocol will allow rapid and efficient data capture to strengthen the evidence base, including the dosing and monitoring data required to establish PT on the national formulary.

Objectives

This research aims to determine the safety and tolerability of PT in adults and children with bacterial infections in both the short and long term; and to assess the feasibility of a standardised protocol used for the administration and monitoring of PT. A range of other exploratory objectives will also be investigated, including to:

a. Report the clinical response to PT 15 days following completion
b. Describe changes to patient-reported quality-of-life indicators during and after PT
c. Describe proportions of patients achieving microbiological clearance, and time to clearance, by phage product and clinical indication, as well as the frequency of emergence of *in vitro* phage resistance
d. Identify biomarker(s) that correlate with clinical efficacy

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e. Explore pharmacokinetics/pharmacodynamics of different phage preparations to guide optimal dosing schedules and durations of treatment according to various routes of administration
f. Characterise immune responses to PT, including age-related differences
g. Explore microbiome changes as assessed by non-human metagenomics during and after completion of PT.

Methods

This is an open-label, single-arm trial investigating a standardised treatment and monitoring protocol for PT. This trial will include multiple subgroups based on clinical indication and route of PT administration. We used the SPIRIT checklist when writing our report (17).

Participant Recruitment and Eligibility

Study participants of all ages will be recruited through existing infectious diseases networks from any public or private hospitals in Australia where site-specific approval is obtained. Eligibility will be limited to patients assessed as having exhausted other therapeutic options to control their infection. This assessment will be performed by two appropriately qualified clinical specialists and must include a specialist in infection management and a specialist with prior PT experience or from within a defined clinical working group of the Phage Australia consortium (Trial Steering Committee, TSC). As PT experience grows this may include external partners.

Inclusion will be dependent on obtaining written informed consent from the patient or guardian and identification of a suitable phage product. Consent must be obtained by the site Principal Investigator (PI) or their qualified designee such as the primary clinician (Supplement A). A phage product must demonstrate high *in vitro* activity against the targeted pathogen(s) to be considered suitable. Similarly, the phage product must comply with all relevant local and national regulatory requirements for therapeutic administration, according to the special access scheme (SAS) for unregistered medicines as determined by the Australian Therapeutic Goods Administration (TGA) (18). Participants unable or unlikely to adhere to the schedule of monitoring and follow-up will be excluded.

Sample size

Sample size was based on logistical considerations and the ability to estimate the proportion of participants with PT-related serious adverse events (SAE). A sample size of at least 50 participants will enable the proportion to be estimated with a 95% confidence interval of maximum width ±15%. If no SAE is observed in 50 participants, this would be consistent with a true rate of SAEs which is no higher than 7% (i.e. 95% CI of 0-7%). In line with this calculation, we aim to recruit 50-100 participants over the five years of the study.

Interventions

The schedule of enrolment, interventions and assessments for each participant is outlined in Table 1. At enrolment, demographic and clinical data will be collected, including primary infection diagnosis and previous and current antimicrobial treatments. Culture confirmation of infection and phage matching of isolated bacteria will be performed. The specific phage product, duration and route of administration will be determined individually for each patient by the clinical team in discussion with the site PI, dependent on the site of infection, bacterial pathogens, patient factors (e.g., immune compromise, intravenous [IV] access) and availability of phage products (e.g. formulation, purification). All other care, including adjunctive antibiotics and interventions during the trial, as well as post-trial care, will be as per the treating clinical team.

Repeat episodes of infection, including relapse or refractory illness, will be assessed for eligibility for re-enrolment in the trial, following a separation of at least 15 days to allow assessment of the primary outcome. The first episode per patient will be used for primary analyses, with additional courses described.

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Table 1: Schedule of enrolment, interventions, and assessments for each participant

PERIOD	Enrolment	Intervention		Follow-up
TIMEPOINT	*-4 weeks* to Day 0*	*Day 1-14***	*Day 15-29*	*Day 30-210****
ENROLMENT:				
Eligibility screen	X			
Informed consent	X			
Pre-treatment work-up*	X			
Determination of duration and route of phage administration	X			
PHAGE THERAPY**		X		
MONITORING***				
Blood and clinical sampling	X	X	X	
Quality-of-life questionnaire		X	X	X
Adverse Event Reporting		X	X	X

* Pre-treatment work-up should be performed within four weeks of starting phage therapy.
** The duration of phage therapy may be longer than 14 days, as determined by the Principal Investigator/infectious disease specialist.
*** For patients receiving longer than 14 days of phage therapy follow-up continues for six months after completion of phage therapy

Phage Therapy

Duration

Where appropriate, a standard 14-day course will be used for IV/oral PT (Table 2) and non-systemic PT as the default option (Table 3). For critically unwell patients needing urgent infection management, initial twice-daily dosing may be used (i.e., from day 1). The dosing frequency will be guided by practical limitations in patients receiving outpatient treatment or PT for longer than 14 days.

Adherence will be ensured with the first 14 days of IV PT administered in hospital. Topical, aerosolised or oral administration can occur in the outpatient setting. All administered doses of phage will be prescribed by a suitably qualified doctor, dispensed from the hospital pharmacy and recorded in standard medical records.

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Table 2: Treatment and laboratory monitoring protocol for standard 14-day intravenous/oral phage therapy.

Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	29
Phage doses		OD	OD	BD	BD	BD	BD	BD	BD	BD	BD	BD	BD	BD	BD		
CRP	X		X		X				X							X	X
ESR	X				X				X							X	X
Procalcitonin (if available)	X		X		X				X							X	
FBC	X		X		X				X			X				X	X
Lymphocyte subsets	X		X		£				£			£				£	£
LFTs	X		X		X				X							X	X
UECs	X		X		X				X							X	X
Phage antibodies*	X											X				X	X
Total IgG	X															X	X
C3, C4, CH50	X															X	X
Microbiology sampling**	X				X				X							X	X
Phage susceptibility***	X				X				X							X	X
Kinetic blood sample			X		X				X			X				X	X
Transcriptomics and metagenomics	X		X		X				X			X				X	X

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Day 0 – up to 24 hours prior to the first dose of phage; OD – once daily; BD – twice daily; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; FBC – full blood count; LFTs – liver function tests; EUCs – electrolytes, urea, creatinine; IgG – total immunoglobulin G; C3, C4, CH50 – complement levels.
* Phage antibodies - antibodies against relevant therapeutic phages, measured in order to define risk of antibody-mediated neutralisation and/or immune responses.
** For invasive samples, baseline (day 0) and post-treatment (day 15) microbiology samples are sufficient for monitoring. For patients bacteraemia at the start of phage therapy, blood cultures should be obtained daily until bacteraemia resolves.
*** All positive cultures of the target pathogen(s) that are isolated after day one should be reassessed for ongoing phage-susceptibility
£ Lymphocyte subsets should be performed at these time points if lymphopaenic. Lymphopenia is defined as <1.0 x 10^9/L in individuals aged >12 years, <1.5 x10^9/L in children aged 1-12 years, <4.0 x10^9/L for infants aged 1-12 months, and <3.0 x10^9/L for neonates <1 month.

Table 3: Treatment and laboratory monitoring protocol for standard 14-day non-systemic phage therapy

Day(s)	0	1	2	3	4	5-7	8	9-14	15	29
Phage doses		OD	OD	OD	OD	OD	OD	OD		
CRP	X		X		X		X		X	
FBC	X		X		X		X		X	X
LFTs	X						X		X	
UECs	X						X		X	
Phage antibodies	X								X	X
Microbiology sampling*	X						X		X	X
Phage susceptibility**	X						X		X	X

OD – once daily; CRP – C-reactive protein; FBC – full blood count; LFTs – liver function tests; EUCs – electrolytes, urea, creatinine.
*For invasive samples baseline (day 0) and post-treatment (day 15) samples are sufficient for monitoring.
**All positive cultures of the target pathogen(s) that are isolated after day 1 should be reassessed for ongoing phage-susceptibility.

Dosage

For intravenously administered phage, the dose will be determined by the endotoxin level of the phage product, keeping below the accepted human pyrogenic threshold of 5 EU/kg per dose set by the United States Food and Drug Administration (FDA), aiming to administer approximately 10^9 plaque-forming units (pfu) of phage at each dose. For non-intravenous routes of administration, approximately 10^{10} pfu/dose will be administered. For multiple routes of administration, the total dose administered will not exceed the 5 EU/kg endotoxin limit.

Dosing strategies at initiation will be guided by distribution volume and clearance by non-specific mechanisms (innate effector cells, renal clearance and non-specific inactivation of viral particles). However, the kinetics of subsequent PT doses can be more dynamic (19). Phage amplification in targeted bacterial populations can change over time. Acquired immune clearance (e.g., the development of neutralising antibodies) can increase phage

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clearance. Thus, phage kinetics will be monitored and assessed during IV/oral PT (Table 2). Phage quantification in blood will be determined by plaque assay and quantitative polymerase chain reaction (qPCR). The timing of blood sampling is outlined in Table 4. Subsequent phage dosing intervals may be adjusted guided by these results (once to twice daily), aiming for a trough level of approximately 10^2 pfu/mL (10) . The dose will be adjusted depending on the phage with the lowest concentration for combination products containing more than one phage.

Table 4: Timing of blood samples for quantification of phage and bacterial loads

	Immediately prior to phage dose	30-60 minutes after phage dose	2-3 hours after phage dose
Phage (plaque assay)	X		X
Phage (qPCR)	X	X	X
Bacteria (qPCR)	X	X	X

All three time-points (prior to dose, 30-minutes, and 2 hours post-dose) should be drawn on days 2, 4, 8 and 11. On days 15 and 29, only a single blood draw in the morning is required as no further phage doses will be administered.

Clinical Monitoring

A complete physical examination will be performed within 24 hours before starting PT. Vitals (heart rate, respiratory rate, blood pressure, oxygen saturation, temperature) will be measured within 15 minutes prior to, and at 15 and 30 minutes after, each dose of phage. For patients receiving only topical or nebulised/aerosolised phage products, vital signs are only required 30 minutes after administration. Additional clinical monitoring will be performed according to routine clinical care.

Laboratory Monitoring

Laboratory monitoring for the first 29 days in patients receiving IV/oral PT and non-systemic PT is outlined in Tables 2 and 3. If abnormalities are detected (including worsening of prior abnormalities) that were not present at baseline, these will be followed up beyond the intervention period until resolution. Bacterial cultures will be obtained from the site of infection or representative site if not practical. Blood cultures should be obtained daily for patients with bacteraemia at the commencement of PT, continuing until resolution of the bacteraemia has been documented. For invasive samples other than blood or endotracheal aspirates (e.g., bronchoalveolar lavage or surgical biopsies), baseline (day 0) and post-treatment (day 15) samples are sufficient for monitoring where practical.

Measurement of anti-phage antibodies, and gene expression profiling of immune responses will characterise the human host's innate and adaptive immune responses following a set schedule in those receiving IV/oral PT (Table 2) and non-systemic PT (Table 3).

Quality-of-Life Assessments

Participants will complete a brief quality-of-life questionnaire using a validated age-appropriate patient reported outcome measures (PROMs) tool (EQ-5D-5L/EQ-5D-Y) during the study from baseline until 12 months following the completion of PT.

Safety and Tolerability

Safety and tolerability will be measured through adverse events (AEs), vital signs, and clinical laboratory assessments. An AE is defined as any untoward medical occurrence in a participant regardless of its causal relationship to the administered phage product. All AEs will be evaluated for severity, causality, and seriousness and will be elicited and assessed from the first dose until 15 days after the last dose of phage. From 15 days to 6 months following the completion of PT, only adverse reactions (ARs; AEs that are at least probably [probably or definitely] related to PT), will be collected. An SAE is defined as any event that results in death, is immediately life-threatening, requires inpatient hospitalisation or

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prolongation of existing hospitalisation, results in persistent or significant disability/incapacity or congenital anomaly. A serious adverse reaction (SAR) is an SAE that is at least probably related to PT. A suspected, unexpected, serious adverse reaction (SUSAR) is defined as an AE that is serious in nature (i.e., meets SAE criteria), is at least probably related to PT and is an unexpected reaction based on what is known and has been reported in the literature. SUSARs will be adjudicated by site PIs. Evidence of severe immune-related phenomena after infusion may occur and may be criteria for cessation of therapy. For any severe adverse reaction, decisions regarding cessation of PT will be made by the primary clinician in consultation with the site PI. Early cessation of PT will not constitute a withdrawal criterion from the trial. The PI should make every effort to continue all other patient monitoring as per the protocol to ensure data integrity and safety monitoring.

Data Collection and Management

Data will be collected using a Research Electronic Data Capture (REDCap) database hosted by the University of Sydney on a controlled, protected server that requires multi-factor authentication and encrypted connections. Clinical data will be coded but re-identifiable by clinicians for their patients. PIs will only have access to re-identifiable data for patients at their respective recruitment sites. De-identified data will be used for analysis. Data quality will be optimised using range checks for data values and error messages for missing data points. The data fields and the associated data dictionary are included in Supplement B. Any data obtained prior to withdrawal of consent from a participant will be retained.

Most biological samples collected as part of the trial will be processed in clinical diagnostic laboratories and stored, processed, and discarded as per routine laboratory procedures. For non-routine assessments, samples may be processed in research laboratories and will be coded prior to shipment, storage and analysis, and re-identifiable to PIs and treating clinicians at the site only. De-identified data and left-over biological samples may be retained up to 15 years after the study is completed, or until the youngest participant reaches 25 years old, whichever is later. Residual samples may be used for additional research, if specific consent for this is obtained.

Primary and Secondary Safety Outcomes

Safety will be defined by the absence of SAEs attributable to study material (phage). AEs related to PT are predominantly expected during active administration or shortly thereafter. The primary endpoint for safety assessments will be any SAE attributable to PT (SARs) occurring from day 1 (first dose of phage administered) until 15 days after completion of therapy (i.e., day 29 for patients receiving 14 days of therapy). The primary outcome of the proportion of participants who experience one or more SAEs attributable to study therapy will be presented with a 95% confidence interval. Secondary safety endpoints will be any AR occurring from day 1 (first dose of phage administered) until six months after completion of PT.

Secondary and Exploratory Outcomes

Feasibility

The feasibility of using a national standardised treatment and monitoring protocol will be measured as the proportion of participants with >80% of minimum data available for analysis entered in the REDCap dataset. The feasibility endpoint will be assessed at least 15 days after completion of PT.

This protocol includes a range of exploratory outcomes. The data we develop here will allow the best quality design of formal clinical trials and help to inform regulatory reviews.

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Clinical Response

Clinical response will be assessed 15 days following completion of PT. "Cure" will be defined as no evidence of ongoing infection (including clinical signs and symptoms, laboratory and radiological abnormalities, and microbiological evidence of infection), with or without persisting disability. Clinical response will be considered "partial" if there are improvements in clinical, radiological or laboratory parameters, or stabilisation of previously documented decline in function, but with evidence of ongoing infection. Worsening clinical signs and symptoms, radiological or laboratory parameters, and evidence of ongoing infection will be defined as "no response". For analysis, cure and partial response will be grouped and termed "good clinical response".

Quality-of-life Indicators

Patient-reported quality-of-life indicators will be measured during and after PT. A carer will complete this report for individuals unable. Changes in the quality-of-life questionnaire will be assessed using a validated PROMs tool (EQ-5D-5L/EQ-5D-Y), and results from baseline will be compared to each subsequent assessment (day 29, 3, 6 or 12 months after starting PT).

Microbiological Clearance

Microbiological clearance will be evaluated using time to clearance and the proportion with sustained clearance at the end of the intervention period (day 29). Time to clearance will be measured for each infected site from the first day of PT to the first negative culture among participants with sustained clearance. Sustained clearance is defined as at least two consecutive negative cultures with no other positive cultures during the intervention and follow-up.

Phage resistance can emerge during PT, contributing to poor microbiological clearance. To identify phage resistance, all positive culture(s) of the target pathogen(s) isolated after day 1 of treatment will be reassessed for ongoing phage susceptibility.

Pharmacokinetics and Immune Response to PT

The pharmacokinetics of different phage preparations will be assessed using the results of qPCR and plaque assays from serum. These data will guide optimal dosing schedules and durations for phage products used according to different routes of administration (IV, oral, nebulised/aerosolised, topical).

Immune responses to PT will be assessed by examining and comparing gene expression profiles coupled with the level of anti-phage neutralising or total antibodies at different time points during and after PT, and between age groups. Gene expression profiling will be restricted to genes belonging to the innate and adaptive immune response regulatory pathways only.

Microbiome changes

Metagenomics will be performed on any available clinical samples (blood, sputum, urine, faeces or other samples that may have been collected) to investigate changes in the microbiome during treatment. The analysis pipeline will be restricted to non-human genetic material and will only be used to determine the microbiome of various clinical specimens during and after PT, including endogenous phages.

Monitoring and Analysis

A review of included and excluded participants and reasons for inclusion/exclusion will be undertaken annually to ensure the appropriateness of patient selection. Interim safety analysis for the primary outcome will be conducted after 30 participants have been followed at 29 days after commencement of treatment. The expected attributable SAE rate is <5%. If

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20% or more participants suffer an SAR, the treatment may not be considered acceptable in its current form. An analysis of the first 30 participants who are followed at least one month after commencing treatment has 80% statistical power at 5% one-sided alpha to rule out a rate of 20% or higher if the true rate is 5% or lower, using an exact one-sample binomial test. If three or more of these 30 participants have experienced an SAR, then consideration will be given to stopping or modifying the study due to safety concerns. Otherwise, recruitment will continue to the target of 50-100 participants to collect data on other outcomes.

The TSC will regularly review study progress, including data on all safety, secondary and exploratory outcomes. Reports will be provided 6-monthly and may be used for amending the trial protocol, external reporting and publication, or early trial termination. A final analysis will be undertaken when the last enrolled participant has been followed up for at least six months after the last dose of phage.

All trial outcomes will be summarised and presented using standard descriptive statistics: frequencies and percentages for categorical data and mean, standard deviation and range or median, quartiles and range for continuous data and the Kaplan-Meier method for time-to-event variables. Results will be presented overall and by sub-groups. Participants may be sub-grouped according to clinical indication (infectious syndrome), route of administration or phage formulation used, or patient demographics (e.g., age). Exploratory comparisons of outcomes between subgroups, including those receiving treatment targeting different groups of organisms, and clinical phenotypes [acute bacteraemia vs. chronic osteoarticular infections]) will use standard statistical methods: t-test, chi-square test, log-rank test, and corresponding regression models.

Safety data will be reported for all participants who receive at least one dose of phage therapy. Clinical response to therapy and microbiological clearance outcomes will be reported for participants who receive at least 5 days of phage therapy (cumulative). All other outcomes will be reported for all enrolled participants based on available data with no adjustment for missing data.

Ethics and dissemination

This trial protocol (version 1, 20/12/2021; Supplement C) was assessed and approved by the Sydney Children's Hospitals Network Human Research Ethics Committee (HREC) in December 2021 (Reference 2021/ETH11861). All major protocol amendments will only be implemented after approval is gained from the HREC and governance committees for participating sites. Amendments will also be notified to the trial registry, and the journal in which the protocol is published.

Following interim and final analyses, trial results will be shared with the investigator group who will have ongoing custody of the data, and will be prepared for scientific publication or presentation. The final results will be submitted for publication in a peer-reviewed scientific journal. A lay summary of the final trial results will be made available for participants and the public on the Phage Australia website (https://criticalinfection.com/phage-australia/). Upon recruitment, a link to the website will be provided to all study participants.

As the protocol is embedded in usual clinical practice, participants may expect to be informed of test results and response to treatment. All routinely available clinical assays will be available for clinicians to discuss with participants. The results may or may not be available during treatment for more specialised tests. Some results such as for transcriptomic and metagenomic analyses will not be reported individually to participants.

Data sharing statement

The full trial protocol (Standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy Protocol, version 1, dated 20/12/2021);

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the database data fields and associated data dictionary, and the participant information sheets and consent forms are made available via supplementary materials submitted with this manuscript and/or via the trial registry.

De-identified individual participant data will be made available for all primary, secondary and exploratory endpoints immediately following publication of trial results. Data will only be made available to researchers who provide a methodologically sound proposal, where the use is not for commercial gain. Access is subject to approvals by Principal Investigators via email (jonathan.iredell@sydney.edu.au or ameneh.khatami@health.nsw.gov.au).

Patient and public involvement

The protocol has been shaped by reviews and comments from stakeholder and consumer representatives including from the cystic fibrosis community and the New South Wales Ministry of Health.

Sponsor information

Sponsor: Western Sydney Local Health District, Research and Education Network Clinical Trial Support Unit, Westmead Hospital, Hawkesbury Road, Westmead, NSW 2145, Australia (WSLHD-ClinicalTrialsSupportUnit@health.nsw.gov.au)

No trial funding is provided by the sponsor. Representatives from the sponsor were involved in the development of the protocol with respect to safety monitoring and reporting procedures. The sponsor will not be involved in collection, management or interpretation of data, writing the study report or the decision to submit the report for publication.

Trial committees:

The TSC includes a multidisciplinary group that, collectively, have experience/expertise in the management of patients with condition(s) relevant to the study, pathways for use of phage therapy, and in the conduct and monitoring of randomised clinical trials. Co-conveners are ST, AK and MW and the committee includes JI. JI and AK are physicians with prior PT experience. The committee also includes members with statistical expertise and stakeholder representatives.

The independent Data Safety Monitoring Board (DSMB) includes a chair with management experience in clinical trials and 5 additional members, of whom at least 1 will be a paediatrician, at least 1 will be an adult physician and at least 1 will have established clinical expertise in the delivery of phage therapy. The DSMB will have access to all safety data available at the time of each meeting and will make a recommendation to the co-ordinating PI and site PIs within 4 weeks regarding:

- Cessation of the trial for all participants or for a subgroup
- Interim suspension while reviewing the data in more detail
- Modification of the trial
- Continuation of the trial

Conclusion

PT is a promising therapeutic option with evidence of clinical efficacy. However, heterogenous reports, limited clinician experience outside specialist centres and restricted access to suitable phage products has undermined its widespread adoption. This protocol builds on an established PT program, expanding it to a national scale. The data obtained in this trial will help to define the safety profile of PT in all age groups and establish the feasibility of a standardised treatment protocol. Downstream effects include overcoming unfamiliarity and increasing both consumer and clinician confidence by collating standardised objective data. Due to the inherent challenges in traditional trial designs for PT,

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large patient registries collating standardised data, such as this one, will allow rapid and efficient data generation to strengthen the PT evidence base, including the dosing and monitoring data required to inform regulatory frameworks. Furthermore, insights from this trial will allow the design of controlled trials that can both measure, and validate diagnostic surrogates of, clinical efficacy.

Author contributions

AK and JI conceived the study. AK, JI, ST and MW initiated the study design and protocol development. AP, TS, JL, SS and RL contributed to refinement of the study protocol. NB provided input into the protocol development in her role as an advocate for the cystic fibrosis community; and JW provided input in her role as the Principal Policy Officer for Advanced Therapeutics at the Office for Health and Medical Research, New South Wales Ministry of Health. JI and AK are grant holders. TS and EB provided statistical expertise. DF and AK drafted the initial manuscript for publication. All authors reviewed and approved the final manuscript for submission.

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Local phage production and development of companion diagnostics are supported by the MRFF Frontiers Stage 1 grant, and a National Health and Medical Research Council Investigator Grant (1197534: Positive Solutions for Critical Infection, CIA Iredell).

Funding bodies do not have any role in the study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

Competing interests

All authors declare no financial or non-financial competing interests with respect to the STAMP protocol.

Acknowledgements

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We also thank Lani Attwood (Kids Advanced Therapeutics Program, Sydney Children's Hospitals Network) for her assistance in developing participant information sheets and obtaining ethical approval for the trial; and Jan Zheng and Jessica Sacher (Phage Directory; Westmead Institute for Medical Research) for their work developing the REDCap database for this trial.

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Ethics Approval Statement

The trial protocol was approved by the Sydney Children's Hospitals Network Human Research Ethics Committee in December 2021 (Reference 2021/ETH11861) .

References

1. Suh GA, Lodise TP, Tamma PD, et al. Considerations for the Use of Phage Therapy in Clinical Practice. Antimicrob Agents Chemother. 2022:AAC. 02071-21.
2. O'Neill J. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. London: Wellcome Trust; 2016.
3. Lin DM, Koskella B, Lin HC. Phage therapy: An alternative to antibiotics in the age of multi-drug resistance. World J Gastrointest Pharmacol Ther. 2017;8(3):162-73.
4. Dedrick RM, Guerrero-Bustamante CA, Garlena RA, et al. Engineered bacteriophages for treatment of a patient with a disseminated drug-resistant Mycobacterium abscessus. Nat Med. 2019;25(5):730-3.
5. Schooley RT, Biswas B, Gill JJ, et al. Development and Use of Personalized Bacteriophage-Based Therapeutic Cocktails To Treat a Patient with a Disseminated Resistant Acinetobacter baumannii Infection. Antimicrob Agents Chemother. 2017;61(10).
6. Maddocks S, Fabijan AP, Ho J, et al. Bacteriophage Therapy of Ventilator-associated Pneumonia and Empyema Caused by Pseudomonas aeruginosa. Am J Respir Crit Care Med. 2019;200(9):1179-81.
7. Gilbey T, Ho J, Cooley LA, et al. Adjunctive bacteriophage therapy for prosthetic valve endocarditis due to Staphylococcus aureus. Med J Aust. 2019;211(3):142-3 e1.
8. Petrovic Fabijan A, Lin RCY, Ho J, et al. Safety of bacteriophage therapy in severe Staphylococcus aureus infection. Nat Microbiol. 2020;5(3):465-72.
9. Khawaldeh A, Morales S, Dillon B, et al. Bacteriophage therapy for refractory Pseudomonas aeruginosa urinary tract infection. J Med Microbiol. 2011;60(Pt 11):1697-700.
10. Khatami A, Lin RCY, Petrovic-Fabijan A, et al. Bacterial lysis, autophagy and innate immune responses during adjunctive phage therapy in a child. EMBO Mol Med. 2021;13(9):e13936.
11. Gordillo Altamirano F, Forsyth JH, Patwa R, et al. Bacteriophage-resistant Acinetobacter baumannii are resensitized to antimicrobials. Nat Microbiol. 2021;6(2):157-61.
12. Duplessis C, Biswas B, Hanisch B, et al. Refractory Pseudomonas Bacteremia in a 2-Year-Old Sterilized by Bacteriophage Therapy. J Pediatric Infect Dis Soc. 2018;7(3):253-6.
13. Petrovic Fabijan A, Khalid A, Maddocks S, et al. Phage therapy for severe bacterial infections: a narrative review. Med J Aust. 2020;212(6):279-85.
14. Sharma D, Misba L, Khan AU. Antibiotics versus biofilm: an emerging battleground in microbial communities. Antimicrob Resist Infect Control. 2019;8(1):76.
15. Chang RYK, Das T, Manos J, et al. Bacteriophage PEV20 and Ciprofloxacin Combination Treatment Enhances Removal of Pseudomonas aeruginosa Biofilm Isolated from Cystic Fibrosis and Wound Patients. AAPS J. 2019;21(3):49.
16. Lin RC, Sacher JC, Ceyssens PJ, et al. Phage Biobank: Present Challenges and Future Perspectives. Curr Opin Biotechnol. 2021;68:221-30.
17. Chan AW, Tetzlaff JM, Gotzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ. 2013;346:e7586.
18. Therapeutic Goods Administration. Special access scheme 2022 [updated 28th March 2022. Available from: https://www.tga.gov.au/form/special-access-scheme.
19. Dabrowska K. Phage therapy: What factors shape phage pharmacokinetics and bioavailability? Systematic and critical review. Med Res Rev. 2019;39(5):2000-25.

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Supplementary Material

Supplementary Material A: Master copies of participant information sheets and consent forms, version 1, dated 08/12/2021.

Supplementary Material B: Research Electronic Data Capture (REDCap) data fields and associated data dictionary.

Supplementary Material C: Standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy Protocol, version 1, dated 20/12/2021.

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Insert Header with institution's name or institution's letterhead

Executive Summary of the

Participant Information Sheet/Consent Form - Adult

Standardised Treatment and Monitoring of Phage Therapy (STAMP)

[Local Chief Investigator]

You are invited to participate in the above research study because you have a bacterial infection that your doctor has determined would benefit from Phage Therapy and your doctor believes this could be a suitable treatment option for you. A detailed Information Statement about the study is attached and this is a summary of the essential information about the trial and where to find the relevant detailed information later in the Information Statement. You should read the Information Statement in full and discuss it with your family and medical practitioners before deciding to participate in this study. You may contact the study staff *[or provide a name]* to discuss or asks questions about the study on [phone number] or by email [email address].

This study aims to look at how Phage Therapy can be given to patients in a standardised way that will help better understand how the treatment affects you and other patients. If you agree you will receive a specific Phage Therapy product that is suitable for you as decided by your doctor. For a full description of the purpose and rationale for this research see pages 2-4.

Participation in this study is voluntary and refusal to participate or withdrawal from the study at a later stage will not affect the treatment you receive at *[department/hospital]*

If you decide to participate in this study you will be required to receive Phage Therapy as directed by your doctor. How long you will need to take the Phage Therapy for will be decided by your doctor by taking into consideration your medical history and the type of infection you have. During your treatment information about your background medical condition, your infection, the reason for Phage Therapy and your response to treatment will be collected. You will have blood and other samples (swabs, sputum samples etc.) collected. The schedule for study visits and a full list of all tests and procedures is on pages 3-4. After the study treatment has finished you will be followed by your primary doctor for at least 6 months and asked to complete a questionnaire after treatment.

The most common risks to participants from Phage Therapy is a brief inflammatory reaction (fever, headache, muscle aches). A full list of the side-effects from Phage Therapy and other risks associated with the study procedures are on page 6.

There is additional information about what information will be collected about you during the study, how that information will be used, and your privacy protected on pages 8-9. Your rights and additional regulatory information that we are obligated to provide on pages 9-10.

Please make sure you have completely understood what the study involves before you decide to participate.

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Participant Information Sheet/Consent Form - Adult

Standardised Treatment and Monitoring of Phage therapy (STAMP) *Adult providing own consent*

Title	Standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy
Short Title	Standardised Treatment and Monitoring of Phage therapy (STAMP)
Project Sponsor	Western Sydney Local Health District
Coordinating Principal Investigator	Prof Jonathan Iredell
Site Principal Investigator	*[Site PI name]*
Location	*[Location]*

What does my participation involve?

1 Introduction

You are invited to take part in this research project because you have a bacterial infection that your doctor has determined would benefit from Phage Therapy. The research project is investigating the best way to provide Phage Therapy to patients, including how doctors should monitor the treatment.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your doctors.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
• Understand what you have read
• Consent to take part in the research project
• Consent to have the tests and treatments that are described
• Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information Sheet and Consent Form to keep.

2 What is the purpose of this research?

Phage Therapy is an experimental treatment. This means that it is not an approved treatment for bacterial infections in Australia. You will be receiving this treatment under the Special Access Scheme (SAS) of the Australian Therapeutic Goods Administration (TGA) which is sometimes referred to as "compassionate access". The decision to provide Phage Therapy to you and the specific phage product you will receive, has been decided by your doctors and is not part of this research project. This research will investigate how the treatment can be given to you in a standardised way so that we can better understand how the treatment affects you and other patients.

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This research has been initiated by the study doctors, Professor Iredell, Associate Professor Steven Tong and Dr's Ameneh Khatami and Morgyn Warner. It has been funded by the National Health and Medical Research Council (NHMRC) and the Medical Research Future Fund (MRFF) of Australia. It is being conducted by the Phage Australia Network of researchers (https://criticalinfection.com/phage-australia/).

3 What does participation in this research involve?

Once your doctor has determined that you may benefit from Phage Therapy, and a suitable phage product has been found, they will refer you to one of the study doctors. The study doctors will confirm that you are eligible to be enrolled in this research. This will include checking that all of the approvals that are required from Government agencies and other local hospital approvals that may be required have been obtained by your doctor. You will then be asked to sign a consent form before you can participate in the study.

The dose and duration of treatment with Phage Therapy, and the way in which it will be given to you (e.g. intravenously, by mouth, nebulised or topically) will be decided by one of the study doctors, after discussion with your primary (referring) doctor, taking into consideration your background medical conditions and the specific infection you have. Most patients will receive Phage Therapy for 2 weeks, given intravenously (through a drip, in a vein), and this will be provided to you in hospital. For some patients, if the Phage Therapy is required for a longer duration, this may be given to you in your home or an outpatient clinic. For other patients who only need Phage Therapy topically (e.g. onto a wound) or by a nebuliser (to be breathed into your lungs), this may also be given to you in your home or an outpatient clinic. In any circumstance, Phage Therapy will be given by qualified doctors and nurses, and prescribed to you in the same way as other medications.

For most people receiving 2 weeks of Phage Therapy intravenously (through a drip), this will be given once daily, in the morning for the first 2 days, and then twice a day (morning and evening) for the next 12 days. It is possible that you have once daily treatment for longer than 2 days during the 2 weeks, based on blood levels of the phage that will be measured throughout the treatment. Your doctors and nurses will also monitor your heart rate, breathing rate, blood pressure and temperature before and after each dose of phage.

Information regarding your background medical condition, your infection, the reason for Phage Therapy and your response to treatment will be collected in a standardised database. We will also collect blood and other samples that might be relevant for your specific infection (e.g. swabs or sputum samples). These samples will be collected at specified time-points before, during and after completion of the treatment to investigate how effective the treatment has been at clearing your infection, how it has affected your body in other ways, such as your kidneys and liver, and how your immune system has responded to the treatment.

For most people receiving 2 weeks of Phage Therapy intravenously (through a drip), blood samples will be collected the day before starting Phage Therapy (day 0), and again, 1, 3, 7, 10 and 14 days **after** your first dose (day 1). 4 weeks after your first dose of phage, which is about 2 weeks after your last dose of phage, you will have a follow-up visit with more blood tests and collection of relevant samples. On some days you will be asked to provide a blood sample 3 times: once before the morning dose of phage, and then 30-60 minutes, and 2-3 hours after the dose. This will help the study doctors understand how quickly phage is cleared from the body, and will also help determine whether you should receive once or twice daily treatment. The table below shows what days you will have blood tests compared to the first and last dose of phage you receive, and how many blood samples are needed each time.

Day	**0**	**1**	**2**	**4**	**8**	**11**	**14**	**15**	**29**
Number of blood samples	x1	First dose of phage	x3	x3	x3	x3	Last dose of phage	x1	x1

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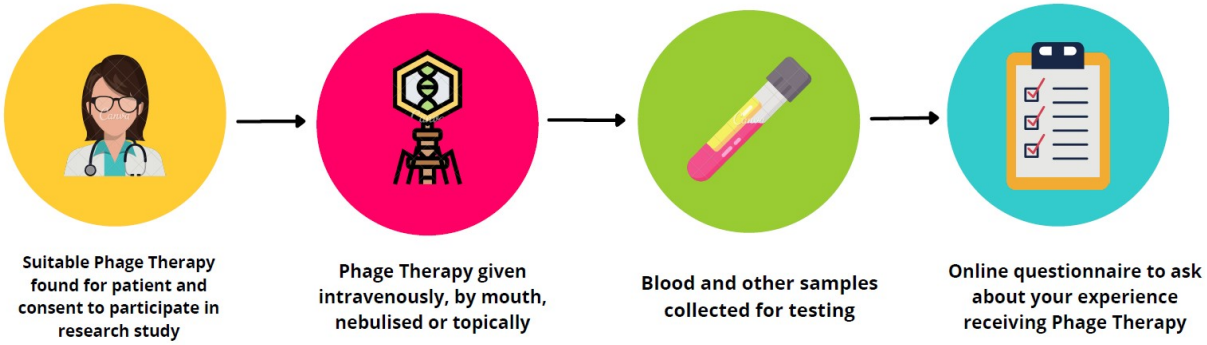
Patients who do not receive any Phage Therapy through a drip in the vein, or by mouth, will have fewer blood tests. They will not have any blood tests on day 11, and on each day will only have a single set of blood samples taken.

Day	0	1	2	4	8	14	15	29
Number of blood samples	x1	First dose of phage	x1	x1	x1	Last dose of phage	x1	x1

Patients who have longer courses of Phage Therapy will continue to have blood tests to monitor their treatment every month. All blood samples will be collected by qualified health professionals (e.g. doctors, nurses or blood collectors).

Before starting Phage Therapy, at the end of the course and again 3 and 6 months after your treatment you will also be asked to complete an online questionnaire. This will ask you questions about your experience of the Phage Therapy and how it may have affected your quality of life. It will take 10 minutes to complete. Although we would like you to complete the entire questionnaire, you can skip any questions that you do not wish to answer.



For most patients, your main involvement in the study will be for 1 month. This includes the 2 weeks of Phage Therapy and the follow-up visit 2 weeks after completing Phage Therapy. During this time, in addition to the tests described above, you will be asked about any symptoms and health events that may have occurred so that study doctors can determine the safety of Phage Therapy. For some patients who are receiving longer courses of Phage Therapy, their involvement in the study will be determined by the duration of Phage Therapy that has been recommended for them. Once the Phage Therapy has finished, you will be followed up by your primary doctor for at least 6 months. The frequency of follow-up visits will be determined by your doctor, based on any underlying medical conditions. During this follow-up period you will also continue to receive invitations to complete the quality-of-life questionnaire at 3 and 6 months after your initial course of treatment.

There are no additional costs associated with participating in this research project, nor will you be paid. All medication, tests and medical care required as part of the research project will be provided to you free of charge.

It is desirable that your local (family) doctor be advised of your decision to participate in this research project. If you have a local doctor, we strongly recommend that you inform them of your participation in this research project.

4 What do I have to do?

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions. It is

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important that administration of phage (including any dose changes) and all of the monitoring tests are done in a standardised way as written in the study protocol. It is also important that all of the information is collected in a standardised way so that the data from all participants in the study can be collated and analysed together. This includes answers you provide in the quality-of-life questionnaire. However, there will be no other restrictions on you with respect to diet, exercise or other activities, or other medications you may need. All of your other routine health care will continue as normal, and as determined by your doctor(s).

5 Other relevant information about the research project

This research is being conducted at multiple hospitals around Australia and will continue for 5 years. We are aiming to recruit 50-100 participants in the study during this time. At *[Location where the research will be conducted]* we expect around 2-3 participants to be recruited each year. The research is a collaboration between multiple hospitals, universities and research institutes working together.

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information Sheet and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with *[Institution]*.

7 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this hospital. If you choose not to participate in this research, your doctor(s) may still decide to offer you Phage Therapy but it may not be monitored in the way outlined in this research. This includes having access to some of the special tests that are not available in routine hospital or community labs. Your study doctor will discuss these options with you before you decide whether or not to take part in this research project. You can also discuss the options with your primary or local doctor.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research; however, possible benefits may include clearance of your infection, or stabilisation or improvement in your symptoms. In addition, your treatment will be overseen and monitored by a group of study doctors which include specialists in infectious diseases and Phage Therapy from around Australia and internationally. Importantly, the information that we collect in this research will help us and other researchers determine the best way to provide Phage Therapy to patients in the future. It may also help us be able to make Phage Therapy more widely available in Australia.

9 What are the possible risks and disadvantages of taking part?

Any medical treatment can cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

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The specific phage product you will receive will be determined by your own doctor. This will be discussed with one of the study doctors, but this decision is not included in the research. Your doctor can provide you with specific information about the phage product you will receive, including where it has been sourced from and how it has been manufactured. Below is some general information about possible risks that might occur for patients receiving Phage Therapy.

Phage Therapy general information and risks

Phages are viruses that infect and kill bacterial cells, but they do not attack human cells. For this reason, phage therapy is considered very safe. It has been used for over 100 years to treat patients with bacterial infections. When phages are well purified to remove contaminants, they cause very few side effects. Only phage products that meet regulatory requirements regarding purification standards will be used in this research.

Sometimes a brief inflammatory reaction is seen after the initial doses of phage. This is mostly due to the phage attacking and killing the bacteria causing your infection. It is usually a good sign that the phages are doing their job but it may be uncomfortable for you. You may have a fever or feel unwell in other ways (chills, headache, muscle aches). Depending on the site of your bacterial infection, you may also experience pain at the site. Usually this inflammatory response is brief, lasting a few hours and can be managed with simple medication like paracetamol or ibuprofen. Rarely, there may be a severe reaction which may mean that further doses of phage are delayed or not given.

Other side effects that may occur during your treatment include abnormalities in results of tests of your liver or kidney function, blood cells and immune responses. If such abnormalities are seen, they will be monitored until they return to their baseline value. In our experience of treating patients in Australia, as well as reports from patients treated in other countries, these abnormalities in lab tests are usually not severe and resolve after a few weeks of stopping the Phage Therapy.

Unknown risks of Phage Therapy

There may also be side effects that we do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you experience. Sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you. Any side effects that may occur during your treatment will be managed or treated by the study doctors and your own doctors according to usual health care practice.

Risks of Phage Therapy of pregnancy and breastfeeding

Since phages do not attack human cells, we do not believe there are any additional risks of using Phage Therapy during pregnancy. However, if you are pregnant or breastfeeding, or you are trying to conceive a child and you have concerns about receiving Phage Therapy, please speak to your study doctors. You will not need to avoid pregnancy, breastfeeding, sperm or egg donation as a result of your participation in this research.

Risks of taking part in this research project

There are very few risks or disadvantages to taking part in this research because the study is mainly investigating how Phage Therapy should be given and monitored. As part of the research, you will be asked to provide blood and other samples at specific timepoints, and the phage will be given to you at specific times of the day, for most patients injected through an intravenous drip. Having a treatment injected or blood samples taken may cause some discomfort, bruising, minor infection or bleeding. If this happens, it can be easily treated.

If you become upset or distressed as a result of your participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who are not members of the research project team. This counselling will be provided free of charge.

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10 What will happen to my test samples?

Most of the tests that will be performed to monitor your treatment are the same routine lab tests used by doctors to monitor infections. These tests will be performed at the usual labs where patient samples from *[Location where the research will be conducted]* are always processed. Once the testing is completed in these labs, the samples will be discarded and destroyed in the same way as other patient samples are handled by labs.

Some of the tests are specific to the Phage Therapy, including tests to determine the levels of phage in your blood, tests to look at how your immune system is responding to the Phage Therapy and tests that will investigate your microbiome (the collection of bacteria and other microorganisms, including viruses, which live in your body). Your blood and other samples (e.g. urine, sputum, faeces) for these tests may need to be sent to another lab in Australia that specialises in Phage Therapy. If this is the case, the samples will be sent in an anonymised way, using only a study code that will be assigned to you for the research project. No personal or identifiable information will be sent outside of *[Location where the research will be conducted]*. Only study doctors from *[Location where the research will be conducted]* and your clinical team will be able to re-identify these samples as yours, using your specific study code.

These tests are all required as part of your participation in the research. Once testing on these samples is completed, any remaining samples will be stored in the external lab in case further testing is required in the future (for this research project). We will also ask your permission to use these stored samples in other related research projects in the future, however this is optional. You can still take part in this research if you do not wish to have your samples used in other projects. Any leftover samples will be destroyed 15 years after the end of the study in the usual safe way that human samples are discarded and destroyed and according to law.

Genetic tests that will be performed in this research will be:
1) to investigate your microbiome which includes all of the bacteria, fungi and viruses that normally live in our bodies, and how these might change during Phage Therapy. This test will not look at any human genetic material, only at the genetic material of microorganisms.
2) to investigate the genes responsible for your immune system and how it responds to the Phage Therapy. This test will not look at any of your other genes so it is unlikely that it will identify any genetic disorders. There is a small chance that we may find that your immune system is not responding as well to infections as in other people. If that is the case, study doctors would let your doctor know the results so that they can discuss these with you and arrange any other investigations that might be needed.

11 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue.

12 Can I have other treatments during this research project?

Participating in this research project will not affect your ability to take other medications or treatments for your condition or for other reasons. However, it is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including

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over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project.

13 What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional information from or about you, although information already collected will be kept as part of the research to ensure that the results of the research can be measured properly and to comply with law. This information will only ever be used in an anonymised way and no personal or identifiable information about you will be used for research purposes. You should be aware that data collected by the sponsor up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell the study team before you join the research project.

14 Could this research project be stopped unexpectedly?

Although unlikely, this research project may be stopped unexpectedly for a variety of reasons, including unacceptable side effects or safety concerns.

15 What happens when the research project ends?

Once you have completed your course of Phage Therapy for your infection, no further ongoing access to Phage Therapy will be required. If further episodes of infection occur, including relapses or recurrence of the same infection, that require further courses of Phage Therapy, these future episodes will be treated as separate events and will be assessed for eligibility for you to be re-enrolled in the research project in the same way as for the initial course of treatment.

All other health care that may be required by you after the end of Phage Therapy will be according to routine practice and will be managed by your primary or local doctor.

After the project is completed in 5 years' time, the results of the research will be published in a scientific journal or may be presented at scientific meetings. A summary of publications and presentations will be made available for participants and the public on the Phage Australia website (https://criticalinfection.com/phage-australia/).

Part 2 How is the research project being conducted?

16 What will happen to information about me?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal and health information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential and securely stored. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research (e.g. results of lab tests or scans). By signing the consent form you agree to the study team accessing health records if they are relevant to your participation in this research project.

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All study information will be entered into a web-based database called REDCap. This is hosted by the University of Sydney and is protected so that only the study team can access the information. Within this database you would be assigned a study code. Your personal and identifiable information would only be available to the clinical team looking after you and the study team at *[Location where the research will be conducted]* so that they can discuss the best possible way to provide Phage Therapy to you, including any changes that might be needed in the dose of phage you are receiving. The rest of the research team would only have access to non-personal information through your anonymised study code.

Any of your blood or other samples that need to be sent to external labs will also only be identified with your study code and none of your personal or identifiable information will be sent outside of *[Location where the research will be conducted]*. It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission. All personal and identifiable information will be removed from the data when it is analysed and reported.

Paper documents, including copies of signed consent forms that include any personal or identifiable information will be stored in locked cupboards in offices at *[Location where the research will be conducted]*. All research data will be stored for 15 years after completion of the project, at which point all electronic documents with any identifiable information will be destroyed by permanent deletion and all paper files will be destroyed by shredding.

We will ask your permission to use your anonymised information in other related research projects in the future, however this is optional. You can still take part in this research if you do not wish to have your information used in other projects. Only anonymised information would be used for other future research projects and your personal or identifiable information will not be shared with anyone outside of the clinical team looking after you and the study team at *[Location where the research will be conducted]* without your permission.

Your health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives of the Sponsor, Western Sydney Local Health District, the institution relevant to this Participant Information Sheet, Sydney Children's Hospitals Network Human Research Ethics Committee, or as required by law. By signing the consent form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

In accordance with relevant Australian and *[Name of state/territory]* privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

17 Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

18 Who is organising and funding the research?

This research has been funded by the National Health and Medical Research Council (NHMRC) and the Medical Research Future Fund (MRFF) of Australia. It is being conducted by the Phage

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Australia Network of researchers (https://criticalinfection.com/phage-australia/), including *[Name of local PI and relevant study staff]*.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

19 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Sydney Children's Hospitals Network.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor *[Name of local PI]* on *[phone number]* or any of the following people:

Clinical contact person

Name	During normal working hours: *[Site PI name]* After hours or if unable to contact *[Site PI name]*: Infectious diseases registrar or consultant on call
Position	*[Title/position/department of Site PI]*
Telephone	During normal working hours: *[Site PI contact number]* After hours: Infectious diseases registrar or consultant on call via *[Hospital switch/on call Phone number]*
Email	*[Site PI Email address]*

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Sydney Children's Hospital Network
HREC Executive Officer	Clare Bayram
Telephone	(02) 9845 3066
Email	SCHN-Ethics@health.nsw.gov.au

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Consent Form - Adult providing own consent

Title	Standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy
Short Title	Standardised Treatment and Monitoring of Phage therapy (STAMP)
Project Sponsor	Western Sydney Local Health District
Coordinating Principal Investigator	Prof Jonathan Iredell
Site Principal Investigator	*[Site PI name]*
Location	*[Location]*

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to *[Name of Institution]* concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

I consent to the storage and use of blood and tissue samples taken from me for use, as described in the relevant section of the Participant Information Sheet, for:

- This specific research project only
- This research project and other research that is closely related to this research project

Strike out one option above and initial next to your choice.

I consent to the storage and use of my de-identified (anonymous) information, as described in the relevant section of the Participant Information Sheet, for:

- This specific research project only
- This research project and other research that is closely related to this research project

Strike out one option above and initial next to your choice.

I agree to the use of my samples for genetic testing, as outlined in the relevant Section of the Participant Information Sheet.

Name of Participant (please print) _____

Signature _____ Date _____

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If the person providing consent is unable to read, an impartial witness should be present during the entire informed consent discussion

Name of Witness* to
Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

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Form for Withdrawal of Participation - Adult

Title	Standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy
Short Title	Standardised Treatment and Monitoring of Phage therapy (STAMP)
Project Sponsor	Western Sydney Local Health District
Coordinating Principal Investigator	Prof Jonathan Iredell
Site Principal Investigator	*[Site PI name]*
Location	*[Location]*

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with *[Institution]*.

- I wish to withdraw from any further collection of samples and clinical data for this research
- I wish to withdraw from any further collection of samples but I am allowing continued collection of my clinical data for this research

Strike out one option above and initial next to your choice.

Name of Participant (please print) _____

Signature _____ Date _____

In the event that the participant's decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.

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Insert Header with institution's name or institution's letterhead

Executive Summary of the

Participant Information Sheet/Consent Form – Parent/Guardian

Standardised Treatment and Monitoring of Phage Therapy (STAMP)

[Local Chief Investigator]

Your child is invited to participate in the above research study because they have a bacterial infection that their doctor has determined would benefit from Phage Therapy and their doctor believes this could be a suitable treatment option for your child. A detailed Information Statement about the study is attached and this is a summary of the essential information about the trial and where to find the relevant detailed information later in the Information Statement. You should read the Information Statement in full and discuss it with your family and medical practitioners before deciding to consent to your child participating in this study. You may contact the study staff *[or provide a name]* to discuss or asks questions about the study on [phone number] or by email [email address].

This study aims to look at how Phage Therapy can be given to patients in a standardised way that will help better understand how the treatment affects them and other patients. If you agree your child will receive a specific Phage Therapy product that is suitable for them as decided by their doctor. For a full description of the purpose and rationale for this research see pages 2-4.

Participation in this study is voluntary and refusal to participate or withdrawal from the study at a later stage will not affect the treatment your child receives at *[department/hospital]*

If you decide to participate in this study your child will be required to receive Phage Therapy as directed by their doctor. How long they will need to take the Phage Therapy for will be decided by their doctor by taking into consideration medical history and the type of infection they have. During your treatment information about your child's background medical condition infection, the reason for Phage Therapy and their response to treatment will be collected. They will have blood and other samples (swabs, sputum samples etc.) collected. The schedule for study visits and a full list of all tests and procedures is on page 4. After the study treatment has finished your child will be followed by their primary doctor for at least 6 months and asked to complete a questionnaire after treatment.

The most common risks to participants from Phage Therapy is a brief inflammatory reaction (fever, headache, muscle aches). A full list of the side-effects from Phage Therapy and other risks associated with the study procedures are on page 6.

There is additional information about what information will be collected about your child during the study, how that information will be used, and their privacy protected on pages 8-9. Your rights and additional regulatory information that we are obligated to provide on pages 9-10.

Please make sure you have completely understood what the study involves before you decide to participate.

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Participant Information Sheet/Consent Form – Parent/Guardian

Standardised Treatment and Monitoring of Phage therapy (STAMP)
Parent/Guardian consenting on behalf of participant

Title	Standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy
Short Title	Standardised Treatment and Monitoring of Phage therapy (STAMP)
Project Sponsor	Western Sydney Local Health District
Coordinating Principal Investigator	Prof Jonathan Iredell
Site Principal Investigator	*[Site PI name]*
Location	*[Location]*

Part 1 What does my child's participation involve?

1 Introduction

Your child is invited to take part in this research project because they have a bacterial infection that their doctor has determined would benefit from Phage Therapy. The research project is investigating the best way to provide Phage Therapy to patients, including how doctors should monitor the treatment.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want your child to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not your child should take part, you might want to talk about it with a relative, friend or your doctors.

Participation in this research is voluntary. If you don't wish for your child to take part, they don't have to. They will receive the best possible care whether or not they take part.

If you decide you want your child to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
• Understand what you have read
• Consent for your child to take part in the research project
• Consent for your child to have the tests and treatments that are described
• Consent to the use of your child's personal and health information as described.

You will be given a copy of this Participant Information Sheet and Consent Form to keep.

2 What is the purpose of this research?

Phage Therapy is an experimental treatment. This means that it is not an approved treatment for bacterial infections in Australia. Your child will be receiving this treatment under the Special Access Scheme (SAS) of the Australian Therapeutic Goods Administration (TGA) which is sometimes referred to as "compassionate access". The decision to provide Phage Therapy to your child and the specific phage product they will receive, has been decided by their doctors and is not part of this research project. This research will investigate how the treatment can be

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given to your child in a standardised way so that we can better understand how the treatment affects your child and other patients.

This research has been initiated by the study doctors, Professor Iredell, Associate Professor Steven Tong and Dr's Ameneh Khatami and Morgyn Warner. It has been funded by the National Health and Medical Research Council (NHMRC) and the Medical Research Future Fund (MRFF) of Australia. It is being conducted by the Phage Australia Network of researchers (https://criticalinfection.com/phage-australia/).

3 What does participation in this research involve?

Once your doctor has determined that your child may benefit from Phage Therapy, and a suitable phage product has been found, they will refer your child to one of the study doctors. The study doctors will confirm that they are eligible to be enrolled in this research. This will include checking that all of the approvals that are required from Government agencies and other local hospital approvals that may be required have been obtained by their doctor. You will then be asked to sign a consent form before your child can participate in the study.

The dose and duration of treatment with Phage Therapy, and the way in which it will be given to your child (e.g. intravenously, by mouth, nebulised or topically) will be decided by one of the study doctors, after discussion with your child's primary (referring) doctor, taking into consideration your child's background medical conditions and the specific infection they have. Most patients will receive Phage Therapy for 2 weeks, given intravenously (through a drip, in a vein), and this will be provided to your child in hospital. For some patients, if the Phage Therapy is required for a longer duration, this may be given to your child in your home or an outpatient clinic. For other patients who only need Phage Therapy topically (e.g. onto a wound) or by a nebuliser (to be breathed into your lungs), this may also be given to your child in your home or an outpatient clinic. In any circumstance, Phage Therapy will be given by qualified doctors and nurses, and prescribed to your child in the same way as other medications.

For most people receiving 2 weeks of Phage Therapy intravenously (through a drip), this will be given once daily, in the morning for the first 2 days, and then twice a day (morning and evening) for the next 12 days. It is possible that your child may have once daily treatment for longer than 2 days during the 2 weeks, based on blood levels of the phage that will be measured throughout the treatment. Your child's doctors and nurses will also monitor their heart rate, breathing rate, blood pressure and temperature before and after each dose of phage.

Information regarding your child's background medical condition, their infection, the reason for Phage Therapy and their response to treatment will be collected in a standardised database. We will also collect blood and other samples that might be relevant for your child's specific infection (e.g. swabs or sputum samples). These samples will be collected at specified time-points before, during and after completion of the treatment to investigate how effective the treatment has been at clearing your child's infection, how it has affected their body in other ways, such as their kidneys and liver, and how their immune system has responded to the treatment.

For most people receiving 2 weeks of Phage Therapy intravenously (through a drip), blood samples will be collected the day before starting Phage Therapy (day 0), and again, 1, 3, 7, 10 and 14 days **after** their first dose (day 1). 4 weeks after your child's first dose of phage, which is about 2 weeks after their last dose of phage, your child will have a follow-up visit with more blood tests and collection of relevant samples. On some days your child will be asked to provide a blood sample 3 times: once before the morning dose of phage, and then 30-60 minutes, and 2-3 hours after the dose. This will help the study doctors understand how quickly phage is cleared from the body, and will also help determine whether they should receive once or twice daily treatment. The table below shows what days your child will have blood tests compared to the first and last dose of Phage Therapy they get, and how many blood samples are needed each time.

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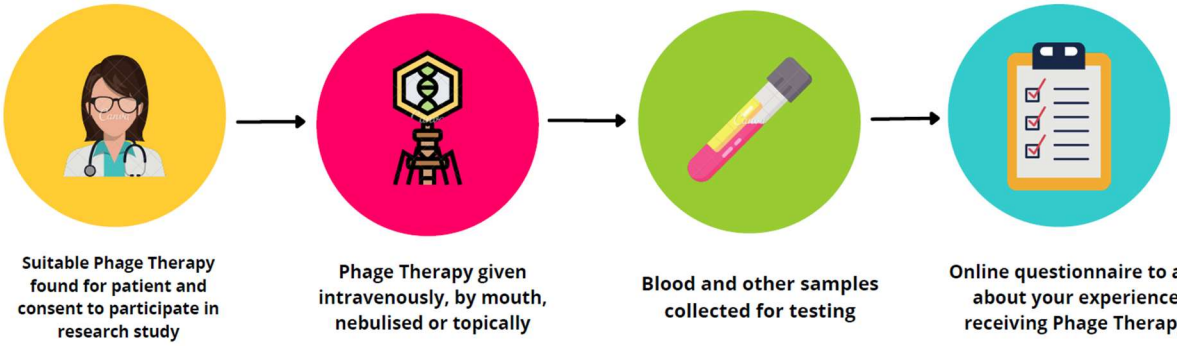
Day	0	1	2	4	8	11	14	15	29
Number of blood samples	x1	First dose of phage	x3	x3	x3	x3	Last dose of phage	x1	x1

Patients who do not receive any Phage Therapy through a drip in the vein, or by mouth, will have fewer blood tests. They will not have any blood tests on day 11, and on each day will only have a single set of blood samples taken.

Day	0	1	2	4	8	14	15	29
Number of blood samples	x1	First dose of phage	x1	x1	x1	Last dose of phage	x1	x1

Patients who have longer courses of Phage Therapy will continue to have blood tests to monitor their treatment every month. All blood samples will be collected by qualified health professionals (e.g. doctors, nurses or blood collectors).

Before starting Phage Therapy, at the end of the course and again 3 and 6 months after your child's treatment patients enrolled in the research who are at least 5 years old will also be asked to complete an online questionnaire. This will ask questions about their experience of the Phage Therapy and how it may have affected their quality of life. It will take 10 minutes to complete. We would ask that you help your child complete these questionnaires. Although we would like your child to complete the entire questionnaire, they and you can skip any questions that you do not wish to answer.



For most patients, their main involvement in the study will be for 1 month. This includes the 2 weeks of Phage Therapy and the follow-up visit 2 weeks after completing Phage Therapy. During this time, in addition to the tests described above, you and your child will be asked about any symptoms and health events that may have occurred so that study doctors can determine the safety of Phage Therapy. For some patients who are receiving longer courses of Phage Therapy, their involvement in the study will be determined by the duration of Phage Therapy that has been recommended for them. Once the Phage Therapy has finished, your child will be followed up by your child's primary doctor for at least 6 months. The frequency of follow-up visits will be determined by your child's doctor, based on any underlying medical conditions. During this follow-up period, if your child is at least 5 years old, they will also continue to receive invitations to complete the quality-of-life questionnaire at 3 and 6 months after their initial course of treatment.

There are no additional costs associated with participating in this research project, nor will you or your child be paid. All medication, tests and medical care required as part of the research project will be provided to your child free of charge.

It is desirable that your local (family) doctor be advised of your decision to participate in this research project. If you have a local doctor, we strongly recommend that you inform them of your child's participation in this research project.

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4 What does my child have to do?

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions. It is important that administration of phage (including any dose changes) and all of the monitoring tests are done in a standardised way as written in the study protocol. It is also important that all of the information is collected in a standardised way so that the data from all participants in the study can be collated and analysed together. This includes answers you and your child provide in the quality-of-life questionnaires. However, there will be no other restrictions on your child with respect to diet, exercise or other activities, or other medications they may need. All of your child's other routine health care will continue as normal, and as determined by their doctor(s).

5 Other relevant information about the research project

This research is being conducted at multiple hospitals around Australia and will continue for 5 years. We are aiming to recruit 50-100 participants in the study during this time (including adults and children). At *[Location where the research will be conducted]* we expect around 2-3 participants to be recruited each year. The research is a collaboration between multiple hospitals, universities and research institutes working together.

6 Does my child have to take part in this research project?

Participation in any research project is voluntary. If you do not wish for your child to take part, they do not have to. If you decide to take part and later change your mind, you are free to withdraw your child from the project at any stage.

If you do decide to take part, you will be given this Participant Information Sheet and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your child's routine treatment, you or your child's relationship with those treating your child or you or your child's relationship with *[Institution]*.

7 What are the alternatives to participation?

Your child does not have to take part in this research project to receive treatment at this hospital. If you choose not to participate in this research, your child's doctor(s) may still decide to offer them Phage Therapy but it may not be monitored in the way outlined in this research. This includes having access to some of the special tests that are not available in routine hospital or community labs. Your child's study doctor will discuss these options with you before you decide whether or not you want your child to take part in this research project. You can also discuss the options with your child's primary or local doctor.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that your child will receive any benefits from this research; however, possible benefits may include clearance of their infection, or stabilisation or improvement in their symptoms. In addition, your child's treatment will be overseen and monitored by a group of study doctors which include specialists in infectious diseases and Phage Therapy from around Australia and internationally. Importantly, the information that we collect in this research will help us and other researchers determine the best way to provide Phage Therapy to patients in the future. It may also help us be able to make Phage Therapy more widely available in Australia.

9 What are the possible risks and disadvantages of taking part?

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Any medical treatment can cause side effects. Your child may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If your child has any of these side effects, or you are worried about them, talk with your child's study doctor. Your child's study doctor will also be looking out for side effects.

The specific phage product your child will receive will be determined by their own doctor. This will be discussed with one of the study doctors, but this decision is not included in the research. Your child's doctor can provide you with specific information about the phage product your child will receive, including where it has been sourced from and how it has been manufactured. Below is some general information about possible risks that might occur for patients receiving Phage Therapy.

Phage Therapy general information and risks

Phages are viruses that infect and kill bacterial cells, but they do not attack human cells. For this reason, phage therapy is considered very safe. It has been used for over 100 years to treat patients with bacterial infections. When phages are well purified to remove contaminants, they cause very few side effects. Only phage products that meet regulatory requirements regarding purification standards will be used in this research.

Sometimes a brief inflammatory reaction is seen after the initial doses of phage. This is mostly due to the phage attacking and killing the bacteria causing your child's infection. It is usually a good sign that the phages are doing their job but it may be uncomfortable for your child. They may have a fever or feel unwell in other ways (chills, headache, muscle aches). Depending on the site of your child's bacterial infection, they may also experience pain at the site. Usually this inflammatory response is brief, lasting a few hours and can be managed with simple medication like paracetamol or ibuprofen. Rarely, there may be a severe reaction which may mean that further doses of phage are delayed or not given.

Other side effects that may occur during your child's treatment include abnormalities in results of tests of their liver or kidney function, blood cells and immune responses. If such abnormalities are seen, they will be monitored until they return to their baseline value. In our experience of treating patients in Australia, as well as reports from patients treated in other countries, these abnormalities in lab tests are usually not severe and resolve after a few weeks of stopping the Phage Therapy.

Unknown risks of Phage Therapy

There may also be side effects that we do not expect or do not know about and that may be serious. Tell your child's study doctor immediately about any new or unusual symptoms that your child experiences. Sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your child's study doctor may need to stop your treatment. Your child's study doctor will discuss the best way of managing any side effects with you. Any side effects that may occur during your treatment will be managed or treated by the study doctors and your child's own doctors according to usual health care practice.

Risks of taking part in this research project

There are very few risks or disadvantages to taking part in this research because the study is mainly investigating how Phage Therapy should be given and monitored. As part of the research, your child will be asked to provide blood and other samples at specific timepoints, and the phage will be given to your child at specific times of the day, for most patients injected through an intravenous drip. Having a treatment injected or blood samples taken may cause some discomfort, bruising, minor infection or bleeding. If this happens, it can be easily treated.

If your child becomes upset or distressed as a result of their participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who are not members of the research project team. This counselling will be provided free of charge.

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10 What will happen to my child's test samples?

Most of the tests that will be performed to monitor your child's treatment are the same routine lab tests used by doctors to monitor infections. These tests will be performed at the usual labs where patient samples from *[Location where the research will be conducted]* are always processed. Once the testing is completed in these labs, the samples will be discarded and destroyed in the same way as other patient samples are handled by labs.

Some of the tests are specific to the Phage Therapy, including tests to determine the levels of phage in your child's blood, tests to look at how your child's immune system is responding to the Phage Therapy and tests that will investigate your child's microbiome (the collection of bacteria and other microorganisms, including viruses, which live in your body). Your child's blood and other samples (e.g. urine, sputum, faeces) for these tests may need to be sent to another lab in Australia that specialises in Phage Therapy. If this is the case, the samples will be sent in an anonymised way, using only a study code that will be assigned to your child for the research project. No personal or identifiable information will be sent outside of *[Location where the research will be conducted]*. Only study doctors from *[Location where the research will be conducted]* and your child's clinical team will be able to re-identify these samples as belonging to your child, using their specific study code.

These tests are all required as part of your child's participation in the research. Once testing on these samples is completed, any remaining samples will be stored in the external lab in case further testing is required in the future (for this research project). We will also ask your permission to use these stored samples in other related research projects in the future, however this is optional. Your child can still take part in this research if you do not wish to have their samples used in other projects. Any leftover samples will be destroyed 15 years after the end of the study in the usual safe way that human samples are discarded and destroyed and according to law.

Genetic tests that will be performed in this research will be:
1) to investigate your child's microbiome which includes all of the bacteria, fungi and viruses that normally live in our bodies, and how these might change during Phage Therapy. This test will not look at any human genetic material, only at the genetic material of microorganisms.
2) to investigate the genes responsible for your child's immune system and how it responds to the Phage Therapy. This test will not look at any of your child's other genes so it is unlikely that it will identify any genetic disorders. There is a small chance that we may find that your child's immune system is not responding as well to infections as in other people. If that is the case, study doctors would let your child's doctor know the results so that they can discuss these with you and arrange any other investigations that might be needed.

11 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your child's study doctor will tell you about it and discuss with you whether you want your child to continue in the research project. If you decide to withdraw, your child's study doctor will make arrangements for your child's regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, your child's study doctor might consider it to be in your child's best interests to withdraw them from the research project. If this happens, he/ she will explain the reasons and arrange for your child's regular health care to continue.

12 Can my child have other treatments during this research project?

Participating in this research project will not affect your child's ability to take other medications or treatments for their condition or for other reasons. However, it is important to tell your child's

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study doctor and the study staff about any treatments or medications they may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your child's study doctor about any changes to these during your child's participation in the research project.

13 What if I withdraw my child from this research project?

If you decide to withdraw your child from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional information from or about your child, although information already collected will be kept as part of the research to ensure that the results of the research can be measured properly and to comply with law. This information will only ever be used in an anonymised way and no personal or identifiable information about your child will be used for research purposes. You should be aware that data collected by the sponsor up to the time you withdraw your child will form part of the research project results. If you do not want them to do this, you must tell the study team before your child joins the research project.

14 Could this research project be stopped unexpectedly?

Although unlikely, this research project may be stopped unexpectedly for a variety of reasons, including unacceptable side effects or safety concerns.

15 What happens when the research project ends?

Once your child has completed their course of Phage Therapy for their infection, no further ongoing access to Phage Therapy will be required. If further episodes of infection occur, including relapses or recurrence of the same infection, that require further courses of Phage Therapy, these future episodes will be treated as separate events and will be assessed for eligibility for your child to be re-enrolled in the research project, in the same way as for the initial course of treatment.

All other health care that may be required by your child after the end of Phage Therapy will be according to routine practice and will be managed by your child's primary or local doctor.

After the project is completed in 5 years' time, the results of the research will be published in a scientific journal or may be presented at scientific meetings. A summary of publications and presentations will be made available for participants and the public on the Phage Australia website (https://criticalinfection.com/phage-australia/).

Part 2 How is the research project being conducted?

16 What will happen to information about my child?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal and health information about your child for the research project. Any information obtained in connection with this research project that can identify your child will remain confidential and securely stored. Your child's information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information about your child may be obtained from their health records held at this and other health services for the purpose of this research (e.g. results of lab tests or scans). By signing the consent form you agree to the study team accessing health records if they are relevant to your child's participation in this research project.

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All study information will be entered into a web-based database called REDCap. This is hosted by the University of Sydney and is protected so that only the study team can access the information. Within this database your child would be assigned a study code. Your child's personal and identifiable information would only be available to the clinical team looking after your child and the study team at *[Location where the research will be conducted]* so that they can discuss the best possible way to provide Phage Therapy to your child, including any changes that might be needed in the dose of phage they are receiving. The rest of the research team would only have access to non-personal information through your child's anonymised study code.

Any of your child's blood or other samples that need to be sent to external labs will also only be identified with their study code and none of your child's personal or identifiable information will be sent outside of *[Location where the research will be conducted]*. It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that your child cannot be identified, except with your permission. All personal and identifiable information will be removed from the data when it is analysed and reported.

Paper documents, including copies of signed consent forms that include any personal or identifiable information will be stored in locked cupboards in offices at *[Location where the research will be conducted]*. All research data will be stored for 15 years after completion of the project, at which point all electronic documents with any identifiable information will be destroyed by permanent deletion and all paper files will be destroyed by shredding.

We will ask your permission to use your child's anonymised information in other related research projects in the future, however this is optional. Your child can still take part in this research if you do not wish to have their information used in other projects. Only anonymised information would be used for other future research projects and your child's personal or identifiable information will not be shared with anyone outside of the clinical team looking after your child and the study team at *[Location where the research will be conducted]* without your permission.

Your child's health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives of the Sponsor, Western Sydney Local Health District, the institution relevant to this Participant Information Sheet, Sydney Children's Hospitals Network Human Research Ethics Committee, or as required by law. By signing the consent form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

In accordance with relevant Australian and *[Name of state/territory]* privacy and other relevant laws, you have the right to request access to your child's information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your child's information.

17 Complaints and Compensation

If your child suffers any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If your child is eligible for Medicare, they can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

18 Who is organising and funding the research?

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This research has been funded by the National Health and Medical Research Council (NHMRC) and the Medical Research Future Fund (MRFF) of Australia. It is being conducted by the Phage Australia Network of researchers (https://criticalinfection.com/phage-australia/), including *[Name of local PI and relevant study staff]*.

No member of the research team will receive a personal financial benefit from your child's involvement in this research project (other than their ordinary wages).

19 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Sydney Children's Hospitals Network.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if your child has any medical problems which may be related to their involvement in the project (for example, any side effects), you can contact the principal study doctor *[Name of local PI]* on *[phone number]* or any of the following people:

Clinical contact person

Name	During normal working hours: *[Site PI name]* After hours or if unable to contact *[Site PI name]*: Infectious diseases registrar or consultant on call
Position	*[Title/position/department of Site PI]*
Telephone	During normal working hours: *[Site PI contact number]* After hours: Infectious diseases registrar or consultant on call via *[Hospital switch/on call Phone number]*
Email	*[Site PI Email address]*

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Sydney Children's Hospital Network
HREC Executive Officer	Clare Bayram
Telephone	(02) 9845 3066
Email	SCHN-Ethics@health.nsw.gov.au

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Consent Form – Parent/Guardian

Title	Standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy
Short Title	Standardised Treatment and Monitoring of Phage therapy (STAMP)
Project Sponsor	Western Sydney Local Health District
Coordinating Principal Investigator	Prof Jonathan Iredell
Site Principal Investigator	*[Site PI name]*
Location	*[Location]*

Declaration by Parent/Guardian

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my child's doctors, other health professionals, hospitals or laboratories outside this hospital to release information to *[Name of Institution]* concerning my child's disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to have my child participate in this research project as described and understand that I am free to withdraw my child at any time during the study without affecting their future health care.

I understand that I will be given a signed copy of this document to keep.

I consent to the storage and use of blood and tissue samples taken from my child for use, as described in the relevant section of the Participant Information Sheet, for:

- This specific research project only
- This research project and other research that is closely related to this research project

Strike out one option above and initial next to your choice.

I consent to the storage and use of my child's de-identified (anonymous) information, as described in the relevant section of the Participant Information Sheet, for:

- This specific research project only
- This research project and other research that is closely related to this research project

Strike out one option above and initial next to your choice.

I agree to the use of my child's samples for genetic testing, as outlined in the relevant Section of the Participant Information Sheet.

Name of Child (please print) _____

Signature of Child _____ Date _____

Name of Parent/Guardian (please print)

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Signature of Parent/Guardian _____ Date _____

If the person providing consent is unable to read, an impartial witness should be present during the entire informed consent discussion

Name of Witness* to Parent/Guardian's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the parent/guardian has understood that explanation.

Name of Study Doctor/ Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

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Form for Withdrawal of Participation – Parent/Guardian

Title	Standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy
Short Title	Standardised Treatment and Monitoring of Phage therapy (STAMP)
Project Sponsor	Western Sydney Local Health District
Coordinating Principal Investigator	Prof Jonathan Iredell
Site Principal Investigator	*[Site PI name]*
Location	*[Location]*

Declaration by Parent/Guardian

I wish to withdraw my child from participation in the above research project and understand that such withdrawal will not affect my child's routine treatment, our relationship with those treating my child or our relationship with *[Institution]*.

- I wish to withdraw my child from any further collection of samples and clinical data for this research
- I wish to withdraw my child from any further collection of samples but I am allowing continued collection of my child's clinical data for this research

Strike out one option above and initial next to your choice.

Name of Child (please print) _____

Name of Parent/Guardian (please print) _____

Signature of Parent/Guardian _____ Date_____

In the event that the parent/guardian's decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the parent/guardian has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.

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Insert Header with institution's name or institution's letterhead

Executive Summary of the
Participant Information Sheet/Consent Form – Person Responsible

Standardised Treatment and Monitoring of Phage Therapy (STAMP)

[Local Chief Investigator]

The participant is invited to participate in the above research study because they have a bacterial infection that their doctor has determined would benefit from Phage Therapy and their doctor believes this could be a suitable treatment option. A detailed Information Statement about the study is attached and this is a summary of the essential information about the trial and where to find the relevant detailed information later in the Information Statement. You should read the Information Statement in full and discuss it with your family and medical practitioners before deciding to agree to participation of the person you are responsible for in this study. You may contact the study staff *[or provide a name]* to discuss or asks questions about the study on [phone number] or by email [email address].

This study aims to look at how Phage Therapy can be given to patients in a standardised way that will help better understand how the treatment affects them and other patients. If you agree, the person you are responsible for will receive a specific Phage Therapy product that is suitable for them as decided by their doctor. For a full description of the purpose and rationale for this research see pages 2-4.

Participation in this study is voluntary and refusal to participate or withdrawal from the study at a later stage will not affect the treatment they receive at *[department/hospital]*

If you decide the person you are responsible for should participate in this study they will be required to receive Phage Therapy as directed by their doctor. How long they will need to take the Phage Therapy for will be decided by their doctor, taking into consideration medical history and the type of infection they have. During treatment information about the participant's background medical condition, infection, the reason for Phage Therapy and response to treatment will be collected. They will have blood and other samples (swabs, sputum samples etc.) collected. The schedule for study visits and a full list of all tests and procedures is on page 4. After the study treatment has finished they will be followed by their primary doctor for at least 6 months and asked to complete a questionnaire after treatment.

The most common risks to participants from Phage Therapy is a brief inflammatory reaction (fever, headache, muscle aches). A full list of the side-effects from Phage Therapy and other risks associated with the study procedures are on page 6.

There is additional information about what information will be collected about the participant during the study, how that information will be used, and their privacy protected on pages 8-9. Their rights and additional regulatory information that we are obligated to provide on pages 9-10.

Please make sure you have completely understood what the study involves before you decide to consent to participation on behalf of the person you are responsible for.

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Participant Information Sheet/Consent Form – Person Responsible

Standardised Treatment and Monitoring of Phage therapy (STAMP)
Person responsible consenting on behalf of participant

Title	Standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy
Short Title	Standardised Treatment and Monitoring of Phage therapy (STAMP)
Project Sponsor	Western Sydney Local Health District
Coordinating Principal Investigator	Prof Jonathan Iredell
Site Principal Investigator	*[Site PI name]*
Location	*[Location]*

Part 1 What does participation involve?

1 Introduction

The participant is invited to take part in this research project because they have a bacterial infection that their doctor has determined would benefit from Phage Therapy. The research project is investigating the best way to provide Phage Therapy to patients, including how doctors should monitor the treatment.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want the participant to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not the participant should take part, you might want to talk about it with a relative, friend or your doctors.

Participation in this research is voluntary. If you don't wish for the participant to take part, they don't have to. They will receive the best possible care whether or not they take part.

If you decide you want the participant to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
• Understand what you have read
• Consent for the participant to take part in the research project
• Consent for the participant to have the tests and treatments that are described
• Consent to the use of the participant's personal and health information as described.

You will be given a copy of this Participant Information Sheet and Consent Form to keep.

2 What is the purpose of this research?

Phage Therapy is an experimental treatment. This means that it is not an approved treatment for bacterial infections in Australia. The participant will be receiving this treatment under the Special Access Scheme (SAS) of the Australian Therapeutic Goods Administration (TGA) which is sometimes referred to as "compassionate access". The decision to provide Phage Therapy to the participant and the specific phage product they will receive, has been decided by their

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doctors and is not part of this research project. This research will investigate how the treatment can be given to the participant in a standardised way so that we can better understand how the treatment affects the participant and other patients.

This research has been initiated by the study doctors, Professor Iredell, Associate Professor Steven Tong and Dr's Ameneh Khatami and Morgyn Warner. It has been funded by the National Health and Medical Research Council (NHMRC) and the Medical Research Future Fund (MRFF) of Australia. It is being conducted by the Phage Australia Network of researchers (https://criticalinfection.com/phage-australia/).

3 What does participation in this research involve?

Once your doctor has determined that the participant may benefit from Phage Therapy, and a suitable phage product has been found, they will refer the participant to one of the study doctors. The study doctors will confirm that they are eligible to be enrolled in this research. This will include checking that all of the approvals that are required from Government agencies and other local hospital approvals that may be required have been obtained by their doctor. You will then be asked to sign a consent form before the participant can take part in the study.

The dose and duration of treatment with Phage Therapy, and the way in which it will be given to the participant (e.g. intravenously, by mouth, nebulised or topically) will be decided by one of the study doctors, after discussion with the participant's primary (referring) doctor, taking into consideration the participant's background medical conditions and the specific infection they have. Most patients will receive Phage Therapy for 2 weeks, given intravenously (through a drip, in a vein), and this will be provided to the participant in hospital. For some patients, if the Phage Therapy is required for a longer duration, this may be given to the participant in their home or an outpatient clinic. For other patients who only need Phage Therapy topically (e.g. onto a wound) or by a nebuliser (to be breathed into your lungs), this may also be given to the participant in their home or an outpatient clinic. In any circumstance, Phage Therapy will be given by qualified doctors and nurses, and prescribed to the participant in the same way as other medications.

For most people receiving 2 weeks of Phage Therapy intravenously (through a drip), this will be given once daily, in the morning for the first 2 days, and then twice a day (morning and evening) for the next 12 days. It is possible that the participant may have once daily treatment for longer than 2 days during the 2 weeks, based on blood levels of the phage that will be measured throughout the treatment. The participant's doctors and nurses will also monitor their heart rate, breathing rate, blood pressure and temperature before and after each dose of phage.

Information regarding the participant's background medical condition, their infection, the reason for Phage Therapy and their response to treatment will be collected in a standardised database. We will also collect blood and other samples that might be relevant for the participant's specific infection (e.g. swabs or sputum samples). These samples will be collected at specified time-points before, during and after completion of the treatment to investigate how effective the treatment has been at clearing the participant's infection, how it has affected their body in other ways, such as their kidneys and liver, and how their immune system has responded to the treatment.

For most people receiving 2 weeks of Phage Therapy intravenously (through a drip), blood samples will be collected the day before starting Phage Therapy (day 0), and again, 1, 3, 7, 10 and 14 days **after** their first dose (day 1). 4 weeks after the participant's first dose of phage, which is about 2 weeks after their last dose of phage, the participant will have a follow-up visit with more blood tests and collection of relevant samples. On some days the participant will be asked to provide a blood sample 3 times: once before the morning dose of phage, and then 30-60 minutes, and 2-3 hours after the dose. This will help the study doctors understand how quickly phage is cleared from the body, and will also help determine whether they should receive once or twice daily treatment. The table below shows what days the participant will have blood tests compared to the first and last dose of phage they receive, and how many blood samples are needed each time.

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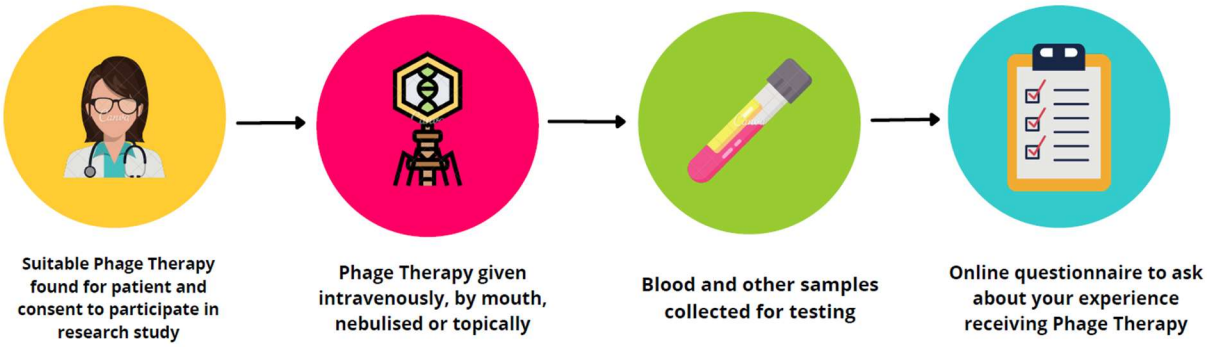
Day	0	1	2	4	8	11	14	15	29
Number of blood samples	x1	First dose of phage	x3	x3	x3	x3	Last dose of phage	x1	x1

Patients who do not receive any Phage Therapy through a drip in the vein, or by mouth, will have fewer blood tests. They will not have any blood tests on day 11, and on each day will only have a single set of blood samples taken.

Day	0	1	2	4	8	14	15	29
Number of blood samples	x1	First dose of phage	x1	x1	x1	Last dose of phage	x1	x1

Patients who have longer courses of Phage Therapy will continue to have blood tests to monitor their treatment every month. All blood samples will be collected by qualified health professionals (e.g. doctors, nurses or blood collectors).

Before starting Phage Therapy, at the end of the course and again 3 and 6 months after the participant's treatment they will also be asked to complete an online questionnaire. This will ask questions about their experience of the Phage Therapy and how it may have affected their quality of life. It will take 10 minutes to complete. We would ask that you help the participant complete these questionnaires. Although we would like the participant to complete the entire questionnaire, they and you can skip any questions that you do not wish to answer.



For most patients, their main involvement in the study will be for 1 month. This includes the 2 weeks of Phage Therapy and the follow-up visit 2 weeks after completing Phage Therapy. During this time, in addition to the tests described above, you and the participant will be asked about any symptoms and health events that may have occurred so that study doctors can determine the safety of Phage Therapy. For some patients who are receiving longer courses of Phage Therapy, their involvement in the study will be determined by the duration of Phage Therapy that has been recommended for them. Once the Phage Therapy has finished, the participant will be followed up by the participant's primary doctor for at least 6 months. The frequency of follow-up visits will be determined by the participant's doctor, based on any underlying medical conditions. During this follow-up period, they will also continue to receive invitations to complete the quality-of-life questionnaire at 3 and 6 months after their initial course of treatment.

There are no additional costs associated with participating in this research project, nor will you or the participant be paid. All medication, tests and medical care required as part of the research project will be provided to the participant free of charge.

It is desirable that your local (family) doctor be advised of your decision to participate in this research project. If you have a local doctor, we strongly recommend that you inform them of the participant's participation in this research project.

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4 What does the participant have to do?

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions. It is important that administration of phage (including any dose changes) and all of the monitoring tests are done in a standardised way as written in the study protocol. It is also important that all of the information is collected in a standardised way so that the data from all participants in the study can be collated and analysed together. This includes answers you and the participant provide in the quality-of-life questionnaires. However, there will be no other restrictions on the participant with respect to diet, exercise or other activities, or other medications they may need. All of the participant's other routine health care will continue as normal, and as determined by their doctor(s).

5 Other relevant information about the research project

This research is being conducted at multiple hospitals around Australia and will continue for 5 years. We are aiming to recruit 50-100 participants in the study during this time. At *[Location where the research will be conducted]* we expect around 2-3 participants to be recruited each year. The research is a collaboration between multiple hospitals, universities and research institutes working together.

6 Does the participant have to take part in this research project?

Participation in any research project is voluntary. If you do not wish for the participant to take part, they do not have to. If you decide to take part and later change your mind, you are free to withdraw the participant from the project at any stage.

If you do decide to take part, you will be given this Participant Information Sheet and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect the participant's routine treatment, you or the participant's relationship with those treating the participant or you or the participant's relationship with *[Institution]*.

7 What are the alternatives to participation?

The participant does not have to take part in this research project to receive treatment at this hospital. If you choose not to participate in this research, the participant's doctor(s) may still decide to offer them Phage Therapy but it may not be monitored in the way outlined in this research. This includes having access to some of the special tests that are not available in routine hospital or community labs. The study doctor will discuss these options with you before you decide whether or not you want the participant to take part in this research project. You can also discuss the options with the participant's primary or local doctor.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that the participant will receive any benefits from this research; however, possible benefits may include clearance of their infection, or stabilisation or improvement in their symptoms. In addition, the participant's treatment will be overseen and monitored by a group of study doctors which include specialists in infectious diseases and Phage Therapy from around Australia and internationally. Importantly, the information that we collect in this research will help us and other researchers determine the best way to provide Phage Therapy to patients in the future. It may also help us be able to make Phage Therapy more widely available in Australia.

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9 What are the possible risks and disadvantages of taking part?

Any medical treatment can cause side effects. The participant may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If the participant has any of these side effects, or you are worried about them, talk with the study doctor. The study doctor will also be looking out for side effects.

The specific phage product the participant will receive will be determined by their own doctor. This will be discussed with one of the study doctors, but this decision is not included in the research. The participant's doctor can provide you with specific information about the phage product the participant will receive, including where it has been sourced from and how it has been manufactured. Below is some general information about possible risks that might occur for patients receiving Phage Therapy.

Phage Therapy general information and risks
Phages are viruses that infect and kill bacterial cells, but they do not attack human cells. For this reason, phage therapy is considered very safe. It has been used for over 100 years to treat patients with bacterial infections. When phages are well purified to remove contaminants, they cause very few side effects. Only phage products that meet regulatory requirements regarding purification standards will be used in this research.

Sometimes a brief inflammatory reaction is seen after the initial doses of phage. This is mostly due to the phage attacking and killing the bacteria causing the participant's infection. It is usually a good sign that the phages are doing their job but it may be uncomfortable for the participant. They may have a fever or feel unwell in other ways (chills, headache, muscle aches). Depending on the site of the participant's bacterial infection, they may also experience pain at the site. Usually this inflammatory response is brief, lasting a few hours and can be managed with simple medication like paracetamol or ibuprofen. Rarely, there may be a severe reaction which may mean that further doses of phage are delayed or not given.

Other side effects that may occur during the participant's treatment include abnormalities in results of tests of their liver or kidney function, blood cells and immune responses. If such abnormalities are seen, they will be monitored until they return to their baseline value. In our experience of treating patients in Australia, as well as reports from patients treated in other countries, these abnormalities in lab tests are usually not severe and resolve after a few weeks of stopping the Phage Therapy.

Unknown risks of Phage Therapy
There may also be side effects that we do not expect or do not know about and that may be serious. Tell the study doctor immediately about any new or unusual symptoms that the participant experiences. Sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, the study doctor may need to stop your treatment. The study doctor will discuss the best way of managing any side effects with you. Any side effects that may occur during your treatment will be managed or treated by the study doctors and the participant's own doctors according to usual health care practice.

Risks of taking part in this research project
There are very few risks or disadvantages to taking part in this research because the study is mainly investigating how Phage Therapy should be given and monitored. As part of the research, the participant will be asked to provide blood and other samples at specific timepoints, and the phage will be given to the participant at specific times of the day, for most patients injected through an intravenous drip. Having a treatment injected or blood samples taken may cause some discomfort, bruising, minor infection or bleeding. If this happens, it can be easily treated.

If the participant becomes upset or distressed as a result of their participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any

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counselling or support will be provided by qualified staff who are not members of the research project team. This counselling will be provided free of charge.

10 What will happen to the participant's test samples?

Most of the tests that will be performed to monitor the participant's treatment are the same routine lab tests used by doctors to monitor infections. These tests will be performed at the usual labs where patient samples from *[Location where the research will be conducted]* are always processed. Once the testing is completed in these labs, the samples will be discarded and destroyed in the same way as other patient samples are handled by labs.

Some of the tests are specific to the Phage Therapy, including tests to determine the levels of phage in the participant's blood, tests to look at how the participant's immune system is responding to the Phage Therapy and tests that will investigate the participant's microbiome (the collection of bacteria and other microorganisms, including viruses, which live in your body). The participant's blood and other samples (e.g. urine, sputum, faeces) for these tests may need to be sent to another lab in Australia that specialises in Phage Therapy. If this is the case, the samples will be sent in an anonymised way, using only a study code that will be assigned to the participant for the research project. No personal or identifiable information will be sent outside of *[Location where the research will be conducted]*. Only study doctors from *[Location where the research will be conducted]* and the participant's clinical team will be able to re-identify these samples as belonging to the participant, using their specific study code.

These tests are all required for the participant to take part in the research. Once testing on these samples is completed, any remaining samples will be stored in the external lab in case further testing is required in the future (for this research project). We will also ask your permission to use these stored samples in other related research projects in the future, however this is optional. The participant can still take part in this research if you do not wish to have their samples used in other projects. Any leftover samples will be destroyed 15 years after the end of the study in the usual safe way that human samples are discarded and destroyed and according to law.

Genetic tests that will be performed in this research will be:
1) to investigate the participant's microbiome which includes all of the bacteria, fungi and viruses that normally live in our bodies, and how these might change during Phage Therapy. This test will not look at any human genetic material, only at the genetic material of microorganisms.
2) to investigate the genes responsible for the participant's immune system and how it responds to the Phage Therapy. This test will not look at any of the participant's other genes so it is unlikely that it will identify any genetic disorders. There is a small chance that we may find that the participant's immune system is not responding as well to infections as in other people. If that is the case, study doctors would let the participant's doctor know the results so that they can discuss these with you and arrange any other investigations that might be needed.

11 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, the study doctor will tell you about it and discuss with you whether you want the participant to continue in the research project. If you decide to withdraw, the study doctor will make arrangements for the participant's regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, the study doctor might consider it to be in the participant's best interests to withdraw them from the research project. If this happens, he/ she will explain the reasons and arrange for the participant's regular health care to continue.

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12 Can the participant have other treatments during this research project?

Participating in this research project will not affect the participant's ability to take other medications or treatments for their condition or for other reasons. However, it is important to tell the study doctor and the study staff about any treatments or medications they may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell the study doctor about any changes to these while the participant is taking part in the research project.

13 What if I withdraw the participant from this research project?

If you decide to withdraw the participant from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional information from or about the participant, although information already collected will be kept as part of the research to ensure that the results of the research can be measured properly and to comply with law. This information will only ever be used in an anonymised way and no personal or identifiable information about the participant will be used for research purposes. You should be aware that data collected by the sponsor up to the time you withdraw the participant will form part of the research project results. If you do not want them to do this, you must tell the study team before the participant joins the research project.

14 Could this research project be stopped unexpectedly?

Although unlikely, this research project may be stopped unexpectedly for a variety of reasons, including unacceptable side effects or safety concerns.

15 What happens when the research project ends?

Once the participant has completed their course of Phage Therapy for their infection, no further ongoing access to Phage Therapy will be required. If further episodes of infection occur, including relapses or recurrence of the same infection, that require further courses of Phage Therapy, these future episodes will be treated as separate events and will be assessed for eligibility for the participant to be re-enrolled in the research project, in the same way as for the initial course of treatment.

All other health care that may be required by the participant after the end of Phage Therapy will be according to routine practice and will be managed by the participant's primary or local doctor.

After the project is completed in 5 years' time, the results of the research will be published in a scientific journal or may be presented at scientific meetings. A summary of publications and presentations will be made available for participants and the public on the Phage Australia website (https://criticalinfection.com/phage-australia/).

Part 2 How is the research project being conducted?

16 What will happen to information about the participant?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal and health information about the participant for the research project. Any information obtained in connection with this research project that can identify the participant will remain confidential and securely stored. The participant's information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

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Information about the participant may be obtained from their health records held at this and other health services for the purpose of this research (e.g. results of lab tests or scans). By signing the consent form you agree to the study team accessing health records if they are relevant to the participant taking part in this research project.

All study information will be entered into a web-based database called REDCap. This is hosted by the University of Sydney and is protected so that only the study team can access the information. Within this database the participant would be assigned a study code. The participant's personal and identifiable information would only be available to the clinical team looking after the participant and the study team at *[Location where the research will be conducted]* so that they can discuss the best possible way to provide Phage Therapy to the participant, including any changes that might be needed in the dose of phage they are receiving. The rest of the research team would only have access to non-personal information through the participant's anonymised study code.

Any of the participant's blood or other samples that need to be sent to external labs will also only be identified with their study code and none of the participant's personal or identifiable information will be sent outside of *[Location where the research will be conducted]*. It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that the participant cannot be identified, except with your permission. All personal and identifiable information will be removed from the data when it is analysed and reported.

Paper documents, including copies of signed consent forms that include any personal or identifiable information will be stored in locked cupboards in offices at *[Location where the research will be conducted]*. All research data will be stored for 15 years after completion of the project, at which point all electronic documents with any identifiable information will be destroyed by permanent deletion and all paper files will be destroyed by shredding.

We will ask your permission to use the participant's anonymised information in other related research projects in the future, however this is optional. The participant can still take part in this research if you do not wish to have their information used in other projects. Only anonymised information would be used for other future research projects and the participant's personal or identifiable information will not be shared with anyone outside of the clinical team looking after the participant and the study team at *[Location where the research will be conducted]* without your permission.

The participant's health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives of the Sponsor, Western Sydney Local Health District, the institution relevant to this Participant Information Sheet, Sydney Children's Hospitals Network Human Research Ethics Committee, or as required by law. By signing the consent form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

In accordance with relevant Australian and *[Name of state/territory]* privacy and other relevant laws, you have the right to request access to the participant's information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access the participant's information.

17 Complaints and Compensation

If the participant suffers any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If the participant is eligible for Medicare, they can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

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18 Who is organising and funding the research?

This research has been funded by the National Health and Medical Research Council (NHMRC) and the Medical Research Future Fund (MRFF) of Australia. It is being conducted by the Phage Australia Network of researchers (https://criticalinfection.com/phage-australia/), including *[Name of local PI and relevant study staff]*.

No member of the research team will receive a personal financial benefit from the participant's involvement in this research project (other than their ordinary wages).

19 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Sydney Children's Hospitals Network.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if the participant has any medical problems which may be related to their involvement in the project (for example, any side effects), you can contact the principal study doctor *[Name of local PI]* on *[phone number]* or any of the following people:

Clinical contact person

Name	During normal working hours: *[Site PI name]* After hours or if unable to contact *[Site PI name]*: Infectious diseases registrar or consultant on call
Position	*[Title/position/department of Site PI]*
Telephone	During normal working hours: *[Site PI contact number]* After hours: Infectious diseases registrar or consultant on call via *[Hospital switch/on call Phone number]*
Email	*[Site PI Email address]*

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Sydney Children's Hospital Network
HREC Executive Officer	Clare Bayram
Telephone	(02) 9845 3066
Email	SCHN-Ethics@health.nsw.gov.au

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Consent Form – Person Responsible

Title	Standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy
Short Title	Standardised Treatment and Monitoring of Phage therapy (STAMP)
Project Sponsor	Western Sydney Local Health District
Coordinating Principal Investigator	Prof Jonathan Iredell
Site Principal Investigator	*[Site PI name]*
Location	*[Location]*

Declaration by Person Responsible

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for the participant's doctors, other health professionals, hospitals or laboratories outside this hospital to release information to *[Name of Institution]* concerning the participant's disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to the participant taking part in this research project as described and understand that I am free to withdraw the participant at any time during the study without affecting their future health care.

I understand that I will be given a signed copy of this document to keep.

I consent to the storage and use of blood and tissue samples taken from the participant for use, as described in the relevant section of the Participant Information Sheet, for:

- This specific research project only
- This research project and other research that is closely related to this research project

Strike out one option above and initial next to your choice.

I consent to the storage and use of the participant's de-identified (anonymous) information, as described in the relevant section of the Participant Information Sheet, for:

- This specific research project only
- This research project and other research that is closely related to this research project

Strike out one option above and initial next to your choice.

I agree to the use of the participant's samples for genetic testing, as outlined in the relevant Section of the Participant Information Sheet.

Name of Participant (please print) _____

Name of Person Responsible (please print) _____

Signature of Person Responsible _____ Date _____

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If the person providing consent is unable to read, an impartial witness should be present during the entire informed consent discussion

Name of Witness* to Person Responsible's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the Person Responsible has understood that explanation.

Name of Study Doctor/ Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

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Form for Withdrawal of Participation – Person Responsible

Title	Standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy
Short Title	Standardised Treatment and Monitoring of Phage therapy (STAMP)
Project Sponsor	Western Sydney Local Health District
Coordinating Principal Investigator	Prof Jonathan Iredell
Site Principal Investigator	*[Site PI name]*
Location	*[Location]*

Declaration by Person Responsible

I wish to withdraw the participant from participation in the above research project and understand that such withdrawal will not affect the participant's routine treatment, our relationship with those treating the participant or our relationship with *[Institution]*.

- I wish to withdraw the participant from any further collection of samples and clinical data for this research
- I wish to withdraw the participant from any further collection of samples but I am allowing continued collection of the participant's clinical data for this research

Strike out one option above and initial next to your choice.

Name of Participant (please print) _____

Name of Person Responsible (please print) _____

Signature of Person Responsible _____ Date_____

In the event that the person responsible's decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the Person Responsible has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.

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Insert Header with institution's name or institution's letterhead

Participant Information Sheet – Young Person

Standardised Treatment and Monitoring of Phage therapy (STAMP)

Title	Standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy
Short Title	Standardised Treatment and Monitoring of Phage therapy (STAMP)
Project Sponsor	Western Sydney Local Health District
Coordinating Principal Investigator	Prof Jonathan Iredell
Site Principal Investigator	*[Site PI name]*
Location	*[Location]*

What does my participation involve?

1 Introduction

You are invited to take part in this research project because you have an infection that your doctor thinks would benefit from Phage Therapy. The research project is investigating the best way to provide Phage Therapy to patients, including how doctors should monitor the treatment.

This Participant Information Sheet tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you should talk about it with your parents or guardians and your doctor.

Participation in this research is voluntary. If you don't want to take part, you don't have to. You will receive the best possible care whether or not you take part.

2 What is the purpose of this research?

Phage Therapy is an experimental treatment. This means that it is not an approved treatment for infections in Australia. The decision to give you Phage Therapy and the specific phage product you will get, has been decided by your doctor and is not part of this research project. This research will look at **how** the treatment should be given to you so that we can better understand how it affects you and other patients like you.

3 What does participation in this research involve?

Once your doctor has decided that Phage Therapy might be good for you, and a suitable phage product has been found for you, they will refer you to one of the study doctors. The study doctors will check that it is o.k. to enrol you in this research. Your parent or guardian will then be asked to sign a consent form before you can take part in the study.

How much of the phage you get, and for how long, and the way in which it will be given to you (through a drip in your vein, by mouth, breathed in or another way) will be decided by one of the

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study doctors, after talking with your doctor. They will make these decisions by thinking about your medical conditions and the specific infection you have. Most patients will get Phage Therapy for 2 weeks in hospital, given through a drip in a vein. For some patients, if the Phage Therapy is needed for longer, this might be given to you in your home or an outpatient clinic. Phage Therapy will always be given by doctors and nurses, and prescribed to you in the same way as other medications.

For most people who get 2 weeks of Phage Therapy through a drip, this will be given only once a day, in the morning for the first 2 days, and then twice a day (morning and evening) for the next 12 days. It is possible that you have once daily treatment for longer than 2 days during the 2 weeks, based on levels of the phage in your blood that will be measured throughout the treatment. Your doctors and nurses will also monitor your heart rate, breathing rate, blood pressure and temperature before and after each dose of phage.

Information regarding your medical condition, your infection, the reason why you are getting Phage Therapy and how your body responds to the treatment will be collected in a database. We will also collect blood and other samples that might be needed for your specific infection (such as swabs or sputum samples). These samples will be collected at specific time-points before, during and after completion of the treatment to try to understand how good the treatment has been at clearing your infection, how it has affected your body in other ways, such as your kidneys and liver, and how your immune system has responded to the treatment.

For most people who get 2 weeks of Phage Therapy through a drip, blood samples will be collected the day before starting Phage Therapy (day 0), and again, 1, 3, 7, 10 and 14 days **after** your first dose (day 1). 4 weeks after your first dose of phage, which is about 2 weeks after your last dose of phage, you will have a follow-up visit with more blood tests. On some of these days, you will be asked to give a blood sample 3 times: once before the morning dose of phage, and then 30-60 minutes, and 2-3 hours after the dose. This will help the study doctors understand how quickly the phage leaves your body, and will also help work out if you should get once or twice daily treatment. The table below shows what days you will have blood tests compared to the first and last dose of phage you get, and how many blood samples are needed each time.

Day	**0**	**1**	**2**	**4**	**8**	**11**	**14**	**15**	**29**
Number of blood samples	x1	First dose of phage	x3	x3	x3	x3	Last dose of phage	x1	x1

Patients who do not get any Phage Therapy through a drip in the vein, or by mouth, will have fewer blood tests. They will not have any blood tests on day 11, and on each day will only have a single set of blood samples taken.

Day	**0**	**1**	**2**	**4**	**8**	**14**	**15**	**29**
Number of blood samples	x1	First dose of phage	x1	x1	x1	Last dose of phage	x1	x1

Patients who have longer courses of Phage Therapy will continue to have blood tests to monitor their treatment every month. All blood samples will be collected by staff who have done lots of blood tests on children and young people, such as doctors, nurses or blood collectors.

Before starting Phage Therapy, at the end of the course and again 3 and 6 months after your treatment you will also be asked to complete an online questionnaire. This will ask you questions about your experience of the Phage Therapy and how it may have affected your quality of life. It will take 10 minutes to complete. Although we would like you to complete the entire questionnaire, you can skip any questions that you don't want to answer.

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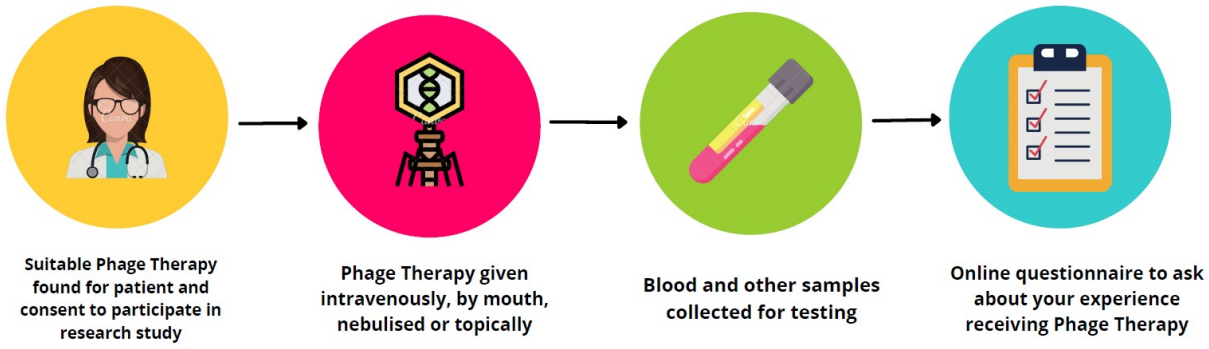

Most patients will be in the study for 1 month. This includes the 2 weeks of Phage Therapy and the follow-up visit 2 weeks after completing Phage Therapy. During this time, in addition to the tests described already, you will be asked about any symptoms and health events that may have occurred so that study doctors can work out how safe Phage Therapy is.

For some patients who are receiving longer courses of Phage Therapy, how long they are in the study will depend on how long Phage Therapy has been recommended for them. Once the Phage Therapy has finished, you will be followed up by your own doctor for at least 6 months. During this time, you will continue to receive invitations to complete the quality-of-life questionnaire at 3 and 6 months after your initial Phage Therapy treatment.

4 What do I have to do?

This research project has been designed to make sure the researchers interpret the results correctly and avoids study doctors or participants jumping to conclusions. It is important that the phage is given in the way it is written in the study protocol (study design) and all of the monitoring tests are done as written in the study protocol. It is also important that all of the information is collected accurately so that data from all patients in the study can be analysed together. This includes answers you give to the quality-of-life questionnaire. However, being part of this research will not affect you in other ways, such as what you can eat, any exercise or other activities you do, or other medications you may need. All of your other usual health care will continue as normal.

5 Other relevant information about the research project

This research is being conducted at many hospitals around Australia and will continue for 5 years. We would like to enrol 50-100 people in the study during this time. At *[Location where the research will be conducted]* we expect around 2-3 people to be enrolled each year. The research is a collaboration (teamwork) between multiple hospitals, universities and research institutes working together.

6 Do I have to take part in this research project?

Taking part in any research project is voluntary. If you do not want to take part, you do not have to. If you decide to take part and later change your mind, you can stop taking part (withdraw) at any time. Your decision to take part or not, or to take part and then later stop taking part, will not affect your usual health care, your relationship with those treating you or your relationship with *[Institution]*.

7 What are the alternatives (other options) to taking part in this research?

You do not have to take part in this research project to receive treatment at this hospital. If you choose not to take part in this research, your doctor(s) may still decide to give you Phage Therapy but it may not be monitored in the way described in this research. This includes having

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access to some of the special tests that are not available in usual hospital or community labs. Your study doctor will discuss these options with you before you decide whether or not to take part in this research project. You can also discuss the options with your own doctor and your parents or guardians.

8 What are the possible benefits of taking part?

We can't promise that you will receive any benefits from this research; however, possible benefits might be clearing your infection or improving how you feel. In addition, your treatment will be overseen and monitored by a group of study doctors which include specialists in infectious diseases and Phage Therapy from around Australia and the world. The information that we collect in this research will also help us and other researchers work out the best way to give Phage Therapy to other patients in the future. It may also help us make Phage Therapy more widely available in Australia to other patients.

9 What are the possible risks of taking part?

Any medical treatment can cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

The specific phage product you will get will be decided by your own doctor. This will be discussed with one of the study doctors, but this decision is not included in the research. Your doctor can give you information about the phage product you will get, including where it has come from and how it has been produced. Below is some general information about possible risks that might occur for patients receiving Phage Therapy.

Phage Therapy general information and risks
Phages are viruses that infect and kill bacteria, but they do not attack human cells. For this reason, phage therapy is very safe. It has been used for over 100 years to treat patients with bacterial infections. When phages are purified well, they cause very few side effects. Only phages that are highly purified will be used in this research.

Sometimes patients can have a brief reaction after the first few doses of phage. This is mostly due to the phage attacking and killing the bacteria causing your infection. It is usually a good sign that the phages are doing their job but it may be a little uncomfortable for you. You may have a fever or feel unwell in other ways (chills, headache, muscle aches). Depending on where your infection is, you may also get some pain there. Usually, this reaction only lasts a few hours and can be treated easily with simple medication like paracetamol or ibuprofen. Very occasionally, there may be a severe reaction which might mean that further doses of phage are delayed or not given.

Other side effects that might occur during your treatment include abnormalities in results of lab tests of your liver or kidneys, blood cells and immune system. If study doctors see any abnormalities on your blood tests, they will monitor them until they go back to normal for you. In our experience of treating patients in Australia, as well as reports from patients treated in other countries, these abnormalities in lab tests are usually not severe and all get better a few weeks after stopping the Phage Therapy.

Unknown risks of Phage Therapy
There might be other side effects that we do not expect or do not know about. Tell your study doctor immediately about any new or unusual symptoms that you get. Sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor might need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you. Any side effects that might occur during your treatment will

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be managed or treated by the study doctors and your own doctors according to usual health care practice.

Risks of taking part in this research project
There are very few risks to taking part in this research because the study is mainly looking at how Phage Therapy should be given and monitored. As part of the research, you will be asked to give blood and other samples at specific timepoints, and the phage will be given to you at specific times of the day, for most patients injected through a drip in the vein. Having a treatment injected or blood samples taken might be uncomfortable and might cause bruising, minor infection or bleeding. If this happens, it can be easily treated.

If any problems happen for you because you are taking part in this research project, you should contact the study team as soon as possible. They will make sure you get the help and treatment you need. If you become upset at any time because you are taking part in this research, the study doctor will be able to get counselling or other support to help you.

10 What will happen to my test samples?

Most of the tests that will be done to monitor your treatment are the same lab tests that are usually used by doctors to monitor infections. These tests will be done at the usual labs where tests for patients from *[Location where the research will be conducted]* are done. Once the testing is finished, the samples will be destroyed in the same way as other patient samples are normally handled by labs.

Some of the tests are specific to the Phage Therapy, including tests to look for the levels of phage in your blood, tests to look at how your immune system is responding to the Phage Therapy and tests that will look at your microbiome (the collection of bacteria and other microorganisms, including viruses, which live in your body). Your blood and other samples such as urine, sputum, faeces (poo) that are collected for these tests may need to be sent to another lab in Australia that specialises in Phage Therapy. If this is the case, the samples will be sent in an anonymous way, using only a study code that will be given to you for the research project. None of your personal information (such as your name or address) will be sent outside of *[Location where the research will be conducted]*. Only study doctors from *[Location where the research will be conducted]* and your clinical team will know that these samples are yours, using your specific study code.

These tests are all needed for you to take part in the research. Once testing on these samples is finished, the samples will be kept in the outside lab in case more testing is required later for this research project. We will also ask your permission to use these stored samples in other similar research projects in the future, but this is optional. You can still take part in this research if you do not want to have your samples used in other projects. Any leftover samples will be destroyed 15 years after the end of the study in the usual safe way that human samples are destroyed and according to the law.

Some genetic tests that will be performed in this research will be:
1) to look at your microbiome which includes all of the bacteria, fungi and viruses (microorganisms) that normally live in our bodies, and how these might change during Phage Therapy. This test will not look at your genes, only at the genes of these microorganisms.
2) to look at the genes responsible for your immune system and how it responds to the Phage Therapy. This test will not look at any of your other genes. There is a small chance that we may find that your immune system is not responding as well to infections as in other people. If that happens, study doctors would let your doctor know so that they can discuss these with you and your parents or guardians.

11 What if new information comes up during this research project?

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Sometimes, during a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue to take part in the research. If you decide you don't want to continue in the research, your study doctor will make sure your regular health care continues.

Also, on receiving new information, your study doctor might think it is better for you not to continue in the research project. If this happens, he/she will explain the reasons.

12 Can I have other treatments during this research project?

Taking part in this research project will not affect whether or not you can take other medications or treatments. But it is important to tell your study doctor and the study staff about any treatments or medications you are taking, including vitamins or herbal medicines. You should also tell your study doctor if any of your medications change during the time you are taking part in the research project.

13 What if I want to stop taking part in this research project?

If you decide to stop taking part in the research project, please let a member of the research team know so they can discuss with you anything that needs to happen or anything that you may need to do when you stop taking part in the research.

If you decide to stop taking part in the research project at any point, the study doctor and study staff will not collect any more information from or about you, although information already collected will be kept as part of the research to make sure that the results of the research can be measured properly.

14 Could this research project be stopped unexpectedly?

Although unlikely, this research project may be stopped unexpectedly for a variety of reasons, including unacceptable side effects or safety concerns.

15 What happens when the research project ends?

Once you have completed your course of Phage Therapy for your infection, you won't need any more Phage Therapy. If the infection comes back, gets worse or you get another infection that needs Phage Therapy again, your doctor can refer you to the study doctors again to see if you can be re-enrolled in the research project.

All other health care that you might need after the end of Phage Therapy will be according to usual practice and will be managed by your doctor.

When the project is completed in 5 years' time, the results of the research will be published in a scientific journal or may be presented at scientific meetings. A summary of publications and presentations will be made available for everyone on the Phage Australia website (https://criticalinfection.com/phage-australia/).

Part 2 How is the research project being conducted?

16 What will happen to information about me?

By agreeing to take part in this research project you agree to let the study doctor and other study staff collect and use information about you for the research project. Any information that is collected as part of this research project that can identify you (like your name or address) will be kept confidential (private) and stored securely. Your information will only be used for this

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research project and it will not be shared with anyone without your permission, except if it is required by law.

Information about you may be collected from your health records held at this and other health services (labs, clinics, hospitals) for this research (such as the results of lab tests or scans).

All study information will be entered into a web-based database called REDCap. This is provided by the University of Sydney and is protected so that only the study team can see the information. Within this database you will be given a study code. Your personal information will only be available to the team looking after you and the study team at *[Location where the research will be conducted]* so that they can discuss the best possible way to give you Phage Therapy, including any changes that might be needed in the dose of phage you are receiving. The rest of the research team would only be able to see non-personal information through your anonymous study code.

Any of your blood or other samples that need to be sent to outside labs will only have your study code and none of your personal information will be sent outside of *[Location where the research will be conducted]*. We expect to publish and/or present the results of this research project in scientific journals and meetings. In any publication and/or presentation, only anonymous information will be used so that you can't be identified, except with your permission.

Paper documents that have any of your personal information will be kept in locked cupboards in offices at *[Location where the research will be conducted]*. All research data will be stored for 15 years after the end of the project, and then everything with any personal information will be destroyed by permanently deleting electronic files and shredding any paper documents.

We will also ask your permission to use your anonymous information in other similar research projects in the future, but this is optional. You can still take part in this research if you do not want to have your information used in other projects.
According to the law in Australia and *[Name of state/territory]*, you are allowed to ask to see the information collected by the research team about you. You can also ask to have any information about you corrected if you disagree with it. Please contact the study team member named at the end of this Information Sheet if you would like to see your information.

17 Who is organising and funding the research?

Money for this research comes from the National Health and Medical Research Council (NHMRC) and the Medical Research Future Fund (MRFF) of Australia. The research is being done by the Phage Australia Network of researchers (https://criticalinfection.com/phage-australia/), including *[Name of local PI and relevant study staff]*.

No member of the research team will get any money because you are taking part in this research project (other than their normal salary/wages).

18 Who has reviewed the research project?

All research in Australia involving humans is reviewed (checked) by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Sydney Children's Hospitals Network.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This has been developed to protect people who agree to take part in research projects.

19 Further information and who to contact

The person you need to contact will depend on what your question is.

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If you want any more information about this project or if you have any medical problems which might be related to taking part in the project (for example, any side effects), you can contact the main study doctor *[Name of local PI]* on *[phone number]* or any of the following people:

Clinical (medical) contact person

Name	During normal working hours: *[Site PI name]* After hours or if unable to contact *[Site PI name]*: Infectious diseases registrar or consultant on call
Position	*[Title/position/department of Site PI]*
Telephone	During normal working hours: *[Site PI contact number]* After hours: Infectious diseases registrar or consultant on call via *[Hospital switch/on call Phone number]*
Email	*[Site PI Email address]*

If you have any complaints about the project or the way it is being done, or any questions about being part of a research project in general, you can contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Sydney Children's Hospital Network
HREC Executive Officer	Clare Bayram
Telephone	(02) 9845 3066
Email	SCHN-Ethics@health.nsw.gov.au

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Variable / F	Form Name	Section Hea	Field Typ	Field Label	Choices, Ca	Field Note	Text Validat	min	max	Identifier?	Branching L	Requir	Custom A	Questior	Matrix Gr	Matrix Gro	Field Annotation
phage_pati	screening_log_beta		text	Phage Patient ID													
sc_date	screening_log_beta		text	Date of referral			date_dmy					y					
sc_ptp_initi	screening_log_beta		text	Patient initials		Only two letters allowed						y					@CHARLIMIT=2
sc_dob	screening_log_beta		text	DOB			date_dmy			y		y					
sc_meets_i	screening_log_beta		yesno	Meets inclusion criteria								y					
sc_exclusio	screening_log_beta		checkbox	Reason for	1, Source control sub-optimal | 2, Polymicrobial infection (>2 key						[sc_meets_	y					
sc_exclusio	screening_log_beta		checkbox	If phage pro	1, Phage activity against target pathogen(s) limited/undocumente						[sc_exclusic	y					@CHARLIMIT=100
sc_exclusio	screening_log_beta		notes	Specify other exclusion reasons							[sc_exclusic	y					
dm_no_inc	demographics_beta		descriptiv	<h3><span style="background-color: #e03e2							[sc_meets_inclusion] < 1						
dm_picf_sig	demographics_beta		text	Date PICF signed			date_dmy				[sc_meets_	y					
dm_consen	demographics_beta		calc	Age at time	round(datediff([sc_dob], "today", "y"),2)						[sc_meets_	y					
dm_gender	demographics_beta		radio	Gender	m, M | f, F						[sc_meets_	y					
dm_recruit	demographics_beta		radio	Recruitmen	westmd, Westmead Hospital | schn, Sydney Children's Hospitals N						[sc_meets_	y					
pre_no_inc	pretreatment_beta		descriptiv	<h3><span style="background-color: #e03e2							[sc_meets_inclusion] < 1						
pre_primar	pretreatment_beta		radio	Primary infe	1, Endovascular infection | 2, Lung infection | 3, Musculoskeletal i						[sc_meets_	y					
pre_primar	pretreatment_beta		notes	Other prima	1, Endovascular infection | 2, Lung infection | 3, Musculoskeletal i						[sc_meets_	y					@CHARLIMIT='50'
pre_infectio	pretreatment_beta		radio	Duration of	1, Acute (< 2 weeks) | 2, Subacute (2 weeks-2 months) | 3, Chroni						[sc_meets_	y					
pre_other_	pretreatment_beta		notes	Other medical or surgical diagnoses (please list if directly relevant to infection							[sc_meets_	y					
pre_has_im	pretreatment_beta		yesno	Immune suppression							[sc_meets_	y					
pre_immu_	pretreatment_beta		radio	Primary cor	1, HIV | 2, Malignancy with or without chemotherapy | 3, SOT | 4						[sc_meets_	y					
pre_immu_	pretreatment_beta		text	Other primary condition							[sc_meets_	y					@CHARLIMIT='50'
pre_immu_	pretreatment_beta		checkbox	Acquired co	1, HIV | 2, Malignancy with or without chemotherapy | 3, SOT | 4						[sc_meets_	y					
pre_immu_	pretreatment_beta		text	Other acquired conditions							[sc_meets_	y					@CHARLIMIT='50'
pre_has_pr	pretreatment_beta		yesno	Prosthesis involved							[sc_meets_	y					
pre_prosth	pretreatment_beta		checkbox	Types of pr	1, Prosthetic valve | 2, Vascular shunt | 3, Ventricular assist devic						[sc_meets_	y					
pre_prosth	pretreatment_beta		text	Please specify	Other endovascular prosthesis						[sc_meets_	y					@CHARLIMIT='50'
pre_prosth	pretreatment_beta		text	Please specify	Other osteoartciular prosthesis						[sc_meets_	y					@CHARLIMIT='50'
pre_prosth	pretreatment_beta		text	Please specify	Other drain						[sc_meets_	y					@CHARLIMIT='50'
pre_prosth	pretreatment_beta		text	Please specify	Other prosthesis						[sc_meets_	y					@CHARLIMIT='50'
pre_pt_indi	pretreatment_beta		checkbox	Indication f	1, Intolerance of standard therapy due to side effects | 2, Failure o						[sc_meets_	y					
pre_pt_indi	pretreatment_beta		text	Specify other indication for phage therapy							[sc_meets_	y					@CHARLIMIT='50'
pre_num_t	pretreatme	Pathogen S	radio	How many	1,1 | 2,2 | 3,3 | 4,4 | 5,5						[sc_meets_	y					
pre_pth1_d	pretreatment_beta		descriptiv	Pathogen 1							[sc_meets_inclusion] = "1" and [pre_num_target_pathogen] > 0						
pre_pth1_t	pretreatment_beta		radio	[Pathogen 1	1, E. coli | 2, P. aeruginosa | 3, M. abscessus | 4, S. aureus | 11, Kl						[sc_meets_	y					
pre_pth1_s	pretreatment_beta		text	[Pathogen 1] Full Genus	e.g. Salmonella enterica						[sc_meets_	y					@CHARLIMIT='50'
pre_pth1_is	pretreatment_beta		yesno	[Pathogen 1] ESBL?							[sc_meets_	y					
pre_pth1_is	pretreatment_beta		yesno	[Pathogen 1] MRSA?							[sc_meets_	y					
pre_pth1_is	pretreatment_beta		yesno	[Pathogen 1] VRE?							[sc_meets_	y					
pre_pth1_s	pretreatment_beta		radio	[Pathogen 1	confirmed, Confirmed (isolated from site of infection) | suspected						[sc_meets_	y					
pre_pth1_is	pretreatment_beta		checkbox	[Pathogen 1	1, Blood | 2, Sputum/endotracheal aspirate | 3, BAL fluid | 4, Join						[sc_meets_	y					

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pre_pth1_i	pretreatment_beta	text	[Pathogen 1] Specify Intra-operative pus site	[sc_meets_ y	@CHARLIMIT='50'
pre_pth1_i	pretreatment_beta	text	[Pathogen 1] Specify Intra-operative tissue type	[sc_meets_ y	@CHARLIMIT='50'
pre_pth1_i	pretreatment_beta	text	[Pathogen 1] Specify Non-operative swab site	[sc_meets_ y	@CHARLIMIT='50'
pre_pth1_h	pretreatment_beta	yesno	[Pathogen 1] Is WGS data available?	[sc_meets_ y	
pre_pth1_v	pretreatment_beta	notes	[Pathogen 1] Where is the WGS data stored?	[sc_meets_ y	
pre_pth1_h	pretreatment_beta	yesno	[Pathogen 1] Is the isolate available for further testing?	[sc_meets_ y	
pre_pth1_i	pretreatment_beta	notes	[Pathogen 1] Where is the isolate stored?	[sc_meets_ y	
pre_pth2_d	pretreatment_beta	descriptiv	Pathogen 2	[sc_meets_inclusion] = "1" and [pre_num_target_pathogen] > 1	
pre_pth2_t	pretreatment_beta	radio	[Pathogen 2] 1, E. coli | 2, P. aeruginosa | 3, M. abscessus | 4, S. aureus | 11, Kl	[sc_meets_ y	
pre_pth2_s	pretreatment_beta	text	[Pathogen 2] Full Genus e.g. Salmonella enterica	[sc_meets_ y	@CHARLIMIT='50'
pre_pth2_i	pretreatment_beta	yesno	[Pathogen 2] ESBL?	[sc_meets_ y	
pre_pth2_i	pretreatment_beta	yesno	[Pathogen 2] MRSA?	[sc_meets_ y	
pre_pth2_i	pretreatment_beta	yesno	[Pathogen 2] VRE?	[sc_meets_ y	
pre_pth2_s	pretreatment_beta	radio	[Pathogen 2 confirmed, Confirmed (isolated from site of infection) | suspected	[sc_meets_ y	
pre_pth2_i	pretreatment_beta	checkbox	[Pathogen 2] 1, Blood | 2, Sputum/endotracheal aspirate | 3, BAL fluid | 4, Join	[sc_meets_ y	
pre_pth2_i	pretreatment_beta	text	[Pathogen 2] Specify Intra-operative pus site	[sc_meets_ y	@CHARLIMIT='50'
pre_pth2_i	pretreatment_beta	text	[Pathogen 2] Specify Intra-operative tissue type	[sc_meets_ y	@CHARLIMIT='50'
pre_pth2_i	pretreatment_beta	text	[Pathogen 2] Specify Non-operative swab site	[sc_meets_ y	@CHARLIMIT='50'
pre_pth2_h	pretreatment_beta	yesno	[Pathogen 2] Is WGS data available?	[sc_meets_ y	
pre_pth2_v	pretreatment_beta	notes	[Pathogen 2] Where is the WGS data stored?	[sc_meets_ y	
pre_pth2_h	pretreatment_beta	yesno	[Pathogen 2] Is the isolate available for further testing?	[sc_meets_ y	
pre_pth2_i	pretreatment_beta	notes	[Pathogen 2] Where is the isolate stored?	[sc_meets_ y	
pre_pth3_d	pretreatment_beta	descriptiv	Pathogen 3	[sc_meets_inclusion] = "1" and [pre_num_target_pathogen] > 2	
pre_pth3_t	pretreatment_beta	radio	[Pathogen 3] 1, E. coli | 2, P. aeruginosa | 3, M. abscessus | 4, S. aureus | 11, Kl	[sc_meets_ y	
pre_pth3_s	pretreatment_beta	text	[Pathogen 3] Full Genus e.g. Salmonella enterica	[sc_meets_ y	@CHARLIMIT='50'
pre_pth3_i	pretreatment_beta	yesno	[Pathogen 3] ESBL?	[sc_meets_ y	
pre_pth3_i	pretreatment_beta	yesno	[Pathogen 3] MRSA?	[sc_meets_ y	
pre_pth3_i	pretreatment_beta	yesno	[Pathogen 3] VRE?	[sc_meets_ y	
pre_pth3_s	pretreatment_beta	radio	[Pathogen 3 confirmed, Confirmed (isolated from site of infection) | suspected	[sc_meets_ y	
pre_pth3_i	pretreatment_beta	checkbox	[Pathogen 3] 1, Blood | 2, Sputum/endotracheal aspirate | 3, BAL fluid | 4, Join	[sc_meets_ y	
pre_pth3_i	pretreatment_beta	text	[Pathogen 3] Specify Intra-operative pus site	[sc_meets_ y	@CHARLIMIT='50'
pre_pth3_i	pretreatment_beta	text	[Pathogen 3] Specify Intra-operative tissue type	[sc_meets_ y	@CHARLIMIT='50'
pre_pth3_i	pretreatment_beta	text	[Pathogen 3] Specify Non-operative swab site	[sc_meets_ y	@CHARLIMIT='50'
pre_pth3_h	pretreatment_beta	yesno	[Pathogen 3] Is WGS data available?	[sc_meets_ y	
pre_pth3_v	pretreatment_beta	notes	[Pathogen 3] Where is the WGS data stored?	[sc_meets_ y	
pre_pth3_h	pretreatment_beta	yesno	[Pathogen 3] Is the isolate available for further testing?	[sc_meets_ y	
pre_pth3_i	pretreatment_beta	notes	[Pathogen 3] Where is the isolate stored?	[sc_meets_ y	
pre_pth4_d	pretreatment_beta	descriptiv	Pathogen 4	[sc_meets_inclusion] = "1" and [pre_num_target_pathogen] > 3	
pre_pth4_t	pretreatment_beta	radio	[Pathogen 4] 1, E. coli | 2, P. aeruginosa | 3, M. abscessus | 4, S. aureus | 11, Kl	[sc_meets_ y	
pre_pth4_s	pretreatment_beta	text	[Pathogen 4] Full Genus e.g. Salmonella enterica	[sc_meets_ y	@CHARLIMIT='50'
pre_pth4_i	pretreatment_beta	yesno	[Pathogen 4] ESBL?	[sc_meets_ y	

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pre_pth4_i	pretreatment_beta	yesno	[Pathogen 4] MRSA?	[sc_meets_ y	
pre_pth4_i	pretreatment_beta	yesno	[Pathogen 4] VRE?	[sc_meets_ y	
pre_pth4_s	pretreatment_beta	radio	[Pathogen 4 confirmed, Confirmed (isolated from site of infection) | suspected	[sc_meets_ y	
pre_pth4_i	pretreatment_beta	checkbox	[Pathogen 4 1, Blood | 2, Sputum/endotracheal aspirate | 3, BAL fluid | 4, Join	[sc_meets_ y	
pre_pth4_i	pretreatment_beta	text	[Pathogen 4] Specify Intra-operative pus site	[sc_meets_ y	@CHARLIMIT='50'
pre_pth4_i	pretreatment_beta	text	[Pathogen 4] Specify Intra-operative tissue type	[sc_meets_ y	@CHARLIMIT='50'
pre_pth4_i	pretreatment_beta	text	[Pathogen 4] Specify Non-operative swab site	[sc_meets_ y	@CHARLIMIT='50'
pre_pth4_h	pretreatment_beta	yesno	[Pathogen 4] Is WGS data available?	[sc_meets_ y	
pre_pth4_v	pretreatment_beta	notes	[Pathogen 4] Where is the WGS data stored?	[sc_meets_ y	
pre_pth4_h	pretreatment_beta	yesno	[Pathogen 4] Is the isolate available for further testing?	[sc_meets_ y	
pre_pth4_i	pretreatment_beta	notes	[Pathogen 4] Where is the isolate stored?	[sc_meets_ y	
pre_pth5_d	pretreatment_beta	descripti	Pathogen 5	[sc_meets_inclusion] = "1" and [pre_num_target_pathogen] > 4	
pre_pth5_t	pretreatment_beta	radio	[Pathogen 5 1, E. coli | 2, P. aeruginosa | 3, M. abscessus | 4, S. aureus | 11, Kl	[sc_meets_ y	
pre_pth5_s	pretreatment_beta	text	[Pathogen 5] Full Genus e.g. Salmonella enterica	[sc_meets_ y	@CHARLIMIT='50'
pre_pth5_i	pretreatment_beta	yesno	[Pathogen 5] ESBL?	[sc_meets_ y	
pre_pth5_i	pretreatment_beta	yesno	[Pathogen 5] MRSA?	[sc_meets_ y	
pre_pth5_i	pretreatment_beta	yesno	[Pathogen 5] VRE?	[sc_meets_ y	
pre_pth5_s	pretreatment_beta	radio	[Pathogen 5 confirmed, Confirmed (isolated from site of infection) | suspected	[sc_meets_ y	
pre_pth5_i	pretreatment_beta	checkbox	[Pathogen 5 1, Blood | 2, Sputum/endotracheal aspirate | 3, BAL fluid | 4, Join	[sc_meets_ y	
pre_pth5_i	pretreatment_beta	text	[Pathogen 5] Specify Intra-operative pus site	[sc_meets_ y	@CHARLIMIT='50'
pre_pth5_i	pretreatment_beta	text	[Pathogen 5] Specify Intra-operative tissue type	[sc_meets_ y	@CHARLIMIT='50'
pre_pth5_i	pretreatment_beta	text	[Pathogen 5] Specify Non-operative swab site	[sc_meets_ y	@CHARLIMIT='50'
pre_pth5_h	pretreatment_beta	yesno	[Pathogen 5] Is WGS data available?	[sc_meets_ y	
pre_pth5_v	pretreatment_beta	notes	[Pathogen 5] Where is the WGS data stored?	[sc_meets_ y	
pre_pth5_h	pretreatment_beta	yesno	[Pathogen 5] Is the isolate available for further testing?	[sc_meets_ y	
pre_pth5_i	pretreatment_beta	notes	[Pathogen 5] Where is the isolate stored?	[sc_meets_ y	
pre_num_p	pretreatme Phages	radio	How many 1,1 | 2,2 | 3,3 | 4,4 | 5,5 | -1, Proprietary cocktail | 0, Unable to define separa	y	
pre_phage1	pretreatment_beta	descripti	Phage 1	[sc_meets_inclusion] = "1" and abs([pre_num_phage]) > 0	
pre_phage1	pretreatment_beta	text	[Phage 1] Phage 1 name or identifier	[sc_meets_ y	
pre_phage1	pretreatment_beta	radio	[Phage 1] A 1, E. coli | 2, P. aeruginosa | 3, M. abscessus | 4, S. aureus | 11, Kl	[sc_meets_ y	
pre_phage1	pretreatment_beta	text	[Phage 1] A 1, E. coli | 2 Enter both genus and species name, e.g. (Pseudomon	[sc_meets_inclusion] = "1" and abs([pre_phage1_active_	@CHARLIMIT='50'
pre_phage1	pretreatment_beta	radio	[Phage 1] E 1, >= 0.9 | 2, 0.5-0.899 | 3, 0.1-0.499 | 4, <0.1	[sc_meets_ y	
pre_phage1	pretreatment_beta	notes	[Phage 1] Source/supplier	[sc_meets_ y	
pre_phage1	pretreatment_beta	text	[Phage 1] Endotoxin level (XXXX.X E number_1dp	[sc_meets_ y	
pre_phage1	pretreatment_beta	yesno	[Phage 1] Is sequencing data for the phage available?	[sc_meets_ y	
pre_phage1	pretreatment_beta	text	[Phage 1] Where is the sequencing data stored?	[sc_meets_ y	
pre_phage2	pretreatment_beta	descripti	Phage 2	[sc_meets_inclusion] = "1" and abs([pre_num_phage]) > 1	
pre_phage2	pretreatment_beta	text	[Phage 2] Phage 2 name or identifier	[sc_meets_ y	
pre_phage2	pretreatment_beta	radio	[Phage 2] A 1, E. coli | 2, P. aeruginosa | 3, M. abscessus | 4, S. aureus | 11, Kl	[sc_meets_ y	
pre_phage2	pretreatment_beta	text	[Phage 2] A 1, E. coli | 2 Enter both genus and species name, e.g. (Pseudomon	[sc_meets_inclusion] = "1" and abs([pre_phage2_active_	@CHARLIMIT='50'
pre_phage2	pretreatment_beta	radio	[Phage 2] E 1, >= 0.9 | 2, 0.5-0.899 | 3, 0.1-0.499 | 4, <0.1	[sc_meets_ y	

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pre_phage2	pretreatment_beta	notes	[Phage 2] Source/supplier	[sc_meets_ y	
pre_phage2	pretreatment_beta	text	[Phage 2] Endotoxin level (XXXX.X E number_1dp	[sc_meets_ y	
pre_phage2	pretreatment_beta	yesno	[Phage 2] Is sequencing data for the phage available?	[sc_meets_ y	
pre_phage2	pretreatment_beta	text	[Phage 2] Where is the sequencing data stored?	[sc_meets_ y	
pre_phage3	pretreatment_beta	descriptiv	Phage 3	[sc_meets_inclusion] = "1" and abs([pre_num_phage]) > 2	
pre_phage3	pretreatment_beta	text	[Phage 3] Phage 3 name or identifier	[sc_meets_ y	
pre_phage3	pretreatment_beta	radio	[Phage 3] A 1, E. coli | 2, P. aeruginosa | 3, M. abscessus | 4, S. aureus | 11, Kl	[sc_meets_ y	
pre_phage3	pretreatment_beta	text	[Phage 3] A 1, E. coli | 2 Enter both genus and species name, e.g. (Pseudomona	[sc_meets_inclusion] = "1" and abs([pre_phage3_active_ @CHARLIMIT='50'	
pre_phage3	pretreatment_beta	radio	[Phage 3] E 1, >= 0.9 | 2, 0.5-0.899 | 3, 0.1-0.499 | 4, <0.1	[sc_meets_ y	
pre_phage3	pretreatment_beta	notes	[Phage 3] Source/supplier	[sc_meets_ y	
pre_phage3	pretreatment_beta	text	[Phage 3] Endotoxin level (XXXX.X E number_1dp	[sc_meets_ y	
pre_phage3	pretreatment_beta	yesno	[Phage 3] Is sequencing data for the phage available?	[sc_meets_ y	
pre_phage3	pretreatment_beta	text	[Phage 3] Where is the sequencing data stored?	[sc_meets_ y	
pre_phage4	pretreatment_beta	descriptiv	Phage 4	[sc_meets_inclusion] = "1" and abs([pre_num_phage]) > 3	
pre_phage4	pretreatment_beta	text	[Phage 4] Phage 4 name or identifier	[sc_meets_ y	
pre_phage4	pretreatment_beta	radio	[Phage 4] A 1, E. coli | 2, P. aeruginosa | 3, M. abscessus | 4, S. aureus | 11, Kl	[sc_meets_ y	
pre_phage4	pretreatment_beta	text	[Phage 4] A 1, E. coli | 2 Enter both genus and species name, e.g. (Pseudomona	[sc_meets_inclusion] = "1" and abs([pre_phage4_active_ @CHARLIMIT='50'	
pre_phage4	pretreatment_beta	radio	[Phage 4] E 1, >= 0.9 | 2, 0.5-0.899 | 3, 0.1-0.499 | 4, <0.1	[sc_meets_ y	
pre_phage4	pretreatment_beta	notes	[Phage 4] Source/supplier	[sc_meets_ y	
pre_phage4	pretreatment_beta	text	[Phage 4] Endotoxin level (XXXX.X E number_1dp	[sc_meets_ y	
pre_phage4	pretreatment_beta	yesno	[Phage 4] Is sequencing data for the phage available?	[sc_meets_ y	
pre_phage4	pretreatment_beta	text	[Phage 4] Where is the sequencing data stored?	[sc_meets_ y	
pre_phage5	pretreatment_beta	descriptiv	Phage 5	[sc_meets_inclusion] = "1" and abs([pre_num_phage]) > 4	
pre_phage5	pretreatment_beta	text	[Phage 5] Phage 5 name or identifier	[sc_meets_ y	
pre_phage5	pretreatment_beta	radio	[Phage 5] A 1, E. coli | 2, P. aeruginosa | 3, M. abscessus | 4, S. aureus | 11, Kl	[sc_meets_ y	
pre_phage5	pretreatment_beta	text	[Phage 5] A 1, E. coli | 2 Enter both genus and species name, e.g. (Pseudomona	[sc_meets_inclusion] = "1" and abs([pre_phage5_active_ @CHARLIMIT='50'	
pre_phage5	pretreatment_beta	radio	[Phage 5] E 1, >= 0.9 | 2, 0.5-0.899 | 3, 0.1-0.499 | 4, <0.1	[sc_meets_ y	
pre_phage5	pretreatment_beta	notes	[Phage 5] Source/supplier	[sc_meets_ y	
pre_phage5	pretreatment_beta	text	[Phage 5] Endotoxin level (XXXX.X E number_1dp	[sc_meets_ y	
pre_phage5	pretreatment_beta	yesno	[Phage 5] Is sequencing data for the phage available?	[sc_meets_ y	
pre_phage5	pretreatment_beta	text	[Phage 5] Where is the sequencing data stored?	[sc_meets_ y	
tre_no_incl	treatment_beta	descriptiv	<h3><span style="background-color: #e03e2	[sc_meets_inclusion] < 1	
tre_start_w	treatment_beta	text	Weight at start of treat XXX.X kg number_1dp	[sc_meets_ y	
tre_ph0	treatment_beta	descriptiv	Phage: "[pre_phage1_name]"	[sc_meets_inclusion] = "1" and [pre_phage1_name] and [pre_num_phage]>0	
tre_ph_0_r	treatment_beta	checkbox	[Phage: "[p aero, Aerosolised / Nebulised | instl, Instillation | iv, Intravenous (	[sc_meets_ y	
tre_ph_0_r	treatment_beta	text	[Phage: "[pre_phage1_name]"] Specify instillation site	[sc_meets_ y	@CHARLIMIT='50'
tre_ph_0_r	treatment_beta	text	[Phage: "[pre_phage1_name]"] Specify 'other'	[sc_meets_ y	@CHARLIMIT='50'
tre_ph_0_d	treatment_beta	radio	[Phage: "[p under2wks, Less than or equal to 2 weeks | over2wks, Longer tha	[sc_meets_ y	
tre_ph_0_d	treatment_beta	text	[Phage: "[pre_phage1_name]"] Dur integer	[sc_meets_ y	
tre_ph_0_d	treatment_beta	radio	[Phage: "[p days, Days | doseperapp, Doses/applications	[sc_meets_ y	
tre_ph_0_d	treatment_beta	radio	[Phage: "[p days, Days | weeks, Weeks | months, Months	[sc_meets_ y	

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tre_ph_0_d	treatment_beta	radio	[Phage: "[p	10e8, 10^8 pfu/mL | 10e9, 10^9 pfu/mL | 10e10, 10^10 pfu/mL |				[sc_meets_ y	
tre_ph_0_d	treatment_beta	text	[Phage: "[pre_phage1_	XXX.X mL	number_1dp			[sc_meets_ y	
tre_ph_0_a	treatment_beta	text	[Phage: "[pre_phage1_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_0_fi	treatment_beta	text	[Phage: "[pre_phage1_name]"] Dat		date_dmy			[sc_meets_ y	
tre_ph_0_ir	treatment_beta	text	[Phage: "[pre_phage1_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_0_iv	treatment_beta	text	[Phage: "[pre_phage1_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_0_c	treatment_beta	text	[Phage: "[pre_phage1_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_0_t	treatment_beta	text	[Phage: "[pre_phage1_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_0_c	treatment_beta	text	[Phage: "[pre_phage1_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph1	treatment_beta	descriptiv	Phage: "[pre_phage2_name]"					[sc_meets_inclusion] = "1" and [pre_phage2_name] and [pre_num_phage]>1	
tre_ph_1_r	treatment_beta	checkbox	[Phage: "[p	aero, Aerosolised / Nebulised | instl, Instillation | iv, Intravenous (				[sc_meets_ y	
tre_ph_1_r	treatment_beta	text	[Phage: "[pre_phage2_name]"] Specify instillation site					[sc_meets_ y	@CHARLIMIT='50'
tre_ph_1_r	treatment_beta	text	[Phage: "[pre_phage2_name]"] Specify 'other'					[sc_meets_ y	@CHARLIMIT='50'
tre_ph_1_d	treatment_beta	radio	[Phage: "[p	under2wks, Less than or equal to 2 weeks | over2wks, Longer tha				[sc_meets_ y	
tre_ph_1_d	treatment_beta	text	[Phage: "[pre_phage2_name]"] Dur	integer				[sc_meets_ y	
tre_ph_1_d	treatment_beta	radio	[Phage: "[p	days, Days | doseperapp, Doses/applications				[sc_meets_ y	
tre_ph_1_d	treatment_beta	radio	[Phage: "[p	days, Days | weeks, Weeks | months, Months				[sc_meets_ y	
tre_ph_1_d	treatment_beta	radio	[Phage: "[p	10e8, 10^8 pfu/mL | 10e9, 10^9 pfu/mL | 10e10, 10^10 pfu/mL |				[sc_meets_ y	
tre_ph_1_d	treatment_beta	text	[Phage: "[pre_phage2_	XXX.X mL	number_1dp			[sc_meets_ y	
tre_ph_1_a	treatment_beta	text	[Phage: "[pre_phage2_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_1_fi	treatment_beta	text	[Phage: "[pre_phage2_name]"] Dat		date_dmy			[sc_meets_ y	
tre_ph_1_ir	treatment_beta	text	[Phage: "[pre_phage2_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_1_iv	treatment_beta	text	[Phage: "[pre_phage2_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_1_c	treatment_beta	text	[Phage: "[pre_phage2_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_1_t	treatment_beta	text	[Phage: "[pre_phage2_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_1_c	treatment_beta	text	[Phage: "[pre_phage2_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph2	treatment_beta	descriptiv	Phage: "[pre_phage3_name]"					[sc_meets_inclusion] = "1" and [pre_phage3_name] and [pre_num_phage]>2	
tre_ph_2_r	treatment_beta	checkbox	[Phage: "[p	aero, Aerosolised / Nebulised | instl, Instillation | iv, Intravenous (				[sc_meets_ y	
tre_ph_2_r	treatment_beta	text	[Phage: "[pre_phage3_name]"] Specify instillation site					[sc_meets_ y	@CHARLIMIT='50'
tre_ph_2_r	treatment_beta	text	[Phage: "[pre_phage3_name]"] Specify 'other'					[sc_meets_ y	@CHARLIMIT='50'
tre_ph_2_d	treatment_beta	radio	[Phage: "[p	under2wks, Less than or equal to 2 weeks | over2wks, Longer tha				[sc_meets_ y	
tre_ph_2_d	treatment_beta	text	[Phage: "[pre_phage3_name]"] Dur	integer				[sc_meets_ y	
tre_ph_2_d	treatment_beta	radio	[Phage: "[p	days, Days | doseperapp, Doses/applications				[sc_meets_ y	
tre_ph_2_d	treatment_beta	radio	[Phage: "[p	days, Days | weeks, Weeks | months, Months				[sc_meets_ y	
tre_ph_2_d	treatment_beta	radio	[Phage: "[p	10e8, 10^8 pfu/mL | 10e9, 10^9 pfu/mL | 10e10, 10^10 pfu/mL |				[sc_meets_ y	
tre_ph_2_d	treatment_beta	text	[Phage: "[pre_phage3_	XXX.X mL	number_1dp			[sc_meets_ y	
tre_ph_2_a	treatment_beta	text	[Phage: "[pre_phage3_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_2_fi	treatment_beta	text	[Phage: "[pre_phage3_name]"] Dat		date_dmy			[sc_meets_ y	
tre_ph_2_ir	treatment_beta	text	[Phage: "[pre_phage3_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_2_iv	treatment_beta	text	[Phage: "[pre_phage3_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_2_c	treatment_beta	text	[Phage: "[pre_phage3_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	

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tre_ph_2_t	treatment_beta	text	[Phage: "[pre_phage3_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_2_c	treatment_beta	text	[Phage: "[pre_phage3_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph3	treatment_beta	descripti	Phage: "[pre_phage4_name]"					[sc_meets_inclusion] = "1" and [pre_phage4_name] and [pre_num_phage]>3	
tre_ph_3_r	treatment_beta	checkbo	[Phage: "[p	aero, Aerosolised / Nebulised | instl, Instillation | iv, Intravenous (				[sc_meets_ y	
tre_ph_3_r	treatment_beta	text	[Phage: "[pre_phage4_name]"] Specify instillation site					[sc_meets_ y	@CHARLIMIT='50'
tre_ph_3_r	treatment_beta	text	[Phage: "[pre_phage4_name]"] Specify 'other'					[sc_meets_ y	@CHARLIMIT='50'
tre_ph_3_d	treatment_beta	radio	[Phage: "[p	under2wks, Less than or equal to 2 weeks | over2wks, Longer tha				[sc_meets_ y	
tre_ph_3_d	treatment_beta	text	[Phage: "[pre_phage4_name]"] Dur	integer				[sc_meets_ y	
tre_ph_3_d	treatment_beta	radio	[Phage: "[p	days, Days | doseperapp, Doses/applications				[sc_meets_ y	
tre_ph_3_d	treatment_beta	radio	[Phage: "[p	days, Days | weeks, Weeks | months, Months				[sc_meets_ y	
tre_ph_3_d	treatment_beta	radio	[Phage: "[p	10e8, 10^8 pfu/mL | 10e9, 10^9 pfu/mL | 10e10, 10^10 pfu/mL |				[sc_meets_ y	
tre_ph_3_d	treatment_beta	text	[Phage: "[pre_phage4_	XXX.X mL	number_1dp			[sc_meets_ y	
tre_ph_3_a	treatment_beta	text	[Phage: "[pre_phage4_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_3_fi	treatment_beta	text	[Phage: "[pre_phage4_name]"] Dat	date_dmy				[sc_meets_ y	
tre_ph_3_i	treatment_beta	text	[Phage: "[pre_phage4_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_3_i	treatment_beta	text	[Phage: "[pre_phage4_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_3_c	treatment_beta	text	[Phage: "[pre_phage4_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_3_t	treatment_beta	text	[Phage: "[pre_phage4_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_3_c	treatment_beta	text	[Phage: "[pre_phage4_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph4	treatment_beta	descripti	Phage: "[pre_phage5_name]"					[sc_meets_inclusion] = "1" and [pre_phage5_name] and [pre_num_phage]>4	
tre_ph_4_r	treatment_beta	checkbo	[Phage: "[p	aero, Aerosolised / Nebulised | instl, Instillation | iv, Intravenous (				[sc_meets_ y	
tre_ph_4_r	treatment_beta	text	[Phage: "[pre_phage5_name]"] Specify instillation site					[sc_meets_ y	@CHARLIMIT='50'
tre_ph_4_r	treatment_beta	text	[Phage: "[pre_phage5_name]"] Specify 'other'					[sc_meets_ y	@CHARLIMIT='50'
tre_ph_4_d	treatment_beta	radio	[Phage: "[p	under2wks, Less than or equal to 2 weeks | over2wks, Longer tha				[sc_meets_ y	
tre_ph_4_d	treatment_beta	text	[Phage: "[pre_phage5_name]"] Dur	integer				[sc_meets_ y	
tre_ph_4_d	treatment_beta	radio	[Phage: "[p	days, Days | doseperapp, Doses/applications				[sc_meets_ y	
tre_ph_4_d	treatment_beta	radio	[Phage: "[p	days, Days | weeks, Weeks | months, Months				[sc_meets_ y	
tre_ph_4_d	treatment_beta	radio	[Phage: "[p	10e8, 10^8 pfu/mL | 10e9, 10^9 pfu/mL | 10e10, 10^10 pfu/mL |				[sc_meets_ y	
tre_ph_4_d	treatment_beta	text	[Phage: "[pre_phage5_	XXX.X mL	number_1dp			[sc_meets_ y	
tre_ph_4_a	treatment_beta	text	[Phage: "[pre_phage5_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_4_fi	treatment_beta	text	[Phage: "[pre_phage5_name]"] Dat	date_dmy				[sc_meets_ y	
tre_ph_4_i	treatment_beta	text	[Phage: "[pre_phage5_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_4_i	treatment_beta	text	[Phage: "[pre_phage5_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_4_c	treatment_beta	text	[Phage: "[pre_phage5_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_4_t	treatment_beta	text	[Phage: "[pre_phage5_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_4_c	treatment_beta	text	[Phage: "[pre_phage5_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
trivcl_no_ir	treatment_iv_clinical_b	descripti	<h3><span style="background-color: #e03e2					[sc_meets_inclusion] < 1	
triv_descrip	treatment_iv_clinical_b	descripti	Clinical IV Administration. This page opens when IV or oral/enteral phage therapy is selected from the Treatment page.						
trivcl_day	treatment_iv_clinical_b	radio	Select clinic	0, D0 | 1, D1 | 2, D2 | 3, D3 | 4, D4 | 5, D5 | 6, D6 | 7, D7 | 8, D8				[sc_meets_ y	
trivcl_d0_c	treatment_iv_clinical_b	checkbo	[D0] Confir	yes, Patient has received full clinical exam				[trivcl_day] y	
trivcl_1_do	treatment_iv_clinical_b	radio	Number of	1,1 | 2,2				([trivcl_day y	

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trivcl_1_do	treatment_iv_clinical_t	yesno	Dose adjusted based or Dose #1	[trivcl_day] y		
trivcl_1_do	treatment_iv_clinical_t	radio	[1] If yes, se inc, Dose increased | dec, Dose decreased	[trivcl_day] y		
trivcl_1_do	treatment_iv_clinical_t	checkbo	Confirm vit confirmed, Dose #1	([trivcl_day y		
trivcl_1_do	treatment_iv_clinical_t	checkbo	Confirm vit confirmed, Dose #1	([trivcl_day y		
trivcl_1_do	treatment_iv_clinical_t	checkbo	Confirm vit confirmed, Dose #1	([trivcl_day y		
trivcl_1_do	treatment_iv_clinical_t	yesno	Dose adjusted based or Dose #2	[trivcl_day] y		
trivcl_1_do	treatment_iv_clinical_t	radio	[2] If yes, se inc, Dose increased | dec, Dose decreased	[trivcl_day] y		
trivcl_1_do	treatment_iv_clinical_t	checkbo	Confirm vit confirmed, Dose #2	([trivcl_day y		
trivcl_1_do	treatment_iv_clinical_t	checkbo	Confirm vit confirmed, Dose #2	([trivcl_day y		
trivcl_1_do	treatment_iv_clinical_t	checkbo	Confirm vit confirmed, Dose #2	([trivcl_day y		
trivcl_2_de	treatment_iv_clinical_t	yesno	Protocol deviation?	([trivcl_day y		
trivcl_2_de	treatment_iv_clinical_t	notes	Describe the protocol deviation	[trivcl_2_de y		
trivcl_3_fev	treatment_iv_clinical_t	yesno	Did fever (temp > 37.9 Â°C) occur today (yes/no)?	([trivcl_day y		
trivcl_3_fev	treatment_iv_clinical_t	text	Specify max temp occurring prior to number_1dp	[trivcl_3_fe y		
trivcl_3_fev	treatment_iv_clinical_t	text	Specify time of max fever in hours a number_1dp	[trivcl_3_fe y		
trivcl_4_tac	treatment_iv_clinical_t	yesno	Did tachycardia occur today (yes/no)?	([trivcl_day y		
trivcl_4_tac	treatment_iv_clinical_t	text	Specify max HR occurring prior to n integer	[trivcl_4_ta y		
trivcl_4_tac	treatment_iv_clinical_t	text	Specify time of max HR in hours aft number_1dp	[trivcl_4_ta y		
trivcl_5_pai	treatment_iv_clinical_t	yesno	Did pain occur today (greater than any baseline pain) - yes/no?	([trivcl_day y		
trivcl_5_pai	treatment_iv_clinical_t	text	Specify time of pain occurrence in h number_1dp	[trivcl_5_pa y		
trivcl_5_pai	treatment_iv_clinical_t	text	Specify site of pain	[trivcl_5_pa y		@CHARLIMIT=50
trivcl_6_inf	treatment_iv_clinical_t	yesno	Any other signs or symptoms of inflammatory response (yes/no)?	([trivcl_day y		
trivcl_6_inf	treatment_iv_clinical_t	notes	If yes, specify what occurred	[trivcl_6_in y		
trivcl_6_inf	treatment_iv_clinical_t	text	Also specify time of occurrence in h number_1dp	[trivcl_6_in y		
trivcl_d15_	treatment_iv_clinical_t	yesno	Is patient still receiving phage therapy (yes/no)?	[trivcl_day] y		
trivcl_d15_	treatment_iv_clinical_t	radio	Number of 1,1 | 2,2 | 3,Has changed during this time	[trivcl_day] y		
trivcl_d15_	treatment_iv_clinical_t	yesno	Were vitals checked each day of treatment as per protocol (yes/no)?	[trivcl_day] y		
trivcl_d15_	treatment_iv_clinical_t	yesno	Will treatment continue >4 weeks (yes/no)?	[trivcl_day] y		
trivcl_d15_	treatment_iv_clinical_t	radio	How many 15,15 | 16,16 | 17,17 | 18,18 | 19,19 | 20,20 | 21,21 | 22,22 | 23	[trivcl_day] y		
trivcl_d15_	treatment_iv_clinical_t	yesno	Did fever (temp > 37.9 Â°C) occur on any (yes/no)?	[trivcl_day] y		
trivcl_d15_	treatment_iv_clinical_t	checkbo	Specify day 15,15 | 16,16 | 17,17 | 18,18 | 19,19 | 20,20 | 21,21 | 22,22 | 23	[trivcl_day] y		
trivcl_d15_	treatment_iv_clinical_t	text	Specify the max fever occurring in 2 number	[trivcl_d15_28_hi_fever_days(15)] = '1'		
trivcl_d15_	treatment_iv_clinical_t	text	Specify the max fever occurring in 2 number	[trivcl_d15_28_hi_fever_days(16)] = '1'		
trivcl_d15_	treatment_iv_clinical_t	text	Specify the max fever occurring in 2 number	[trivcl_d15_28_hi_fever_days(17)] = '1'		
trivcl_d15_	treatment_iv_clinical_t	text	Specify the max fever occurring in 2 number	[trivcl_d15_28_hi_fever_days(18)] = '1'		
trivcl_d15_	treatment_iv_clinical_t	text	Specify the max fever occurring in 2 number	[trivcl_d15_28_hi_fever_days(19)] = '1'		
trivcl_d15_	treatment_iv_clinical_t	text	Specify the max fever occurring in 2 number	[trivcl_d15_28_hi_fever_days(20)] = '1'		
trivcl_d15_	treatment_iv_clinical_t	text	Specify the max fever occurring in 2 number	[trivcl_d15_28_hi_fever_days(21)] = '1'		
trivcl_d15_	treatment_iv_clinical_t	text	Specify the max fever occurring in 2 number	[trivcl_d15_28_hi_fever_days(22)] = '1'		
trivcl_d15_	treatment_iv_clinical_t	text	Specify the max fever occurring in 2 number	[trivcl_d15_28_hi_fever_days(23)] = '1'		
trivcl_d15_	treatment_iv_clinical_t	text	Specify the max fever occurring in 2 number	[trivcl_d15_28_hi_fever_days(24)] = '1'		

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trivcl_d15_	treatment_iv_clinical_t	text	Specify the max fever occurring in 2	number	[trivcl_d15_28_hi_fever_days(25)] = '1'	
trivcl_d15_	treatment_iv_clinical_t	text	Specify the max fever occurring in 2	number	[trivcl_d15_28_hi_fever_days(26)] = '1'	
trivcl_d15_	treatment_iv_clinical_t	text	Specify the max fever occurring in 2	number	[trivcl_d15_28_hi_fever_days(27)] = '1'	
trivcl_d15_	treatment_iv_clinical_t	text	Specify the max fever occurring in 2	number	[trivcl_d15_28_hi_fever_days(28)] = '1'	
trivcl_d15_	treatment_iv_clinical_t	yesno	Did tachycardia on any day (yes/no)?		[trivcl_day] y	
trivcl_d15_	treatment_iv_clinical_t	checkbox	Specify day 15,15 | 16,16 | 17,17 | 18,18 | 19,19 | 20,20 | 21,21 | 22,22 | 23		[trivcl_day] y	
trivcl_d15_	treatment_iv_clinical_t	yesno	Did pain occur on any day (greater than any baseline pain)		[trivcl_day] y	
trivcl_d15_	treatment_iv_clinical_t	checkbox	Specify day 15,15 | 16,16 | 17,17 | 18,18 | 19,19 | 20,20 | 21,21 | 22,22 | 23		[trivcl_day] y	
trivcl_d15_	treatment_iv_clinical_t	text	Specify site of pain for day D15		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_t	text	Specify site of pain for day D16		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_t	text	Specify site of pain for day D17		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_t	text	Specify site of pain for day D18		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_t	text	Specify site of pain for day D19		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_t	text	Specify site of pain for day D20		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_t	text	Specify site of pain for day D21		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_t	text	Specify site of pain for day D22		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_t	text	Specify site of pain for day D23		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_t	text	Specify site of pain for day D24		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_t	text	Specify site of pain for day D25		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_t	text	Specify site of pain for day D26		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_t	text	Specify site of pain for day D27		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_t	text	Specify site of pain for day D28		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_t	yesno	Any other signs or symptoms of inflammatory response on any day (yes/no)?		[trivcl_day] y	
trivcl_d15_	treatment_iv_clinical_t	checkbox	Specify day 15,15 | 16,16 | 17,17 | 18,18 | 19,19 | 20,20 | 21,21 | 22,22 | 23		[trivcl_day] y	
trivcl_d15_	treatment_iv_clinical_t	text	Specify what occurred for day D15		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_t	text	Specify what occurred for day D16		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_t	text	Specify what occurred for day D17		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_t	text	Specify what occurred for day D18		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_t	text	Specify what occurred for day D19		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_t	text	Specify what occurred for day D20		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_t	text	Specify what occurred for day D21		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_t	text	Specify what occurred for day D22		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_t	text	Specify what occurred for day D23		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_t	text	Specify what occurred for day D24		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_t	text	Specify what occurred for day D25		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_t	text	Specify what occurred for day D26		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_t	text	Specify what occurred for day D27		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_t	text	Specify what occurred for day D28		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_t	yesno	Dose adjusted on any day based on "kinetics" results (yes/no)?		[trivcl_day] y	
trivcl_d15_	treatment_iv_clinical_t	radio	Did the dos inc, Dose increased | dec, Dose reduced | both, Both increases an		[trivcl_day] y	
trivcl_d15_	treatment_iv_clinical_t	radio	What has b cure, 1) Cure â€“ no evidence of ongoing infection: resolution of		[trivcl_day] y	

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trivcl_d15_	treatment_iv_clinical_b	radio	Select one (	no_disability, Without persisting disability | disability, With persis	[trivcl_day] y
trivcl_d15_	treatment_iv_clinical_b	radio	Select one (	improvement, Improvement in clinical signs and symptoms, radiol	[trivcl_day] y
trivlab_no_	treatment_iv_labs_beta	descripti	<h3><span style="background-color: #e03e2		[sc_meets_inclusion] < 1
trivlab_des	treatment_iv_labs_beta	descripti	Clinical IV Labs For treatments over TWO weeks, use the Monthly instrument. This page opens when IV and/or oral/		
trivlab_non	treatment_iv_labs_beta	descripti	This patient does not meet oral/enteral phage therapy re		([tre_ph_0_rt(iv)] = '0' and [tre_ph_0_rt(oral)] = '0') and ([tre_ph_1_rt(iv)] = '0'
trivlab_day	treatment_iv_labs_beta	radio	Select clinic	0, D0 | 2, D2 | 4, D4 | 8, D8 | 11, D11 | 15, D15 | 29, D29 | other,	[sc_meets_ y
trivlab_oth	treatment_iv_labs_beta	text	Enter day of treatment (enter a nur	integer	[trivlab_day y
trivlab_oth	treatment_iv_labs_beta	notes	Test performed for day [trivlab_other_day]		[trivlab_oth y
trivlab_oth	treatment_iv_labs_beta	notes	Result for day [trivlab_other_day]		[trivlab_oth y
trivlab_crp	treatment_ CRP results	text	[[trivlab_day]] CRP result (XXX.X mg	number_1dp	[trivlab_day] >= 0 and [trivlab_day] and [trivlab_day] != 11
trivlab_crp_	treatment_iv_labs_beta	checkbox	[[trivlab_da	na, CRP results NOT available for [[trivlab_day]]	[trivlab_crp y
trivlab_esr	treatment_ ESR results	text	[[trivlab_day]] ESR result (XXX mm/	integer	[trivlab_day] >= 0 and [trivlab_day] and [trivlab_day] != 2 and [trivlab_day] != 1
trivlab_esr_	treatment_iv_labs_beta	checkbox	[[trivlab_da	na, ESR results NOT available for [[trivlab_day]]	[trivlab_esr y
trivlab_pro	treatment_ Procalciton	text	[[trivlab_day]] Procalcitonin result (	number_2dp	[trivlab_day] and [trivlab_day] >= 0 and [trivlab_day] != 11 and [trivlab_day] !=
trivlab_pro	treatment_iv_labs_beta	checkbox	[[trivlab_da	na, ESR results NOT available for [[trivlab_day]]	[trivlab_prc y
trivlab_fbc_	treatment_ FBC	yesno	[[trivlab_day]] FBC all within normal range (yes/no)?		[trivlab_day] and [trivlab_day] >= 0
trivlab_hb	treatment_ Hb results	text	[[trivlab_day]] Hb result (XXX g/L)	integer	[trivlab_fbc_isnorm] = '0' and [trivlab_day] and [trivlab_day] >= 0
trivlab_hb_	treatment_iv_labs_beta	checkbox	[[trivlab_da	na, Hb results NOT available for [[trivlab_day]]	[trivlab_hb] y
trivlab_plat	treatment_ Platelet cou	text	[[trivlab_day]] Platelet result (XXX x	integer	[trivlab_fbc_isnorm] = '0' and [trivlab_day] and [trivlab_day] >= 0
trivlab_plat	treatment_iv_labs_beta	checkbox	[[trivlab_da	na, Platelet count results NOT available for [[trivlab_day]]	[trivlab_pla y
trivlab_wcc	treatment_ WCC	text	[[trivlab_day]] WCC (XXX x10^9/L)	integer	[trivlab_fbc_isnorm] = '0' and [trivlab_day] and [trivlab_day] >= 0
trivlab_wcc	treatment_iv_labs_beta	checkbox	[[trivlab_da	na, WCC results NOT available for [[trivlab_day]]	[trivlab_wc y
trivlab_neu	treatment_ Neutrophil	text	[[trivlab_day]] Neutrophil count (X	number_1dp	[trivlab_fbc_isnorm] = '0' and [trivlab_day] and [trivlab_day] >= 0
trivlab_neu	treatment_iv_labs_beta	checkbox	[[trivlab_da	na, neutrophil count results NOT available for [[trivlab_day]]	[trivlab_neu y
trivlab_lym	treatment_ Lymphocyt	text	[[trivlab_day]] Lymphocyte count (	number_1dp	[trivlab_fbc_isnorm] = '0' and [trivlab_day] and [trivlab_day] >= 0
trivlab_lym	treatment_iv_labs_beta	checkbox	[[trivlab_da	na, Lymphocyte count results NOT available for [[trivlab_day]]	[trivlab_lym y
trivlab_lym	treatment_ Lymphoper	yesno	[[trivlab_day]] Lymphopenia?		[trivlab_day] and [trivlab_day] >= 0 and [trivlab_day] != 0 and [trivlab_day] != 2
trivlab_lym	treatment_iv_labs_beta	yesno	[[trivlab_day]] Lymphocyte subsets all within normal range (yes/no)?		[trivlab_prc y
trivlab_cd3	treatment_ CD3 count	text	[[trivlab_day]] CD3 count (XX.XX x1	number_2dp	([trivlab_lymphocyte_isnorm] = '0' or [trivlab_lymphopenia]='1') and [trivlab_c
trivlab_cd3_	treatment_iv_labs_beta	text	[[trivlab_day]] CD3 % (XX%)	integer	([trivlab_lymphocyte_isnorm] = '0' or [trivlab_lymphopenia]='1') and [trivlab_c
trivlab_cd3_	treatment_iv_labs_beta	checkbox	[[trivlab_da	na, CD3 results NOT available for [[trivlab_day]]	[trivlab_cd3 y
trivlab_cd4	treatment_ CD4 count	text	[[trivlab_day]] CD4 count (XX.XX x1	number_2dp	([trivlab_lymphocyte_isnorm] = '0' or [trivlab_lymphopenia]='1') and [trivlab_c
trivlab_cd4_	treatment_iv_labs_beta	text	[[trivlab_day]] CD4 % (XX%)	integer	([trivlab_lymphocyte_isnorm] = '0' or [trivlab_lymphopenia]='1') and [trivlab_c
trivlab_cd4_	treatment_iv_labs_beta	checkbox	[[trivlab_da	na, CD4 results NOT available for [[trivlab_day]]	[trivlab_cd4 y
trivlab_cd8	treatment_ CD8 count	text	[[trivlab_day]] CD8 count (XX.XX x1	number_2dp	([trivlab_lymphocyte_isnorm] = '0' or [trivlab_lymphopenia]='1') and [trivlab_c
trivlab_cd8_	treatment_iv_labs_beta	text	[[trivlab_day]] CD8 % (XX%)	integer	([trivlab_lymphocyte_isnorm] = '0' or [trivlab_lymphopenia]='1') and [trivlab_c
trivlab_cd8_	treatment_iv_labs_beta	checkbox	[[trivlab_da	na, CD8 results NOT available for [[trivlab_day]]	[trivlab_cd8 y
trivlab_nkc	treatment_ CD8 count	text	[[trivlab_day]] NK cell count (XX.XX	number_2dp	([trivlab_lymphocyte_isnorm] = '0' or [trivlab_lymphopenia]='1') and [trivlab_c
trivlab_nkc	treatment_iv_labs_beta	text	[[trivlab_day]] NK cell % (XX%)	integer	([trivlab_lymphocyte_isnorm] = '0' or [trivlab_lymphopenia]='1') and [trivlab_c
trivlab_nkc	treatment_iv_labs_beta	checkbox	[[trivlab_da	na, NK cell count results NOT available for [[trivlab_day]]	[trivlab_nkc y
trivlab_cd1	treatment_ CD19 count	text	[[trivlab_day]] CD19 count (XX.XX x	number_2dp	([trivlab_lymphocyte_isnorm] = '0' or [trivlab_lymphopenia]='1') and [trivlab_c

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trivlab_cd1	treatment_iv_labs_beta	text	[[trivlab_day]] CD19 % (XX%)	integer	([trivlab_lymphocyte_isnorm] = '0' or [trivlab_lymphopenia]='1') and [trivlab_c
trivlab_cd1	treatment_iv_labs_beta	checkbox	[[trivlab_da na, CD19 results NOT available for [[trivlab_day]]		[trivlab_cd1 y
trivlab_lft_i	treatment_iv_labs_beta	yesno	[[trivlab_day]] LFTs all within normal range (yes/no)?		[trivlab_prc y
trivlab_albu	treatment_ Albumin	text	[[trivlab_day]] Albumin (XX g/L)	integer	[trivlab_lft_isnorm] = '0' and [trivlab_day] and [trivlab_day] >= 0 and [trivlab_d
trivlab_albu	treatment_iv_labs_beta	checkbox	[[trivlab_da na, Albumin results are NOT available for [[trivlab_day]]		[trivlab_alb y
trivlab_ast	treatment_ AST	text	[[trivlab_day]] AST (XXXX U/L)	integer	[trivlab_lft_isnorm] = '0' and [trivlab_day] and [trivlab_day] >= 0 and [trivlab_d
trivlab_ast_	treatment_iv_labs_beta	checkbox	[[trivlab_da na, AST results are NOT available for [[trivlab_day]]		[trivlab_ast y
trivlab_alt	treatment_ ALT	text	[[trivlab_day]] ALT (XXXX U/L)	integer	[trivlab_lft_isnorm] = '0' and [trivlab_day] and [trivlab_day] >= 0 and [trivlab_d
trivlab_alt_	treatment_iv_labs_beta	checkbox	[[trivlab_da na, ALT results are NOT available for [[trivlab_day]]		[trivlab_alt] y
trivlab_ggt	treatment_ GGT	text	[[trivlab_day]] GGT (XXXX U/L)	integer	([trivlab_lft_isnorm] = '0' or [trivlab_lymphopenia]='1') and [trivlab_day] and [t
trivlab_ggt_	treatment_iv_labs_beta	checkbox	[[trivlab_da na, GGT results are NOT available for [[trivlab_day]]		[trivlab_ggt y
trivlab_alp	treatment_ ALP	text	[[trivlab_day]] ALP (XXXX U/L)	integer	[trivlab_lft_isnorm] = '0' and [trivlab_day] and [trivlab_day] >= 0 and [trivlab_d
trivlab_alp_	treatment_iv_labs_beta	checkbox	[[trivlab_da na, ALP results are NOT available for [[trivlab_day]]		[trivlab_alp y
trivlab_uec	treatment_iv_labs_beta	yesno	[[trivlab_day]] UECs all within normal range (yes/no)?		[trivlab_prc y
trivlab_sodi	treatment_ Sodium	text	[[trivlab_day]] Sodium (XXX mmol/l	integer	[trivlab_uec_isnorm] = '0' and [trivlab_day] and [trivlab_day] >= 0 and [trivlab_
trivlab_sodi	treatment_iv_labs_beta	checkbox	[[trivlab_da na, Sodium results are NOT available for [[trivlab_day]]		[trivlab_soc y
trivlab_urea	treatment_ Urea	text	[[trivlab_day]] Urea (XX.X mmol/L)	number_1dp	[trivlab_uec_isnorm] = '0' and [trivlab_day] and [trivlab_day] >= 0 and [trivlab_
trivlab_urea	treatment_iv_labs_beta	checkbox	[[trivlab_da na, Urea results are NOT available for [[trivlab_day]]		[trivlab_ure y
trivlab_crea	treatment_ Creatinine	text	[[trivlab_day]] Creatinine (XXX umo	integer	[trivlab_uec_isnorm] = '0' and [trivlab_day] and [trivlab_day] >= 0 and [trivlab_
trivlab_crea	treatment_iv_labs_beta	checkbox	[[trivlab_da na, Creatinine results are NOT available for [[trivlab_day]]		[trivlab_cre y
trivlab_igg	treatment_ IgG	text	[[trivlab_day]] IgG (XX.XX g/L)	number_2dp	[trivlab_day] and ([trivlab_day] = 0 or [trivlab_day] = 29)
trivlab_igg_	treatment_iv_labs_beta	checkbox	[[trivlab_da na, IgG results are NOT available for [[trivlab_day]]		[trivlab_igg y
trivlab_c3	treatment_ C3	text	[[trivlab_day]] C3 (X.XX g/L)	number_2dp	[trivlab_day] and ([trivlab_day] = 0 or [trivlab_day] = 15 or [trivlab_day] = 29)
trivlab_c3_	treatment_iv_labs_beta	checkbox	[[trivlab_da na, C3 results are NOT available for [[trivlab_day]]		[trivlab_c3] y
trivlab_c4	treatment_ C4	text	[[trivlab_day]] C4 (X.XX g/L)	number_2dp	[trivlab_day] and ([trivlab_day] = 0 or [trivlab_day] = 15 or [trivlab_day] = 29)
trivlab_c4_	treatment_iv_labs_beta	checkbox	[[trivlab_da na, C4 results are NOT available for [[trivlab_day]]		[trivlab_c4] y
trivlab_ch5	treatment_ CH50	text	[[trivlab_day]] CH50 (XX U/mL)	integer	[trivlab_day] and ([trivlab_day] = 0 or [trivlab_day] = 15 or [trivlab_day] = 29)
trivlab_ch5	treatment_iv_labs_beta	checkbox	[[trivlab_da na, CH50 results are NOT available for [[trivlab_day]]		[trivlab_ch5 y
trivlab_ph0	treatment_iv_labs_beta	descripti	Phage: "[pre_phage1_name]"		([tre_ph_0_rt(iv)] = '1' or [tre_ph_0_rt(oral)] = '1') and [pre_phage1_name] an
trivlab_ph_	treatment_iv_labs_beta	yesno	[Phage: "[pre_phage1_name]"] Antiphage antibodies tested (yes/no)?		([tre_ph_0_ y
trivlab_ph_	treatment_iv_labs_beta	checkbox	[Phage: "[p neutralising,Neutralising antibody assay | igmigg, IgM/IgG assay |		[trivlab_ph y
trivlab_ph_	treatment_iv_labs_beta	text	[Phage: "[pre_phage1_name]"] Other assay type		[trivlab_ph y @CHARLIMIT='50'
trivlab_ph_	treatment_iv_labs_beta	notes	[Phage: "[pre_phage1_name]"] Antiphage antibody result		[trivlab_ph y
trivlab_ph1	treatment_iv_labs_beta	descripti	Phage: "[pre_phage2_name]"		([tre_ph_1_rt(iv)] = '1' or [tre_ph_1_rt(oral)] = '1') and [pre_phage2_name] an
trivlab_ph_	treatment_iv_labs_beta	yesno	[Phage: "[pre_phage2_name]"] Antiphage antibodies tested (yes/no)?		([tre_ph_1_ y
trivlab_ph_	treatment_iv_labs_beta	checkbox	[Phage: "[p neutralising,Neutralising antibody assay | igmigg, IgM/IgG assay |		[trivlab_ph y
trivlab_ph_	treatment_iv_labs_beta	text	[Phage: "[pre_phage2_name]"] Other assay type		[trivlab_ph y @CHARLIMIT='50'
trivlab_ph_	treatment_iv_labs_beta	notes	[Phage: "[pre_phage2_name]"] Antiphage antibody result		[trivlab_ph y
trivlab_ph2	treatment_iv_labs_beta	descripti	Phage: "[pre_phage3_name]"		([tre_ph_2_rt(iv)] = '1' or [tre_ph_2_rt(oral)] = '1') and [pre_phage3_name] an
trivlab_ph_	treatment_iv_labs_beta	yesno	[Phage: "[pre_phage3_name]"] Antiphage antibodies tested (yes/no)?		([tre_ph_2_ y
trivlab_ph_	treatment_iv_labs_beta	checkbox	[Phage: "[p neutralising,Neutralising antibody assay | igmigg, IgM/IgG assay |		[trivlab_ph y

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trivlab_ph_	treatment_iv_labs_beta	text	[Phage: "[pre_phage3_name]"] Other assay type	[trivlab_ph_y	@CHARLIMIT='50'
trivlab_ph_	treatment_iv_labs_beta	notes	[Phage: "[pre_phage3_name]"] Antiphage antibody result	[trivlab_ph_y	
trivlab_ph3	treatment_iv_labs_beta	descriptiv	Phage: "[pre_phage4_name]"	([tre_ph_3_rt(iv)] = '1' or [tre_ph_3_rt(oral)] = '1') and [pre_phage4_name] an	
trivlab_ph_	treatment_iv_labs_beta	yesno	[Phage: "[pre_phage4_name]"] Antiphage antibodies tested (yes/no)?	([tre_ph_3_y	
trivlab_ph_	treatment_iv_labs_beta	checkbox	[Phage: "[pr neutralising,Neutralising antibody assay | igmigg, IgM/IgG assay |	[trivlab_ph_y	
trivlab_ph_	treatment_iv_labs_beta	text	[Phage: "[pre_phage4_name]"] Other assay type	[trivlab_ph_y	@CHARLIMIT='50'
trivlab_ph_	treatment_iv_labs_beta	notes	[Phage: "[pre_phage4_name]"] Antiphage antibody result	[trivlab_ph_y	
trivlab_ph4	treatment_iv_labs_beta	descriptiv	Phage: "[pre_phage5_name]"	([tre_ph_4_rt(iv)] = '1' or [tre_ph_4_rt(oral)] = '1') and [pre_phage5_name] an	
trivlab_ph_	treatment_iv_labs_beta	yesno	[Phage: "[pre_phage5_name]"] Antiphage antibodies tested (yes/no)?	([tre_ph_4_y	
trivlab_ph_	treatment_iv_labs_beta	checkbox	[Phage: "[pr neutralising,Neutralising antibody assay | igmigg, IgM/IgG assay |	[trivlab_ph_y	
trivlab_ph_	treatment_iv_labs_beta	text	[Phage: "[pre_phage5_name]"] Other assay type	[trivlab_ph_y	@CHARLIMIT='50'
trivlab_ph_	treatment_iv_labs_beta	notes	[Phage: "[pre_phage5_name]"] Antiphage antibody result	[trivlab_ph_y	
trivlab_pth1	treatment_iv_labs_beta	descriptiv	Pathogen 1 "[pre_pth1_target]"	[pre_num_target_pathogen] > 0 and [trivlab_day] and ([trivlab_day] = 0 or [triv	
trivlab_pth_	treatment_iv_labs_beta	radio	[Pathogen 1 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ty	
trivlab_pth_	treatment_iv_labs_beta	notes	[Pathogen 1: [pre_pth1_target]] How come isolation wasn't performed?	[trivlab_pth_y	
trivlab_pth_	treatment_iv_labs_beta	radio	[Pathogen 1 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[trivlab_pth_y	
trivlab_pth_	treatment_iv_labs_beta	notes	[Pathogen 1: [pre_pth1_target]] Please specify anti-phage resistance activity	[trivlab_pth_y	
trivlab_pth_	treatment_iv_labs_beta	radio	[Pathogen 1 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ty	
trivlab_pth_	treatment_iv_labs_beta	text	[Pathogen 1: [pre_pth1_target]] Specify other site where pathogen was isolat	[trivlab_pth_y	
trivlab_pth_	treatment_iv_labs_beta	radio	[Pathogen 1 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[trivlab_pth_y	
trivlab_pth_	treatment_iv_labs_beta	notes	[Pathogen 1: [pre_pth1_target]] Please specify anti-phage resistance activity	[trivlab_pth_y	
trivlab_pth2	treatment_iv_labs_beta	descriptiv	Pathogen 2 "[pre_pth2_target]"	[pre_num_target_pathogen] > 1 and [trivlab_day] and ([trivlab_day] = 0 or [triv	
trivlab_pth_	treatment_iv_labs_beta	radio	[Pathogen 2 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ty	
trivlab_pth_	treatment_iv_labs_beta	notes	[Pathogen 2: [pre_pth2_target]] How come isolation wasn't performed?	[trivlab_pth_y	
trivlab_pth_	treatment_iv_labs_beta	radio	[Pathogen 2 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[trivlab_pth_y	
trivlab_pth_	treatment_iv_labs_beta	notes	[Pathogen 2: [pre_pth2_target]] Please specify anti-phage resistance activity	[trivlab_pth_y	
trivlab_pth_	treatment_iv_labs_beta	radio	[Pathogen 2 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ty	
trivlab_pth_	treatment_iv_labs_beta	text	[Pathogen 2: [pre_pth2_target]] Specify other site where pathogen was isolat	[trivlab_pth_y	
trivlab_pth_	treatment_iv_labs_beta	radio	[Pathogen 2 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[trivlab_pth_y	
trivlab_pth_	treatment_iv_labs_beta	notes	[Pathogen 2: [pre_pth2_target]] Please specify anti-phage resistance activity	[trivlab_pth_y	
trivlab_pth3	treatment_iv_labs_beta	descriptiv	Pathogen 3 "[pre_pth3_target]"	[pre_num_target_pathogen] > 2 and [trivlab_day] and ([trivlab_day] = 0 or [triv	
trivlab_pth_	treatment_iv_labs_beta	radio	[Pathogen 3 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ty	
trivlab_pth_	treatment_iv_labs_beta	notes	[Pathogen 3: [pre_pth3_target]] How come isolation wasn't performed?	[trivlab_pth_y	
trivlab_pth_	treatment_iv_labs_beta	radio	[Pathogen 3 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[trivlab_pth_y	
trivlab_pth_	treatment_iv_labs_beta	notes	[Pathogen 3: [pre_pth3_target]] Please specify anti-phage resistance activity	[trivlab_pth_y	
trivlab_pth_	treatment_iv_labs_beta	radio	[Pathogen 3 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ty	
trivlab_pth_	treatment_iv_labs_beta	text	[Pathogen 3: [pre_pth3_target]] Specify other site where pathogen was isolat	[trivlab_pth_y	
trivlab_pth_	treatment_iv_labs_beta	radio	[Pathogen 3 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[trivlab_pth_y	
trivlab_pth_	treatment_iv_labs_beta	notes	[Pathogen 3: [pre_pth3_target]] Please specify anti-phage resistance activity	[trivlab_pth_y	
trivlab_pth4	treatment_iv_labs_beta	descriptiv	Pathogen 4 "[pre_pth4_target]"	[pre_num_target_pathogen] > 3 and [trivlab_day] and ([trivlab_day] = 0 or [triv	
trivlab_pth_	treatment_iv_labs_beta	radio	[Pathogen 4 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ty	

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trivlab_pth	treatment_iv_labs_beta	notes	[Pathogen 4: [pre_pth4_target]] How come isolation wasn't performed?	[trivlab_pth y
trivlab_pth	treatment_iv_labs_beta	radio	[Pathogen 4 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[trivlab_pth y
trivlab_pth	treatment_iv_labs_beta	notes	[Pathogen 4: [pre_pth4_target]] Please specify anti-phage resistance activity	[trivlab_pth y
trivlab_pth	treatment_iv_labs_beta	radio	[Pathogen 4 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_t y
trivlab_pth	treatment_iv_labs_beta	text	[Pathogen 4: [pre_pth4_target]] Specify other site where pathogen was isolat	[trivlab_pth y
trivlab_pth	treatment_iv_labs_beta	radio	[Pathogen 4 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[trivlab_pth y
trivlab_pth	treatment_iv_labs_beta	notes	[Pathogen 4: [pre_pth4_target]] Please specify anti-phage resistance activity	[trivlab_pth y
trivlab_pth!	treatment_iv_labs_beta	descripti	Pathogen 5 "[pre_pth5_target]"	[pre_num_target_pathogen] > 4 and [trivlab_day] and ([trivlab_day] = 0 or [triv
trivlab_pth	treatment_iv_labs_beta	radio	[Pathogen 5 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_t y
trivlab_pth	treatment_iv_labs_beta	notes	[Pathogen 5: [pre_pth5_target]] How come isolation wasn't performed?	[trivlab_pth y
trivlab_pth	treatment_iv_labs_beta	radio	[Pathogen 5 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[trivlab_pth y
trivlab_pth	treatment_iv_labs_beta	notes	[Pathogen 5: [pre_pth5_target]] Please specify anti-phage resistance activity	[trivlab_pth y
trivlab_pth	treatment_iv_labs_beta	radio	[Pathogen 5 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_t y
trivlab_pth	treatment_iv_labs_beta	text	[Pathogen 5: [pre_pth5_target]] Specify other site where pathogen was isolat	[trivlab_pth y
trivlab_pth	treatment_iv_labs_beta	radio	[Pathogen 5 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[trivlab_pth y
trivlab_pth	treatment_iv_labs_beta	notes	[Pathogen 5: [pre_pth5_target]] Please specify anti-phage resistance activity	[trivlab_pth y
trivlab_wgs	treatment_ WGS	yesno	[[trivlab_day]] Is WGS data available for current isolate?	[trivlab_day] and ([trivlab_day] = 0 or [trivlab_day] = 4 or [trivlab_day] = 8 or [t
trivlab_wgs	treatment_iv_labs_beta	notes	[[trivlab_day]] Where is the WGS data stored?	[trivlab_wgs]='1' and [trivlab_day] and ([trivlab_day] = 0 or [trivlab_day] = 4 or
trivlab_rnat	treatment_iv_labs_beta	radio	[[trivlab_da yes, Yes/Sample obtained + stored | not_analysed,Sample proces	[trivlab_day] and [trivlab_day] >= 0
trivlab_rnat	treatment_iv_labs_beta	notes	[[trivlab_day]] Where is the RNA transcriptomics data stored?	[trivlab_rnatr]='yes' and [trivlab_day] and [trivlab_day] >= 0
trivlab_rnat	treatment_iv_labs_beta	notes	[[trivlab_day]] Where is the RNA transcriptomics sample stored?	([trivlab_rnatr]='yes' or [trivlab_rnatr]='not_analysed') and [trivlab_day] and [t
trivlab_met	treatment_ Metagenon	yesno	[[trivlab_day]] Are clinical samples available for metagenomics?	[trivlab_day] and [trivlab_day] >= 0
trivlab_met	treatment_iv_labs_beta	text	[[trivlab_day]] Specify type of sample	[trivlab_metag_samples]='1' and [trivlab_day] and [trivlab_day] >= 0
trivlab_met	treatment_iv_labs_beta	radio	[[trivlab_da 1,Yes | 0, No, samples stored	[trivlab_metag_samples]='1' and [trivlab_day] and [trivlab_day] >= 0
trivlab_met	treatment_iv_labs_beta	notes	[[trivlab_day]] Where is the metagenome data stored?	[trivlab_metag_has]='1' and [trivlab_day] and [trivlab_day] >= 0
trivlab_met	treatment_iv_labs_beta	notes	[[trivlab_day]] Where is the sample stored?	[trivlab_metag_has]='0' and [trivlab_day] and [trivlab_day] >= 0
kino_no_in	kinetics_labs_beta	descripti	<h3><span style="background-color: #e03e2	[sc_meets_inclusion] < 1
kino_descri	kinetics_labs_beta	descripti	Kinetics Labs This page opens when IV and/or oral/enteral phage therapy are selected from the Treatment page. </	
kino_nonin	kinetics_labs_beta	descripti	This patient does not meet IV or oral/enteral phage thera	([tre_ph_0_rt(iv)] = '0' and [tre_ph_0_rt(oral)] = '0') and ([tre_ph_1_rt(iv)] = '0'
kino_day	kinetics_labs_beta	radio	Select clinic 2, D2 | 4, D4 | 8, D8 | 11, D11 | 15, D15 | 29, D29	[sc_meets_ y
kino_pre_p	kinetics_lat Pre-dose /	text	[[kino_day]][Pre-Dose] Phage resul integer	[kino_day] >= 0 and [kino_day]
kino_pre_p	kinetics_labs_beta	checkbo	[[kino_day] na, Plaque assays are NOT available for [[kino_day]]	[kino_pre_ y
kino_pre_p	kinetics_labs_beta	text	[[kino_day]][Pre-Dose] Phage qPCR integer	[kino_day] >= 0 and [kino_day]
kino_pre_p	kinetics_labs_beta	checkbo	[[kino_day] na, Phage qPCR results are NOT available for [[kino_day]]	[kino_pre_ y
kino_pre_b	kinetics_labs_beta	text	[[kino_day]][Pre-Dose] Bacterial loa integer	[kino_day] >= 0 and [kino_day]
kino_pre_b	kinetics_labs_beta	checkbo	[[kino_day] na, Phage qPCR results are NOT available for [[kino_day]]	[kino_pre_ y
kino_post_	kinetics_lat 30-60 minu	text	[[kino_day]][30-60 minutes post-dc integer	[kino_day] >= 0 and [kino_day] and [kino_day] != 15 and [kino_day] != 29
kino_post_	kinetics_labs_beta	checkbo	[[kino_day] na, Phage qPCR results are NOT available for [[kino_day]]	[kino_post_ y
kino_post_	kinetics_labs_beta	text	[[kino_day]][30-60 minutes post-dc integer	[kino_day] >= 0 and [kino_day] and [kino_day] != 15 and [kino_day] != 29
kino_post_	kinetics_labs_beta	checkbo	[[kino_day] na, Phage qPCR results are NOT available for [[kino_day]]	[kino_post_ y
kino_lngpo	kinetics_lat 2-3 hours p	text	[[kino_day]][2-3 hours post-dose] P integer	[kino_day] >= 0 and [kino_day]

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kino_lngpo	kinetics_labs_beta	checkbo	[[kino_day] na, Plaque assays are NOT available for [[kino_day]]	[kino_lngpc y
kino_lngpo	kinetics_labs_beta	text	[[kino_day]][2-3 hours post-dose] P integer	[kino_day] >= 0 and [kino_day] and [kino_day] != 15 and [kino_day] != 29
kino_lngpo	kinetics_labs_beta	checkbo	[[kino_day] na, Phage qPCR results are NOT available for [[kino_day]]	[kino_lngpc y
kino_lngpo	kinetics_labs_beta	text	[[kino_day]][2-3 hours post-dose] E integer	[kino_day] >= 0 and [kino_day] and [kino_day] != 15 and [kino_day] != 29
kino_lngpo	kinetics_labs_beta	checkbo	[[kino_day] na, Phage qPCR results are NOT available for [[kino_day]]	[kino_lngpc y
trivmo_no_	treatment_iv_monthly_	descripti	<h3><span style="background-color: #e03e2	[sc_meets_inclusion] < 1
trivmo_des	treatment_iv_monthly_	descripti	Clinical IV Labs [Monthly] Use this instrument for monthly treatment monitoring. This page opens when IV and/or or	
trivmo_non	treatment_iv_monthly_	descripti	This patient does not meet IV or oral/enteral phage thera	([tre_ph_0_rt(iv)] = '0' and [tre_ph_0_rt(oral)] = '0') and ([tre_ph_1_rt(iv)] = '0'
trivmo_mth	treatment_iv_monthly_	text	Month after first dose of phage adr integer	[sc_meets_ y
trivmo_pha	treatment_iv_monthly_	yesno	[Month [trivmo_mth]] Is the patient still receiving phage therapy?	[sc_meets_ y
trivmo_pha	treatment_iv_monthly_	yesno	[Month [trivmo_mth]] Did the patient stop phage therapy within the last mon	[trivmo_ph y
trivmo_pha	treatment_iv_monthly_	radio	[Month [tri cure, No evidence of ongoing infection: resolution of clinical symp	[trivmo_ph y
trivmo_pha	treatment_iv_monthly_	radio	[Month [tri no_disability, Without persisting disability | with_disability, With	[trivmo_ph y
trivmo_pha	treatment_iv_monthly_	radio	[Month [tri improvement, Improvement in clinical signs and symptoms, radiol	[trivmo_ph y
trivmo_crp	treatment_ CRP results	text	[Month [trivmo_mth]] CRP result (number_1dp	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1")
trivmo_crp	treatment_iv_monthly_	checkbo	[Month [tri na, CRP results NOT available [Month [trivmo_mth]]	[trivmo_crp y
trivmo_fbc	treatment_ FBC	yesno	[Month [trivmo_mth]] FBC all within normal range (yes/no)?	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1")
trivmo_hb	treatment_ Hb results	text	[Month [trivmo_mth]] Hb result (X integer	[trivmo_fbc_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_st
trivmo_hb_	treatment_iv_monthly_	checkbo	[Month [tri na, Hb results NOT available [Month [trivmo_mth]]	[trivmo_hb y
trivmo_plat	treatment_ Platelet cou	text	[Month [trivmo_mth]] Platelet resu integer	[trivmo_fbc_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_st
trivmo_plat	treatment_iv_monthly_	checkbo	[Month [tri na, Platelet count results NOT available [Month [trivmo_mth]]	[trivmo_pla y
trivmo_wcc	treatment_ WCC	text	[Month [trivmo_mth]] WCC (XXX x integer	[trivmo_fbc_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_st
trivmo_wcc	treatment_iv_monthly_	checkbo	[Month [tri na, WCC results NOT available [Month [trivmo_mth]]	[trivmo_wc y
trivmo_neu	treatment_ Neutrophil	text	[Month [trivmo_mth]] Neutrophil c number_1dp	[trivmo_fbc_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_st
trivmo_neu	treatment_iv_monthly_	checkbo	[Month [tri na, neutrophil count results NOT available [Month [trivmo_mth]]	[trivmo_ne y
trivmo_lym	treatment_ Lymphocyt	text	[Month [trivmo_mth]] Lymphocyte number_1dp	[trivmo_fbc_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_st
trivmo_lym	treatment_iv_monthly_	checkbo	[Month [tri na, Lymphocyte count results NOT available [Month [trivmo_mth]	[trivmo_lyn y
trivmo_lft_	treatment_iv_monthly_	yesno	[Month [trivmo_mth]] LFTs all within normal range (yes/no)?	([trivmo_ph y
trivmo_albu	treatment_ Albumin	text	[Month [trivmo_mth]] Albumin (XX integer	[trivmo_lft_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_sto
trivmo_albu	treatment_iv_monthly_	checkbo	[Month [tri na, Albumin results are NOT available [Month [trivmo_mth]]	[trivmo_alb y
trivmo_ast	treatment_ AST	text	[Month [trivmo_mth]] AST (XXXX U integer	[trivmo_lft_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_sto
trivmo_ast_	treatment_iv_monthly_	checkbo	[Month [tri na, AST results are NOT available [Month [trivmo_mth]]	[trivmo_ast y
trivmo_alt	treatment_ ALT	text	[Month [trivmo_mth]] ALT (XXXX U integer	[trivmo_lft_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_sto
trivmo_alt_	treatment_iv_monthly_	checkbo	[Month [tri na, ALT results are NOT available [Month [trivmo_mth]]	[trivmo_alt y
trivmo_ggt	treatment_ GGT	text	[Month [trivmo_mth]] GGT (XXXX U integer	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1")
trivmo_ggt_	treatment_iv_monthly_	checkbo	[Month [tri na, GGT results are NOT available [Month [trivmo_mth]]	[trivmo_ggt y
trivmo_alp	treatment_ ALP	text	[Month [trivmo_mth]] ALP (XXXX U integer	[trivmo_lft_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_sto
trivmo_alp_	treatment_iv_monthly_	checkbo	[Month [tri na, ALP results are NOT available [Month [trivmo_mth]]	[trivmo_alp y
trivmo_uec	treatment_iv_monthly_	yesno	[Month [trivmo_mth]] UECs all within normal range (yes/no)?	([trivmo_ph y
trivmo_sod	treatment_ Sodium	text	[Month [trivmo_mth]] Sodium (XX integer	[trivmo_uec_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_s
trivmo_sod	treatment_iv_monthly_	checkbo	[Month [tri na, Sodium results are NOT available [Month [trivmo_mth]]	[trivmo_so y

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trivmo_ure	treatment_ Urea	text	[Month [trivmo_mth]] Urea (XX.X n	number_1dp	[trivmo_uec_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_s
trivmo_ure	treatment_iv_monthly_	checkbo	[Month [tri na, Urea results are NOT available [Month [trivmo_mth]]		[trivmo_ure y
trivmo_cre	treatment_ Creatinine	text	[Month [trivmo_mth]] Creatinine (	integer	[trivmo_uec_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_s
trivmo_cre	treatment_iv_monthly_	checkbo	[Month [tri na, Creatinine results are NOT available [Month [trivmo_mth]]		[trivmo_cre y
trivmo_igg	treatment_ IgG	text	[Month [trivmo_mth]] IgG (XX.XX g	number_2dp	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1")
trivmo_igg_	treatment_iv_monthly_	checkbo	[Month [tri na, IgG results are NOT available [Month [trivmo_mth]]		[trivmo_igg y
trivmo_c3	treatment_ C3	text	[Month [trivmo_mth]] C3 (X.XX g/L	number_2dp	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1")
trivmo_c3_	treatment_iv_monthly_	checkbo	[Month [tri na, C3 results are NOT available [Month [trivmo_mth]]		[trivmo_c3] y
trivmo_c4	treatment_ C4	text	[Month [trivmo_mth]] C4 (X.XX g/L	number_2dp	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1")
trivmo_c4_	treatment_iv_monthly_	checkbo	[Month [tri na, C4 results are NOT available [Month [trivmo_mth]]		[trivmo_c4] y
trivmo_ch5	treatment_ CH50	text	[Month [trivmo_mth]] CH50 (XX U/	integer	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1")
trivmo_ch5	treatment_iv_monthly_	checkbo	[Month [tri na, CH50 results are NOT available [Month [trivmo_mth]]		[trivmo_ch! y
trivmo_ph0	treatment_iv_monthly_	descripti	Phage: "[pre_phage1_name]"		([tre_ph_0_rt(iv)] = '1' or [tre_ph_0_rt(oral)] = '1') and [pre_phage1_name] an
trivmo_ph_	treatment_iv_monthly_	yesno	[Phage: "[pre_phage1_name]"] Antiphage antibodies tested (yes/no)?		([tre_ph_0_ y
trivmo_ph_	treatment_iv_monthly_	checkbo	[Phage: "[p neutralising,Neutralising antibody assay | igmigg, IgM/IgG assay |		[trivmo_ph y
trivmo_ph_	treatment_iv_monthly_	text	[Phage: "[pre_phage1_name]"] Other assay type		[trivmo_ph y @CHARLIMIT='50'
trivmo_ph_	treatment_iv_monthly_	notes	[Phage: "[pre_phage1_name]"] Antiphage antibody result		[trivmo_ph y
trivmo_ph1	treatment_iv_monthly_	descripti	Phage: "[pre_phage2_name]"		([tre_ph_1_rt(iv)] = '1' or [tre_ph_1_rt(oral)] = '1') and [pre_phage2_name] an
trivmo_ph_	treatment_iv_monthly_	yesno	[Phage: "[pre_phage2_name]"] Antiphage antibodies tested (yes/no)?		([tre_ph_1_ y
trivmo_ph_	treatment_iv_monthly_	checkbo	[Phage: "[p neutralising,Neutralising antibody assay | igmigg, IgM/IgG assay |		[trivmo_ph y
trivmo_ph_	treatment_iv_monthly_	text	[Phage: "[pre_phage2_name]"] Other assay type		[trivmo_ph y @CHARLIMIT='50'
trivmo_ph_	treatment_iv_monthly_	notes	[Phage: "[pre_phage2_name]"] Antiphage antibody result		[trivmo_ph y
trivmo_ph2	treatment_iv_monthly_	descripti	Phage: "[pre_phage3_name]"		([tre_ph_2_rt(iv)] = '1' or [tre_ph_2_rt(oral)] = '1') and [pre_phage3_name] an
trivmo_ph_	treatment_iv_monthly_	yesno	[Phage: "[pre_phage3_name]"] Antiphage antibodies tested (yes/no)?		([tre_ph_2_ y
trivmo_ph_	treatment_iv_monthly_	checkbo	[Phage: "[p neutralising,Neutralising antibody assay | igmigg, IgM/IgG assay |		[trivmo_ph y
trivmo_ph_	treatment_iv_monthly_	text	[Phage: "[pre_phage3_name]"] Other assay type		[trivmo_ph y @CHARLIMIT='50'
trivmo_ph_	treatment_iv_monthly_	notes	[Phage: "[pre_phage3_name]"] Antiphage antibody result		[trivmo_ph y
trivmo_ph3	treatment_iv_monthly_	descripti	Phage: "[pre_phage4_name]"		([tre_ph_3_rt(iv)] = '1' or [tre_ph_3_rt(oral)] = '1') and [pre_phage4_name] an
trivmo_ph_	treatment_iv_monthly_	yesno	[Phage: "[pre_phage4_name]"] Antiphage antibodies tested (yes/no)?		([tre_ph_3_ y
trivmo_ph_	treatment_iv_monthly_	checkbo	[Phage: "[p neutralising,Neutralising antibody assay | igmigg, IgM/IgG assay |		[trivmo_ph y
trivmo_ph_	treatment_iv_monthly_	text	[Phage: "[pre_phage4_name]"] Other assay type		[trivmo_ph y @CHARLIMIT='50'
trivmo_ph_	treatment_iv_monthly_	notes	[Phage: "[pre_phage4_name]"] Antiphage antibody result		[trivmo_ph y
trivmo_ph4	treatment_iv_monthly_	descripti	Phage: "[pre_phage5_name]"		([tre_ph_4_rt(iv)] = '1' or [tre_ph_4_rt(oral)] = '1') and [pre_phage5_name] an
trivmo_ph_	treatment_iv_monthly_	yesno	[Phage: "[pre_phage5_name]"] Antiphage antibodies tested (yes/no)?		([tre_ph_4_ y
trivmo_ph_	treatment_iv_monthly_	checkbo	[Phage: "[p neutralising,Neutralising antibody assay | igmigg, IgM/IgG assay |		[trivmo_ph y
trivmo_ph_	treatment_iv_monthly_	text	[Phage: "[pre_phage5_name]"] Other assay type		[trivmo_ph y @CHARLIMIT='50'
trivmo_ph_	treatment_iv_monthly_	notes	[Phage: "[pre_phage5_name]"] Antiphage antibody result		[trivmo_ph y
trivmo_pth	treatment_iv_monthly_	descripti	Pathogen 1 "[pre_pth1_target]"		[pre_num_target_pathogen] > 0 and ([trivmo_phage_cont] = "1" or [trivmo_ph
trivmo_pth	treatment_iv_monthly_	radio	[Pathogen 1 isolated,Isolated | not_isolated, Not isolated | na, Not performed		[pre_num_ y
trivmo_pth	treatment_iv_monthly_	notes	[Pathogen 1: [pre_pth1_target]] How come isolation wasn't performed?		[trivmo_pth y
trivmo_pth	treatment_iv_monthly_	radio	[Pathogen 1 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc		[trivmo_pth y

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trivmo_pth	treatment_iv_monthly_ notes	[Pathogen 1: [pre_pth1_target]] Please specify anti-phage resistance activity	[trivmo_pth y
trivmo_pth	treatment_iv_monthly_ radio	[Pathogen 1 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_t y
trivmo_pth	treatment_iv_monthly_ text	[Pathogen 1: [pre_pth1_target]] Specify other site where pathogen was isolat	[trivmo_pth y
trivmo_pth	treatment_iv_monthly_ radio	[Pathogen 1 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[trivmo_pth y
trivmo_pth	treatment_iv_monthly_ notes	[Pathogen 1: [pre_pth1_target]] Please specify anti-phage resistance activity	[trivmo_pth y
trivmo_pth	treatment_iv_monthly_ descriptiv	Pathogen 2 "[pre_pth2_target]"	[pre_num_target_pathogen] > 1 and ([trivmo_phage_cont] = "1" or [trivmo_ph
trivmo_pth	treatment_iv_monthly_ radio	[Pathogen 2 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_t y
trivmo_pth	treatment_iv_monthly_ notes	[Pathogen 2: [pre_pth2_target]] How come isolation wasn't performed?	[trivmo_pth y
trivmo_pth	treatment_iv_monthly_ radio	[Pathogen 2 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[trivmo_pth y
trivmo_pth	treatment_iv_monthly_ notes	[Pathogen 2: [pre_pth2_target]] Please specify anti-phage resistance activity	[trivmo_pth y
trivmo_pth	treatment_iv_monthly_ radio	[Pathogen 2 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_t y
trivmo_pth	treatment_iv_monthly_ text	[Pathogen 2: [pre_pth2_target]] Specify other site where pathogen was isolat	[trivmo_pth y
trivmo_pth	treatment_iv_monthly_ radio	[Pathogen 2 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[trivmo_pth y
trivmo_pth	treatment_iv_monthly_ notes	[Pathogen 2: [pre_pth2_target]] Please specify anti-phage resistance activity	[trivmo_pth y
trivmo_pth	treatment_iv_monthly_ descriptiv	Pathogen 3 "[pre_pth3_target]"	[pre_num_target_pathogen] > 2 and ([trivmo_phage_cont] = "1" or [trivmo_ph
trivmo_pth	treatment_iv_monthly_ radio	[Pathogen 3 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_t y
trivmo_pth	treatment_iv_monthly_ notes	[Pathogen 3: [pre_pth3_target]] How come isolation wasn't performed?	[trivmo_pth y
trivmo_pth	treatment_iv_monthly_ radio	[Pathogen 3 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[trivmo_pth y
trivmo_pth	treatment_iv_monthly_ notes	[Pathogen 3: [pre_pth3_target]] Please specify anti-phage resistance activity	[trivmo_pth y
trivmo_pth	treatment_iv_monthly_ radio	[Pathogen 3 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_t y
trivmo_pth	treatment_iv_monthly_ text	[Pathogen 3: [pre_pth3_target]] Specify other site where pathogen was isolat	[trivmo_pth y
trivmo_pth	treatment_iv_monthly_ radio	[Pathogen 3 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[trivmo_pth y
trivmo_pth	treatment_iv_monthly_ notes	[Pathogen 3: [pre_pth3_target]] Please specify anti-phage resistance activity	[trivmo_pth y
trivmo_pth	treatment_iv_monthly_ descriptiv	Pathogen 4 "[pre_pth4_target]"	[pre_num_target_pathogen] > 3 and ([trivmo_phage_cont] = "1" or [trivmo_ph
trivmo_pth	treatment_iv_monthly_ radio	[Pathogen 4 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_t y
trivmo_pth	treatment_iv_monthly_ notes	[Pathogen 4: [pre_pth4_target]] How come isolation wasn't performed?	[trivmo_pth y
trivmo_pth	treatment_iv_monthly_ radio	[Pathogen 4 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[trivmo_pth y
trivmo_pth	treatment_iv_monthly_ notes	[Pathogen 4: [pre_pth4_target]] Please specify anti-phage resistance activity	[trivmo_pth y
trivmo_pth	treatment_iv_monthly_ radio	[Pathogen 4 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_t y
trivmo_pth	treatment_iv_monthly_ text	[Pathogen 4: [pre_pth4_target]] Specify other site where pathogen was isolat	[trivmo_pth y
trivmo_pth	treatment_iv_monthly_ radio	[Pathogen 4 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[trivmo_pth y
trivmo_pth	treatment_iv_monthly_ notes	[Pathogen 4: [pre_pth4_target]] Please specify anti-phage resistance activity	[trivmo_pth y
trivmo_pth	treatment_iv_monthly_ descriptiv	Pathogen 5 "[pre_pth5_target]"	[pre_num_target_pathogen] > 4 and ([trivmo_phage_cont] = "1" or [trivmo_ph
trivmo_pth	treatment_iv_monthly_ radio	[Pathogen 5 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_t y
trivmo_pth	treatment_iv_monthly_ notes	[Pathogen 5: [pre_pth5_target]] How come isolation wasn't performed?	[trivmo_pth y
trivmo_pth	treatment_iv_monthly_ radio	[Pathogen 5 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[trivmo_pth y
trivmo_pth	treatment_iv_monthly_ notes	[Pathogen 5: [pre_pth5_target]] Please specify anti-phage resistance activity	[trivmo_pth y
trivmo_pth	treatment_iv_monthly_ radio	[Pathogen 5 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_t y
trivmo_pth	treatment_iv_monthly_ text	[Pathogen 5: [pre_pth5_target]] Specify other site where pathogen was isolat	[trivmo_pth y
trivmo_pth	treatment_iv_monthly_ radio	[Pathogen 5 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[trivmo_pth y
trivmo_pth	treatment_iv_monthly_ notes	[Pathogen 5: [pre_pth5_target]] Please specify anti-phage resistance activity	[trivmo_pth y

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trivmo_wgs	treatment_ WGS	yesno	[Month [trivmo_mth]] Is WGS data available for current isolate?	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1")
trivmo_wgs	treatment_iv_monthly_	notes	[Month [trivmo_mth]] Where is the WGS data stored?	[trivmo_wgs]='1' and ([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo]
trivmo_rna	treatment_iv_monthly_	radio	[Month [tri yes, Yes/Sample obtained + stored | not_analysed,Sample proces	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1")
trivmo_rna	treatment_iv_monthly_	notes	[Month [trivmo_mth]] Where is the RNA transcriptomics data stored?	[trivmo_rnatr]='yes' and ([trivmo_phage_cont] = "1" or [trivmo_phage_stop_m
trivmo_rna	treatment_iv_monthly_	notes	[Month [trivmo_mth]] Where is the RNA transcriptomics sample stored?	([trivmo_rnatr]='yes' or [trivmo_rnatr]='not_analysed') and ([trivmo_phage_co
trivmo_met	treatment_ Metagenon	yesno	[Month [trivmo_mth]] Are clinical samples available for metagenomics?	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1")
trivmo_met	treatment_iv_monthly_	text	[Month [trivmo_mth]] Specify type of sample	[trivmo_metag_samples]='1' and ([trivmo_phage_cont] = "1" or [trivmo_phage
trivmo_met	treatment_iv_monthly_	radio	[Month [tri 1,Yes | 0, No, samples stored	[trivmo_metag_samples]='1' and ([trivmo_phage_cont] = "1" or [trivmo_phage
trivmo_met	treatment_iv_monthly_	notes	[Month [trivmo_mth]] Where is the metagenome data stored?	[trivmo_metag_has]='1' and ([trivmo_phage_cont] = "1" or [trivmo_phage_sto
trivmo_met	treatment_iv_monthly_	notes	[Month [trivmo_mth]] Where is the sample stored?	[trivmo_metag_has]='0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_sto
trivmo_kin	treatment_ Pre-dose /	text	[Pre-Dose] Phage result plaque ass integer	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1")
trivmo_kin	treatment_iv_monthly_	checkbo	[Pre-Dose] na, Plaque assays are NOT available	[trivmo_kin y
trivmo_kin	treatment_iv_monthly_	text	[Pre-Dose] Phage qPCR results (XX integer	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1")
trivmo_kin	treatment_iv_monthly_	checkbo	[Pre-Dose] na, Phage qPCR results are NOT available	[trivmo_kin y
trivmo_kin	treatment_iv_monthly_	text	[Pre-Dose] Bacterial load qPCR resu integer	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1")
trivmo_kin	treatment_iv_monthly_	checkbo	[Pre-Dose] na, Phage qPCR results are NOT available	[trivmo_kin y
trivmo_kin	treatment_ 30-60 minu	text	[30-60 minutes post-dose] Phage q integer	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1") and [trivmo_ph
trivmo_kin	treatment_iv_monthly_	checkbo	[30-60 min na, Phage qPCR results are NOT available	[trivmo_kin y
trivmo_kin	treatment_iv_monthly_	text	[30-60 minutes post-dose] Bacteria integer	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1") and [trivmo_ph
trivmo_kin	treatment_iv_monthly_	checkbo	[30-60 min na, Phage qPCR results are NOT available	[trivmo_kin y
trivmo_kin	treatment_ 2-3 hours p	text	[2-3 hours post-dose] Phage result integer	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1") and [trivmo_ph
trivmo_kin	treatment_iv_monthly_	checkbo	[2-3 hours na, Plaque assays are NOT available	[trivmo_kin y
trivmo_kin	treatment_iv_monthly_	text	[2-3 hours post-dose] Phage qPCR r integer	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1") and [trivmo_ph
trivmo_kin	treatment_iv_monthly_	checkbo	[2-3 hours na, Phage qPCR results are NOT available	[trivmo_kin y
trivmo_kin	treatment_iv_monthly_	text	[2-3 hours post-dose] Bacterial load integer	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1") and [trivmo_ph
trivmo_kin	treatment_iv_monthly_	checkbo	[2-3 hours na, Phage qPCR results are NOT available	[trivmo_kin y
othcli_no_i	other_routes_clinical_b	descriptiv	<h3><span style="background-color: #e03e2	[sc_meets_inclusion] < 1
othcli_desc	other_routes_clinical_b	descriptiv	Other Routes - Clinical This page opens when non IV and/or oral/enteral phage therapy are selected from the Treatm	
othcli_noni	other_routes_clinical_b	descriptiv	This instrument is for patients who are NOT receiving IV	([tre_ph_0_rt(iv)] = '1' or [tre_ph_0_rt(oral)] = '1') or ([tre_ph_1_rt(iv)] = '1' or
othcli_day	other_routes_clinical_b	radio	Select clinic 0, D0 | 1, D1 | 2, D2 | 3, D3 | 4, D4 | 5, D5 | 6, D6 | 7, D7 | 8, D8	[sc_meets_ y
othcli_vitals	other_routes_clinical_b	yesno	[[othcli_day]] Vitals performed 30 minutes after dose? [othcli_day]	[sc_meets_ y
othcli_devi	other_routes_clinical_b	yesno	[[othcli_day]] Protocol Deviation?	[sc_meets_ y
othcli_devi	other_routes_clinical_b	notes	[[othcli_day]] Describe the reason for deviation	[othcli_dev y
othcli_hi_fe	other_routes_clinical_b	yesno	[[othcli_day]] Did fever (temp > 37.9Â°C) occur today?	[sc_meets_ y
othcli_hi_fe	other_routes_clinical_b	text	[[othcli_day]] Specify max temp (XX number_1dp	[sc_meets_ y
othcli_hi_fe	other_routes_clinical_b	text	[[othcli_day]] Specify time of max f number_1dp	[sc_meets_ y
othcli_tach	other_routes_clinical_b	yesno	Did tachycardia occur today (yes/no)?	[sc_meets_ y
othcli_tach	other_routes_clinical_b	text	Specify max HR occurring prior to n integer	[othcli_tach y
othcli_tach	other_routes_clinical_b	text	Specify time of max HR in hours aft number_1dp	[othcli_tach y
othcli_pain	other_routes_clinical_b	yesno	Did tachycardia occur today (yes/no)?	[sc_meets_ y
othcli_pain	other_routes_clinical_b	text	Specify max HR occurring prior to n integer	[othcli_pain y

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othcli_pain	other_routes_clinical_t	text	Specify time of max HR in hours aft	number_1dp		[othcli_pair y
othcli_infla	other_routes_clinical_t	yesno	[[othcli_day]] Any other signs or symptoms of inflammatory response (yes/no			[sc_meets_ y
othcli_infla	other_routes_clinical_t	text	[[othcli_day]] Specify what occurre	number_1dp		[sc_meets_ y
othcli_infla	other_routes_clinical_t	text	[[othcli_day]] Also specify time of o	number_1dp		[sc_meets_ y
othcli_cont	other_routes_clinical_t	yesno	[[othcli_day]] Is the patient still receiving phage therapy?			[sc_meets_ y
othcli_phag	other_routes_clinical_t	radio	What has b cure, No evidence of ongoing infection: resolution of clinical symp			[othcli_con y
othcli_phag	other_routes_clinical_t	radio	Any disabili no_disability, Without persisting disability | with_disability, With p			[othcli_pha y
othcli_phag	other_routes_clinical_t	radio	Partial resp improvement, Improvement in clinical signs and symptoms, radiol			[othcli_pha y
othcli_1528	other_routes_clinical_t	yesno	[[othcli_day]] Were vitals checked each day of treatment as per protocol (yes,			[sc_meets_ y
othcli_1528	other_routes_clinical_t	yesno	[[othcli_day]] Will treatment continue >= 4 weeks (yes/no)?			[sc_meets_ y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] How many days of ph	integer	14 28	[sc_meets_ y
othcli_1528	other_routes_clinical_t	checkbox	[[othcli_day	15, D15 | 16, D16 | 17, D17 | 18, D18 | 19, D19 | 20, D20 | 21, D2		[sc_meets_ y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] Specify max temp (X	number_1dp		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] Specify max temp (X	number_1dp		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] Specify max temp (X	number_1dp		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] Specify max temp (X	number_1dp		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] Specify max temp (X	number_1dp		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] Specify max temp (X	number_1dp		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] Specify max temp (X	number_1dp		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] Specify max temp (X	number_1dp		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] Specify max temp (X	number_1dp		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] Specify max temp (X	number_1dp		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] Specify max temp (X	number_1dp		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] Specify max temp (X	number_1dp		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] Specify max temp (X	number_1dp		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] Specify max temp (X	number_1dp		[othcli_152 y
othcli_1528	other_routes_clinical_t	checkbox	[[othcli_day	15, D15 | 16, D16 | 17, D17 | 18, D18 | 19, D19 | 20, D20 | 21, D2		[sc_meets_ y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify max HR occur	integer		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify max HR occur	integer		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify max HR occur	integer		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify max HR occur	integer		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify max HR occur	integer		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify max HR occur	integer		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify max HR occur	integer		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify max HR occur	integer		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify max HR occur	integer		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify max HR occur	integer		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify max HR occur	integer		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify max HR occur	integer		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify max HR occur	integer		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify max HR occur	integer		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify max HR occur	integer		[othcli_152 y

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othcli_1528	other_routes_clinical_b	checkbox	[[othcli_day 15, D15 | 16, D16 | 17, D17 | 18, D18 | 19, D19 | 20, D20 | 21, D2	[sc_meets_ y	
othcli_1528	other_routes_clinical_b	text	[[othcli_day]] specify site of pain for D15	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_b	text	[[othcli_day]] specify site of pain for D16	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_b	text	[[othcli_day]] specify site of pain for D17	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_b	text	[[othcli_day]] specify site of pain for D18	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_b	text	[[othcli_day]] specify site of pain for D19	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_b	text	[[othcli_day]] specify site of pain for D20	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_b	text	[[othcli_day]] specify site of pain for D21	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_b	text	[[othcli_day]] specify site of pain for D22	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_b	text	[[othcli_day]] specify site of pain for D23	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_b	text	[[othcli_day]] specify site of pain for D24	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_b	text	[[othcli_day]] specify site of pain for D25	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_b	text	[[othcli_day]] specify site of pain for D26	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_b	text	[[othcli_day]] specify site of pain for D27	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_b	text	[[othcli_day]] specify site of pain for D28	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_b	checkbox	[[othcli_day 15, D15 | 16, D16 | 17, D17 | 18, D18 | 19, D19 | 20, D20 | 21, D2	[sc_meets_ y	
othcli_1528	other_routes_clinical_b	text	[[othcli_day]] specify what occurred for D15	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_b	text	[[othcli_day]] specify what occurred for D16	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_b	text	[[othcli_day]] specify what occurred for D17	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_b	text	[[othcli_day]] specify what occurred for D18	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_b	text	[[othcli_day]] specify what occurred for D19	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_b	text	[[othcli_day]] specify what occurred for D20	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_b	text	[[othcli_day]] specify what occurred for D21	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_b	text	[[othcli_day]] specify what occurred for D22	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_b	text	[[othcli_day]] specify what occurred for D23	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_b	text	[[othcli_day]] specify what occurred for D24	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_b	text	[[othcli_day]] specify what occurred for D25	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_b	text	[[othcli_day]] specify what occurred for D26	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_b	text	[[othcli_day]] specify what occurred for D27	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_b	text	[[othcli_day]] specify what occurred for D28	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_b	radio	[[othcli_day na, Not adjusted | increased, Dose increased | reduced, Dose redu	[othcli_152 y	
othro_no_i	other_routes_lab_beta	descriptiv	<h3><span style="background-color: #e03e2	[sc_meets_inclusion] < 1	
othro_desc	other_routes_lab_beta	descriptiv	Other Routes - Lab This page opens when non IV and/or oral/enteral phage therapy are selected from the Treatment		
othro_noni	other_routes_lab_beta	descriptiv	This instrument is for patients who are NOT receiving IV (	([tre_ph_0_rt(iv)] = '1' or [tre_ph_0_rt(oral)] = '1') or ([tre_ph_1_rt(iv)] = '1' or	
othro_iv	other_routes_lab_beta	yesno	Is IV phage also being administered (yes/no)?	[sc_meets_ y	
othro_day	other_routes_lab_beta	radio	Select clinic 0, D0 | 2, D2 | 4, D4 | 8, D8 | 15, D15 | 29, D29 | other,Other Day	[sc_meets_ y	
othro_othe	other_routes_lab_beta	text	Enter day of treatment (enter a nur integer	[othro_day y	
othro_othe	other_routes_lab_beta	notes	Test performed for day [othro_other_day]	[othro_oth y	
othro_othe	other_routes_lab_beta	notes	Result for day [othro_other_day]	[othro_oth y	
othro_crp	other_routi	CRP results text	[[othro_day]] CRP result (XXX.X mg number_1dp	[othro_day] >= 0 and [othro_day] and [othro_day] != 11	
othro_crp_	other_routes_lab_beta	checkbox	[[othro_day na, CRP results NOT available for [[othro_day]]	[othro_crp] y	

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othro_fbc_i	other_routi	FBC	yesno	[[othro_day]] FBC all within normal range (yes/no)?		[othro_day] and [othro_day] >= 0
othro_hb	other_routi	Hb results	text	[[othro_day]] Hb result (XXX g/L)	integer	[othro_fbc_isnorm] = '0' and [othro_day] and [othro_day] >= 0
othro_hb_r	other_routes_lab_beta	checkbo	[[othro_da	na, Hb results NOT available for [[othro_day]]		[othro_hb] y
othro_plate	other_routi	Platelet cou	text	[[othro_day]] Platelet result (XXX x	integer	[othro_fbc_isnorm] = '0' and [othro_day] and [othro_day] >= 0
othro_plate	other_routes_lab_beta	checkbo	[[othro_da	na, Platelet count results NOT available for [[othro_day]]		[othro_plat y
othro_wcc	other_routi	WCC	text	[[othro_day]] WCC (XXX x10^9/L)	integer	[othro_fbc_isnorm] = '0' and [othro_day] and [othro_day] >= 0
othro_wcc_	other_routes_lab_beta	checkbo	[[othro_da	na, WCC results NOT available for [[othro_day]]		[othro_wcc y
othro_neut	other_routi	Neutrophil	text	[[othro_day]] Neutrophil count (XX	number_1dp	[othro_fbc_isnorm] = '0' and [othro_day] and [othro_day] >= 0
othro_neut	other_routes_lab_beta	checkbo	[[othro_da	na, neutrophil count results NOT available for [[othro_day]]		[othro_neu y
othro_lymp	other_routi	Lymphocyt	text	[[othro_day]] Lymphocyte count (X	number_1dp	[othro_fbc_isnorm] = '0' and [othro_day] and [othro_day] >= 0
othro_lymp	other_routes_lab_beta	checkbo	[[othro_da	na, Lymphocyte count results NOT available for [[othro_day]]		[othro_lym y
othro_lft_is	other_routes_lab_beta	yesno	[[othro_day]] LFTs all within normal range (yes/no)?			[othro_day y
othro_albu	other_routi	Albumin	text	[[othro_day]] Albumin (XX g/L)	integer	[othro_lft_isnorm] = '0' and [othro_day] and [othro_day] >= 0 and [othro_day]
othro_albu	other_routes_lab_beta	checkbo	[[othro_da	na, Albumin results are NOT available for [[othro_day]]		[othro_albu y
othro_ast	other_routi	AST	text	[[othro_day]] AST (XXXX U/L)	integer	[othro_lft_isnorm] = '0' and [othro_day] and [othro_day] >= 0 and [othro_day]
othro_ast_	other_routes_lab_beta	checkbo	[[othro_da	na, AST results are NOT available for [[othro_day]]		[othro_ast] y
othro_alt	other_routi	ALT	text	[[othro_day]] ALT (XXXX U/L)	integer	[othro_lft_isnorm] = '0' and [othro_day] and [othro_day] >= 0 and [othro_day]
othro_alt_r	other_routes_lab_beta	checkbo	[[othro_da	na, ALT results are NOT available for [[othro_day]]		[othro_alt] y
othro_ggt	other_routi	GGT	text	[[othro_day]] GGT (XXXX U/L)	integer	([othro_lft_isnorm] = '0') and [othro_day] and [othro_day] >= 0 and [othro_da
othro_ggt_	other_routes_lab_beta	checkbo	[[othro_da	na, GGT results are NOT available for [[othro_day]]		[othro_ggt] y
othro_alp	other_routi	ALP	text	[[othro_day]] ALP (XXXX U/L)	integer	[othro_lft_isnorm] = '0' and [othro_day] and [othro_day] >= 0 and [othro_day]
othro_alp_	other_routes_lab_beta	checkbo	[[othro_da	na, ALP results are NOT available for [[othro_day]]		[othro_alp] y
othro_uec_	other_routes_lab_beta	yesno	[[othro_day]] UECs all within normal range (yes/no)?			[othro_day y
othro_sodi	other_routi	Sodium	text	[[othro_day]] Sodium (XXX mmol/L	integer	[othro_uec_isnorm] = '0' and [othro_day] and [othro_day] >= 0 and [othro_da
othro_sodi	other_routes_lab_beta	checkbo	[[othro_da	na, Sodium results are NOT available for [[othro_day]]		[othro_sodi y
othro_urea	other_routi	Urea	text	[[othro_day]] Urea (XX.X mmol/L)	number_1dp	[othro_uec_isnorm] = '0' and [othro_day] and [othro_day] >= 0 and [othro_da
othro_urea	other_routes_lab_beta	checkbo	[[othro_da	na, Urea results are NOT available for [[othro_day]]		[othro_urea y
othro_crea	other_routi	Creatinine	text	[[othro_day]] Creatinine (XXX umol	integer	[othro_uec_isnorm] = '0' and [othro_day] and [othro_day] >= 0 and [othro_da
othro_crea	other_routes_lab_beta	checkbo	[[othro_da	na, Creatinine results are NOT available for [[othro_day]]		[othro_crea y
othro_ph0	other_routes_lab_beta	descripti	Phage: "[pre_phage1_name]"			([tre_ph_0_rt(iv)] = '1' or [tre_ph_0_rt(oral)] = '1') and [pre_phage1_name] an
othro_ph_(	other_routes_lab_beta	yesno	[Phage: "[pre_phage1_name]"] Antiphage antibodies tested (yes/no)?			([tre_ph_0_ y
othro_ph_(	other_routes_lab_beta	checkbo	[Phage: "[p	neutralising,Neutralising antibody assay | igmigg, IgM/IgG assay |		[othro_ph_ y
othro_ph_(	other_routes_lab_beta	text	[Phage: "[pre_phage1_name]"] Other assay type			[othro_ph_ y @CHARLIMIT='50'
othro_ph_(	other_routes_lab_beta	notes	[Phage: "[pre_phage1_name]"] Antiphage antibody result			[othro_ph_ y
othro_ph1	other_routes_lab_beta	descripti	Phage: "[pre_phage2_name]"			([tre_ph_1_rt(iv)] = '1' or [tre_ph_1_rt(oral)] = '1') and [pre_phage2_name] an
othro_ph_1	other_routes_lab_beta	yesno	[Phage: "[pre_phage2_name]"] Antiphage antibodies tested (yes/no)?			([tre_ph_1_ y
othro_ph_1	other_routes_lab_beta	checkbo	[Phage: "[p	neutralising,Neutralising antibody assay | igmigg, IgM/IgG assay |		[othro_ph_ y
othro_ph_1	other_routes_lab_beta	text	[Phage: "[pre_phage2_name]"] Other assay type			[othro_ph_ y @CHARLIMIT='50'
othro_ph_1	other_routes_lab_beta	notes	[Phage: "[pre_phage2_name]"] Antiphage antibody result			[othro_ph_ y
othro_ph2	other_routes_lab_beta	descripti	Phage: "[pre_phage3_name]"			([tre_ph_2_rt(iv)] = '1' or [tre_ph_2_rt(oral)] = '1') and [pre_phage3_name] an
othro_ph_2	other_routes_lab_beta	yesno	[Phage: "[pre_phage3_name]"] Antiphage antibodies tested (yes/no)?			([tre_ph_2_ y

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othro_ph_2	other_routes_lab_beta checkbo	[Phage: "[p neutralising,Neutralising antibody assay | igmigg, IgM/IgG assay |	[othro_ph_ y	
othro_ph_2	other_routes_lab_beta text	[Phage: "[pre_phage3_name]"] Other assay type	[othro_ph_ y	@CHARLIMIT='50'
othro_ph_2	other_routes_lab_beta notes	[Phage: "[pre_phage3_name]"] Antiphage antibody result	[othro_ph_ y	
othro_ph3	other_routes_lab_beta descripti	Phage: "[pre_phage4_name]"	([tre_ph_3_rt(iv)] = '1' or [tre_ph_3_rt(oral)] = '1') and [pre_phage4_name] an	
othro_ph_3	other_routes_lab_beta yesno	[Phage: "[pre_phage4_name]"] Antiphage antibodies tested (yes/no)?	([tre_ph_3_ y	
othro_ph_3	other_routes_lab_beta checkbo	[Phage: "[p neutralising,Neutralising antibody assay | igmigg, IgM/IgG assay |	[othro_ph_ y	
othro_ph_3	other_routes_lab_beta text	[Phage: "[pre_phage4_name]"] Other assay type	[othro_ph_ y	@CHARLIMIT='50'
othro_ph_3	other_routes_lab_beta notes	[Phage: "[pre_phage4_name]"] Antiphage antibody result	[othro_ph_ y	
othro_ph4	other_routes_lab_beta descripti	Phage: "[pre_phage5_name]"	([tre_ph_4_rt(iv)] = '1' or [tre_ph_4_rt(oral)] = '1') and [pre_phage5_name] an	
othro_ph_4	other_routes_lab_beta yesno	[Phage: "[pre_phage5_name]"] Antiphage antibodies tested (yes/no)?	([tre_ph_4_ y	
othro_ph_4	other_routes_lab_beta checkbo	[Phage: "[p neutralising,Neutralising antibody assay | igmigg, IgM/IgG assay |	[othro_ph_ y	
othro_ph_4	other_routes_lab_beta text	[Phage: "[pre_phage5_name]"] Other assay type	[othro_ph_ y	@CHARLIMIT='50'
othro_ph_4	other_routes_lab_beta notes	[Phage: "[pre_phage5_name]"] Antiphage antibody result	[othro_ph_ y	
othro_pth1	other_routes_lab_beta descripti	Pathogen 1 "[pre_pth1_target]"	[pre_num_target_pathogen] > 0 and [othro_day] and ([othro_day] = 0 or [othr	
othro_pth_	other_routes_lab_beta radio	[Pathogen 1 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ y	
othro_pth_	other_routes_lab_beta notes	[Pathogen 1: [pre_pth1_target]] How come isolation wasn't performed?	[othro_pth_ y	
othro_pth_	other_routes_lab_beta radio	[Pathogen 1 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[othro_pth_ y	
othro_pth_	other_routes_lab_beta notes	[Pathogen 1: [pre_pth1_target]] Please specify anti-phage resistance activity	[othro_pth_ y	
othro_pth_	other_routes_lab_beta radio	[Pathogen 1 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ y	
othro_pth_	other_routes_lab_beta text	[Pathogen 1: [pre_pth1_target]] Specify other site where pathogen was isolat	[othro_pth_ y	
othro_pth_	other_routes_lab_beta radio	[Pathogen 1 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[othro_pth_ y	
othro_pth_	other_routes_lab_beta notes	[Pathogen 1: [pre_pth1_target]] Please specify anti-phage resistance activity	[othro_pth_ y	
othro_pth2	other_routes_lab_beta descripti	Pathogen 2 "[pre_pth2_target]"	[pre_num_target_pathogen] > 1 and [othro_day] and ([othro_day] = 0 or [othr	
othro_pth_	other_routes_lab_beta radio	[Pathogen 2 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ y	
othro_pth_	other_routes_lab_beta notes	[Pathogen 2: [pre_pth2_target]] How come isolation wasn't performed?	[othro_pth_ y	
othro_pth_	other_routes_lab_beta radio	[Pathogen 2 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[othro_pth_ y	
othro_pth_	other_routes_lab_beta notes	[Pathogen 2: [pre_pth2_target]] Please specify anti-phage resistance activity	[othro_pth_ y	
othro_pth_	other_routes_lab_beta radio	[Pathogen 2 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ y	
othro_pth_	other_routes_lab_beta text	[Pathogen 2: [pre_pth2_target]] Specify other site where pathogen was isolat	[othro_pth_ y	
othro_pth_	other_routes_lab_beta radio	[Pathogen 2 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[othro_pth_ y	
othro_pth_	other_routes_lab_beta notes	[Pathogen 2: [pre_pth2_target]] Please specify anti-phage resistance activity	[othro_pth_ y	
othro_pth3	other_routes_lab_beta descripti	Pathogen 3 "[pre_pth3_target]"	[pre_num_target_pathogen] > 2 and [othro_day] and ([othro_day] = 0 or [othr	
othro_pth_	other_routes_lab_beta radio	[Pathogen 3 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ y	
othro_pth_	other_routes_lab_beta notes	[Pathogen 3: [pre_pth3_target]] How come isolation wasn't performed?	[othro_pth_ y	
othro_pth_	other_routes_lab_beta radio	[Pathogen 3 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[othro_pth_ y	
othro_pth_	other_routes_lab_beta notes	[Pathogen 3: [pre_pth3_target]] Please specify anti-phage resistance activity	[othro_pth_ y	
othro_pth_	other_routes_lab_beta radio	[Pathogen 3 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ y	
othro_pth_	other_routes_lab_beta text	[Pathogen 3: [pre_pth3_target]] Specify other site where pathogen was isolat	[othro_pth_ y	
othro_pth_	other_routes_lab_beta radio	[Pathogen 3 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[othro_pth_ y	
othro_pth_	other_routes_lab_beta notes	[Pathogen 3: [pre_pth3_target]] Please specify anti-phage resistance activity	[othro_pth_ y	
othro_pth4	other_routes_lab_beta descripti	Pathogen 4 "[pre_pth4_target]"	[pre_num_target_pathogen] > 3 and [othro_day] and ([othro_day] = 0 or [othr	

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othro_pth_	other_routes_lab_beta	radio	[Pathogen 4 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_t	y
othro_pth_	other_routes_lab_beta	notes	[Pathogen 4: [pre_pth4_target]] How come isolation wasn't performed?	[othro_pth	y
othro_pth_	other_routes_lab_beta	radio	[Pathogen 4 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[othro_pth	y
othro_pth_	other_routes_lab_beta	notes	[Pathogen 4: [pre_pth4_target]] Please specify anti-phage resistance activity	[othro_pth	y
othro_pth_	other_routes_lab_beta	radio	[Pathogen 4 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_t	y
othro_pth_	other_routes_lab_beta	text	[Pathogen 4: [pre_pth4_target]] Specify other site where pathogen was isolat	[othro_pth	y
othro_pth_	other_routes_lab_beta	radio	[Pathogen 4 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[othro_pth	y
othro_pth_	other_routes_lab_beta	notes	[Pathogen 4: [pre_pth4_target]] Please specify anti-phage resistance activity	[othro_pth	y
othro_pth5	other_routes_lab_beta	descriptiv	Pathogen 5 "[pre_pth5_target]"	[pre_num_target_pathogen] > 4 and [othro_day] and ([othro_day] = 0 or [othr	
othro_pth_	other_routes_lab_beta	radio	[Pathogen 5 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_t	y
othro_pth_	other_routes_lab_beta	notes	[Pathogen 5: [pre_pth5_target]] How come isolation wasn't performed?	[othro_pth	y
othro_pth_	other_routes_lab_beta	radio	[Pathogen 5 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[othro_pth	y
othro_pth_	other_routes_lab_beta	notes	[Pathogen 5: [pre_pth5_target]] Please specify anti-phage resistance activity	[othro_pth	y
othro_pth_	other_routes_lab_beta	radio	[Pathogen 5 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_t	y
othro_pth_	other_routes_lab_beta	text	[Pathogen 5: [pre_pth5_target]] Specify other site where pathogen was isolat	[othro_pth	y
othro_pth_	other_routes_lab_beta	radio	[Pathogen 5 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[othro_pth	y
othro_pth_	other_routes_lab_beta	notes	[Pathogen 5: [pre_pth5_target]] Please specify anti-phage resistance activity	[othro_pth	y
othro_wgs	other_rout	WGS	yesno	[[othro_day]] Is WGS data available for current isolate?	[othro_day] and ([othro_day] = 0 or [othro_day] = 4 or [othro_day] = 8 or [oth
othro_wgs_	other_routes_lab_beta	notes		[[othro_day]] Where is the WGS data stored?	[othro_wgs]='1' and [othro_day] and ([othro_day] = 0 or [othro_day] = 4 or [ot
othmo_no_	other_routes_monthly_	descriptiv	<h3><span style="background-color: #e03e2	[sc_meets_inclusion] < 1	
othmo_des	other_routes_monthly_	descriptiv	Other Routes [Monthly Monitoring] Use this instrument for monthly treatment monitoring. This page opens when n		
othmo_nor	other_routes_monthly_	descriptiv	This patient does not meet IV or oral/enteral phage thera	([tre_ph_0_rt(iv)] = '1' or [tre_ph_0_rt(oral)] = '1') or ([tre_ph_1_rt(iv)] = '1' or	
othmo_mth	other_routes_monthly_	text	Month after first dose of phage adr	integer	[sc_meets_ y
othmo_pha	other_routes_monthly_	yesno	[Month [othmo_mth]] Is the patient still receiving phage therapy?	[sc_meets_ y	
othmo_pha	other_routes_monthly_	yesno	[Month [othmo_mth]] Did the patient stop phage therapy within the last mon	[othmo_ph y	
othmo_pha	other_routes_monthly_	radio	[Month [otl	cure, No evidence of ongoing infection: resolution of clinical symp	[othmo_ph y
othmo_pha	other_routes_monthly_	radio	[Month [otl	no_disability, Without persisting disability | with_disability, With p	[othmo_ph y
othmo_pha	other_routes_monthly_	radio	[Month [otl	improvement, Improvement in clinical signs and symptoms, radiol	[othmo_ph y
othmo_fbc_	other_rout	FBC	yesno	[Month [othmo_mth]] FBC all within normal range (yes/no)?	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1")
othmo_hb	other_rout	Hb results	text	[Month [othmo_mth]] Hb result (X)	integer	[othmo_fbc_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_st
othmo_hb_	other_routes_monthly_	checkbox	[Month [otl	na, Hb results NOT available [Month [othmo_mth]]	[othmo_hb y
othmo_plat	other_rout	Platelet cou	text	[Month [othmo_mth]] Platelet resu	integer	[othmo_fbc_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_st
othmo_plat	other_routes_monthly_	checkbox	[Month [otl	na, Platelet count results NOT available [Month [othmo_mth]]	[othmo_pla y
othmo_wcc	other_rout	WCC	text	[Month [othmo_mth]] WCC (XXX x	integer	[othmo_fbc_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_st
othmo_wcc	other_routes_monthly_	checkbox	[Month [otl	na, WCC results NOT available [Month [othmo_mth]]	[othmo_wc y
othmo_neu	other_rout	Neutrophil	text	[Month [othmo_mth]] Neutrophil c	number_1dp	[othmo_fbc_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_st
othmo_neu	other_routes_monthly_	checkbox	[Month [otl	na, neutrophil count results NOT available [Month [othmo_mth]]	[othmo_ne y
othmo_lym	other_rout	Lymphocyte	text	[Month [othmo_mth]] Lymphocyte	number_1dp	[othmo_fbc_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_st
othmo_lym	other_routes_monthly_	checkbox	[Month [otl	na, Lymphocyte count results NOT available [Month [othmo_mth]	[othmo_lyn y
othmo_pth	other_routes_monthly_	descriptiv	Pathogen 1 "[pre_pth1_target]"	[pre_num_target_pathogen] > 0 and ([trivmo_phage_cont] = "1" or [trivmo_ph	
othmo_pth	other_routes_monthly_	radio	[Pathogen 1 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_t	y

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othmo_pth	other_routes_monthly_notes	[Pathogen 1: [pre_pth1_target]] How come isolation wasn't performed?	[othmo_pth y
othmo_pth	other_routes_monthly_radio	[Pathogen 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[othmo_pth y
othmo_pth	other_routes_monthly_notes	[Pathogen 1: [pre_pth1_target]] Please specify anti-phage resistance activity	[othmo_pth y
othmo_pth	other_routes_monthly_radio	[Pathogen isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ y
othmo_pth	other_routes_monthly_text	[Pathogen 1: [pre_pth1_target]] Specify other site where pathogen was isolat	[othmo_pth y
othmo_pth	other_routes_monthly_radio	[Pathogen 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[othmo_pth y
othmo_pth	other_routes_monthly_notes	[Pathogen 1: [pre_pth1_target]] Please specify anti-phage resistance activity	[othmo_pth y
othmo_pth	other_routes_monthly_descripti	Pathogen 2 "[pre_pth2_target]"	[pre_num_target_pathogen] > 1 and ([trivmo_phage_cont] = "1" or [trivmo_ph
othmo_pth	other_routes_monthly_radio	[Pathogen isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ y
othmo_pth	other_routes_monthly_notes	[Pathogen 2: [pre_pth2_target]] How come isolation wasn't performed?	[othmo_pth y
othmo_pth	other_routes_monthly_radio	[Pathogen 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[othmo_pth y
othmo_pth	other_routes_monthly_notes	[Pathogen 2: [pre_pth2_target]] Please specify anti-phage resistance activity	[othmo_pth y
othmo_pth	other_routes_monthly_radio	[Pathogen isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ y
othmo_pth	other_routes_monthly_text	[Pathogen 2: [pre_pth2_target]] Specify other site where pathogen was isolat	[othmo_pth y
othmo_pth	other_routes_monthly_radio	[Pathogen 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[othmo_pth y
othmo_pth	other_routes_monthly_notes	[Pathogen 2: [pre_pth2_target]] Please specify anti-phage resistance activity	[othmo_pth y
othmo_pth	other_routes_monthly_descripti	Pathogen 3 "[pre_pth3_target]"	[pre_num_target_pathogen] > 2 and ([trivmo_phage_cont] = "1" or [trivmo_ph
othmo_pth	other_routes_monthly_radio	[Pathogen isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ y
othmo_pth	other_routes_monthly_notes	[Pathogen 3: [pre_pth3_target]] How come isolation wasn't performed?	[othmo_pth y
othmo_pth	other_routes_monthly_radio	[Pathogen 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[othmo_pth y
othmo_pth	other_routes_monthly_notes	[Pathogen 3: [pre_pth3_target]] Please specify anti-phage resistance activity	[othmo_pth y
othmo_pth	other_routes_monthly_radio	[Pathogen isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ y
othmo_pth	other_routes_monthly_text	[Pathogen 3: [pre_pth3_target]] Specify other site where pathogen was isolat	[othmo_pth y
othmo_pth	other_routes_monthly_radio	[Pathogen 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[othmo_pth y
othmo_pth	other_routes_monthly_notes	[Pathogen 3: [pre_pth3_target]] Please specify anti-phage resistance activity	[othmo_pth y
othmo_pth	other_routes_monthly_descripti	Pathogen 4 "[pre_pth4_target]"	[pre_num_target_pathogen] > 3 and ([trivmo_phage_cont] = "1" or [trivmo_ph
othmo_pth	other_routes_monthly_radio	[Pathogen isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ y
othmo_pth	other_routes_monthly_notes	[Pathogen 4: [pre_pth4_target]] How come isolation wasn't performed?	[othmo_pth y
othmo_pth	other_routes_monthly_radio	[Pathogen 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[othmo_pth y
othmo_pth	other_routes_monthly_notes	[Pathogen 4: [pre_pth4_target]] Please specify anti-phage resistance activity	[othmo_pth y
othmo_pth	other_routes_monthly_radio	[Pathogen isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ y
othmo_pth	other_routes_monthly_text	[Pathogen 4: [pre_pth4_target]] Specify other site where pathogen was isolat	[othmo_pth y
othmo_pth	other_routes_monthly_radio	[Pathogen 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[othmo_pth y
othmo_pth	other_routes_monthly_notes	[Pathogen 4: [pre_pth4_target]] Please specify anti-phage resistance activity	[othmo_pth y
othmo_pth	other_routes_monthly_descripti	Pathogen 5 "[pre_pth5_target]"	[pre_num_target_pathogen] > 4 and ([trivmo_phage_cont] = "1" or [trivmo_ph
othmo_pth	other_routes_monthly_radio	[Pathogen isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ y
othmo_pth	other_routes_monthly_notes	[Pathogen 5: [pre_pth5_target]] How come isolation wasn't performed?	[othmo_pth y
othmo_pth	other_routes_monthly_radio	[Pathogen 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[othmo_pth y
othmo_pth	other_routes_monthly_notes	[Pathogen 5: [pre_pth5_target]] Please specify anti-phage resistance activity	[othmo_pth y
othmo_pth	other_routes_monthly_radio	[Pathogen isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ y
othmo_pth	other_routes_monthly_text	[Pathogen 5: [pre_pth5_target]] Specify other site where pathogen was isolat	[othmo_pth y

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othmo_pth	other_routes_monthly_	radio	[Pathogen 5	1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc			[othmo_pth	y
othmo_pth	other_routes_monthly_	notes	[Pathogen 5: [pre_pth5_target]] Please specify anti-phage resistance activity				[othmo_pth	y
othmo_wgs	other_route	WGS	yesno	[Month [othmo_mth]] Is WGS data available for current isolate?			([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1")	
othmo_wgs	other_routes_monthly_	notes	[Month [othmo_mth]] Where is the WGS data stored?				[othmo_wgs]='1' and ([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo]	
ae_no_inclu	adverse_events_beta	descriptiv	<h3><span style="background-color: #e03e2				[sc_meets_inclusion] < 1	
ae_date_of	adverse_events_beta	text	Date of Event â€" this is a change!	date_dmy				y
ae_day_of_	adverse_events_beta	text	If still receiving phage therapy, spec	integer	1			
ae_last_dos	adverse_events_beta	radio	Did the pati	1, Yes, within 72 hours (<= 72h) | 2, No				y
ae_hours_s	adverse_events_beta	text	If last dose	If last dose of phage ad	number_1d	0	72	[ae_last_do y
ae_days_sir	adverse_events_beta	text	If last dose	of phage administered a	number_1d	0	180	[ae_last_do y
ae_phages_	adverse_events_beta	checkbox	Which phag	phage1,phage1 | phage2,phage2 | phage3,phage3 | phage4,phage4 | phage5				y
ae_meddra	adverse_events_beta	text	Event term	BIOPORTAL:MEDDRA				
ae_details	adverse_events_beta	notes	Details of Event					y
ae_severity	adverse_events_beta	radio	Severity (m	1, Mild | 2, Moderate | 3, Severe				y
ae_is_serio	adverse_events_beta	yesno	Is this a Serious Adverse Event?					y
ae_serious_	adverse_events_beta	checkbox	How does e	1, Resulted in death | 2, Was immediately life threatening | 3, Rec			[ae_is_seric	y
ae_has_rep	adverse_events_beta	checkbox	Confirm SA	1, Yes, I have reported to the trial sponsor			[ae_is_seric	y
ae_related_	adverse_events_beta	radio	Is adverse e	1, Unrelated | 2, Unlikely | 3, Possible | 4, Probably | 5, Definite				y
ae_related_	adverse_events_beta	checkbox	What phag	0, Other trial-related procedure (e.g. blood draw) | phage1,phage			[ae_related	y
ae_has_cor	adverse_events_beta	checkbox	Confirm Se	1, Yes, I have confirmed with the site PI			[ae_is_seric	y
ae_is_susar	adverse_events_beta	yesno	Does event qualify as a SUSAR?				[ae_is_seric	y
ae_has_rep	adverse_events_beta	checkbox	<div class=""	1, Yes, SUSAR reported to Sponsor, Chair of the DSMB, and the CP			[ae_is_seric	y
ae_req_tre	adverse_events_beta	notes	Any required treatment or evaluation?					
ae_final_ou	adverse_events_beta	radio	Final outco	1, Resolution | 2, Stabilisation | 3, No longer clinically significant | 4, Participa				y
ae_date_fir	adverse_events_beta	text	Date of final outcome	date_dmy				
wd_no_incl	withdrawal_beta	descriptiv	<h3><span style="background-color: #e03e2				[sc_meets_inclusion] < 1	
wd_reason	withdrawal_beta	radio	Withdrawal	1, Participant completed trial including at least 6 month follow-up			[sc_meets_	y
wd_withdra	withdrawal_beta	text	Date of Withdrawal	date_dmy			[sc_meets_	y
fp_no_inclu	followup_beta	descriptiv	<h3><span style="background-color: #e03e2				[sc_meets_inclusion] < 1	
fp_has_6m	followup_beta	yesno	Was follow-up performed at least 6 months after completion of phage therap				[sc_meets_	y
fp_no_follo	followup_beta	notes	Why wasn't followup performed?				[sc_meets_	y
fp_months_	followup_beta	radio	How long a	1, 1 month after completion | 2, 2 months | 3, 3 months | 4, 4 mo			[sc_meets_	y
fp_months_	followup_beta	radio	How long a	1, 6 months after completion | 2, 6-12 months | 3, > 12 months			[sc_meets_	y
fp_last_visi	followup_beta	text	Date of final follow-up visit	date_dmy			[sc_meets_	y
fp_clinical_	followup_beta	radio	What clinic	1, Cure - no evidence of ongoing infection: resolution of clinical sy			[sc_meets_	y
fp_resp_cu	followup_beta	radio	If Cure:	0, Without persisting disability | 1, With persisting disability			[sc_meets_	y
fp_resp_pa	followup_beta	radio	If Partial re	1, Improvement in clinical signs and symptoms, radiological or lab			[sc_meets_	y
fp_has_ae_	followup_beta	radio	Have all AE	1, Yes | 0, No | 2, Not sure			[sc_meets_	y
fp_has_ae_	followup_beta	radio	Have all SA	1, Yes | 0, Did not receive | 2, Received but did not complete			[sc_meets_	y
fp_has_qol	followup_beta	radio	Has the par	1, Yes | 0, Did not receive | 2, Received but did not complete			[sc_meets_	y
fp_msg_ask	followup_beta	notes	Please ask participant if they are happy to complete the QoL survey now				[sc_meets_inclusion] = "1" and [fp_has_qol_survey] != "1"	

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fp_3mo_pt	followup_beta	radio	For particip	1, Yes | 0, Did not receive | 2, Received but did not complete | 3,	[sc_meets_inclusion] = "1"
abx_no_inc	antibiotics_beta	descriptiv	<h3><span style="background-color: #e03e2		[sc_meets_inclusion] < 1
abx_name	antibiotics_beta	dropdow	Antibiotic n	1, amikacin | 2, amoxyc	autocomplete [sc_meets_ y
abx_other	antibiotics_beta	text	Other antibiotic		[sc_meets_ y @CHARLIMIT=50
abx_usage	antibiotics_beta	checkbox	Specify anti	used_prev, Used previously | used_curr, Used currently | use_cor	[sc_meets_ y
abx_admin	antibiotics_beta	checkbox	How is [abx	aero, Aerosolised / Nebulised | instl, Instillation | iv, Intravenous (	[sc_meets_ y
abx_admin	antibiotics_beta	text	Specify administration method		[sc_meets_ y @CHARLIMIT='50'
abx_pth1_c	antibiotics_beta	descriptiv	Pathogen 1		[sc_meets_inclusion] = "1" and [pre_num_target_pathogen] > 0
abx_pth1_p	antibiotics_beta	yesno	[Pathogen 1] Is phage-antibiotic synergy testing data available for [abx_name]		[abx_name y
abx_pth1_p	antibiotics_beta	yesno	[Pathogen 1] Is phage-antibiotic synergy testing data available for [abx_name]		[abx_name y
abx_pth1_p	antibiotics_beta	descriptiv	[Pathogen 1] :: Phage: "[pre_phage1_name]"		[pre_phage1_name] and [pre_num_phage]>0 and ([abx_pth1_pxb_data_spc] c
abx_pth1_p	antibiotics_beta	yesno	[Pathogen 1] Data available against phage: "[pre_phage1_name]"?		[pre_phage y
abx_pth1_p	antibiotics_beta	radio	[Pathogen 1	synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth1_ y
abx_pth1_p	antibiotics_beta	notes	[Pathogen 1] Additional phage-antibiotic-pathogen synergy notes against pha		([abx_pth1_ y
abx_pth1_p	antibiotics_beta	descriptiv	[Pathogen 1] :: Phage: "[pre_phage2_name]"		[pre_phage2_name] and [pre_num_phage]>1 and ([abx_pth1_pxb_data_spc] c
abx_pth1_p	antibiotics_beta	yesno	[Pathogen 1] Data available against phage: "[pre_phage2_name]"?		[pre_phage y
abx_pth1_p	antibiotics_beta	radio	[Pathogen 1	synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth1_ y
abx_pth1_p	antibiotics_beta	notes	[Pathogen 1] Additional phage-antibiotic-pathogen synergy notes against pha		([abx_pth1_ y
abx_pth1_p	antibiotics_beta	descriptiv	[Pathogen 1] :: Phage: "[pre_phage3_name]"		[pre_phage3_name] and [pre_num_phage]>2 and ([abx_pth1_pxb_data_spc] c
abx_pth1_p	antibiotics_beta	yesno	[Pathogen 1] Data available against phage: "[pre_phage3_name]"?		[pre_phage y
abx_pth1_p	antibiotics_beta	radio	[Pathogen 1	synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth1_ y
abx_pth1_p	antibiotics_beta	notes	[Pathogen 1] Additional phage-antibiotic-pathogen synergy notes against pha		([abx_pth1_ y
abx_pth1_p	antibiotics_beta	descriptiv	[Pathogen 1] :: Phage: "[pre_phage4_name]"		[pre_phage4_name] and [pre_num_phage]>3 and ([abx_pth1_pxb_data_spc] c
abx_pth1_p	antibiotics_beta	yesno	[Pathogen 1] Data available against phage: "[pre_phage4_name]"?		[pre_phage y
abx_pth1_p	antibiotics_beta	radio	[Pathogen 1	synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth1_ y
abx_pth1_p	antibiotics_beta	notes	[Pathogen 1] Additional phage-antibiotic-pathogen synergy notes against pha		([abx_pth1_ y
abx_pth1_p	antibiotics_beta	descriptiv	[Pathogen 1] :: Phage: "[pre_phage5_name]"		[pre_phage5_name] and [pre_num_phage]>4 and ([abx_pth1_pxb_data_spc] c
abx_pth1_p	antibiotics_beta	yesno	[Pathogen 1] Data available against phage: "[pre_phage5_name]"?		[pre_phage y
abx_pth1_p	antibiotics_beta	radio	[Pathogen 1	synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth1_ y
abx_pth1_p	antibiotics_beta	notes	[Pathogen 1] Additional phage-antibiotic-pathogen synergy notes against pha		([abx_pth1_ y
abx_pth2_c	antibiotics_beta	descriptiv	Pathogen 2		[sc_meets_inclusion] = "1" and [pre_num_target_pathogen] > 1
abx_pth2_p	antibiotics_beta	yesno	[Pathogen 2] Is phage-antibiotic synergy testing data available for [abx_name]		[abx_name y
abx_pth2_p	antibiotics_beta	yesno	[Pathogen 2] Is phage-antibiotic synergy testing data available for [abx_name]		[abx_name y
abx_pth2_p	antibiotics_beta	descriptiv	[Pathogen 2] :: Phage: "[pre_phage1_name]"		[pre_phage1_name] and [pre_num_phage]>0 and ([abx_pth2_pxb_data_spc] c
abx_pth2_p	antibiotics_beta	yesno	[Pathogen 2] Data available against phage: "[pre_phage1_name]"?		[pre_phage y
abx_pth2_p	antibiotics_beta	radio	[Pathogen 2	synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth2_ y
abx_pth2_p	antibiotics_beta	notes	[Pathogen 2] Additional phage-antibiotic-pathogen synergy notes against pha		([abx_pth2_ y
abx_pth2_p	antibiotics_beta	descriptiv	[Pathogen 2] :: Phage: "[pre_phage2_name]"		[pre_phage2_name] and [pre_num_phage]>1 and ([abx_pth2_pxb_data_spc] c
abx_pth2_p	antibiotics_beta	yesno	[Pathogen 2] Data available against phage: "[pre_phage2_name]"?		[pre_phage y
abx_pth2_p	antibiotics_beta	radio	[Pathogen 2	synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth2_ y
abx_pth2_p	antibiotics_beta	notes	[Pathogen 2] Additional phage-antibiotic-pathogen synergy notes against pha		([abx_pth2_ y

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abx_pth2_p	antibiotics_beta	descripti	[Pathogen 2] :: Phage: "[pre_phage3_name]"	[pre_phage3_name] and [pre_num_phage]>2 and ([abx_pth2_pxb_data_spc] c
abx_pth2_p	antibiotics_beta	yesno	[Pathogen 2] Data available against phage: "[pre_phage3_name]"?	[pre_phage y
abx_pth2_p	antibiotics_beta	radio	[Pathogen 2 synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth2_ y
abx_pth2_p	antibiotics_beta	notes	[Pathogen 2] Additional phage-antibiotic-pathogen synergy notes against pha	([abx_pth2_ y
abx_pth2_p	antibiotics_beta	descripti	[Pathogen 2] :: Phage: "[pre_phage4_name]"	[pre_phage4_name] and [pre_num_phage]>3 and ([abx_pth2_pxb_data_spc] c
abx_pth2_p	antibiotics_beta	yesno	[Pathogen 2] Data available against phage: "[pre_phage4_name]"?	[pre_phage y
abx_pth2_p	antibiotics_beta	radio	[Pathogen 2 synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth2_ y
abx_pth2_p	antibiotics_beta	notes	[Pathogen 2] Additional phage-antibiotic-pathogen synergy notes against pha	([abx_pth2_ y
abx_pth2_p	antibiotics_beta	descripti	[Pathogen 2] :: Phage: "[pre_phage5_name]"	[pre_phage5_name] and [pre_num_phage]>4 and ([abx_pth2_pxb_data_spc] c
abx_pth2_p	antibiotics_beta	yesno	[Pathogen 2] Data available against phage: "[pre_phage5_name]"?	[pre_phage y
abx_pth2_p	antibiotics_beta	radio	[Pathogen 2 synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth2_ y
abx_pth2_p	antibiotics_beta	notes	[Pathogen 2] Additional phage-antibiotic-pathogen synergy notes against pha	([abx_pth2_ y
abx_pth3_c	antibiotics_beta	descripti	Pathogen 3	[sc_meets_inclusion] = "1" and [pre_num_target_pathogen] > 2
abx_pth3_p	antibiotics_beta	yesno	[Pathogen 3] Is phage-antibiotic synergy testing data available for [abx_name]	[abx_name y
abx_pth3_p	antibiotics_beta	yesno	[Pathogen 3] Is phage-antibiotic synergy testing data available for [abx_name]	[abx_name y
abx_pth3_p	antibiotics_beta	descripti	[Pathogen 3] :: Phage: "[pre_phage1_name]"	[pre_phage1_name] and [pre_num_phage]>0 and ([abx_pth3_pxb_data_spc] c
abx_pth3_p	antibiotics_beta	yesno	[Pathogen 3] Data available against phage: "[pre_phage1_name]"?	[pre_phage y
abx_pth3_p	antibiotics_beta	radio	[Pathogen 3 synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth3_ y
abx_pth3_p	antibiotics_beta	notes	[Pathogen 3] Additional phage-antibiotic-pathogen synergy notes against pha	([abx_pth3_ y
abx_pth3_p	antibiotics_beta	descripti	[Pathogen 3] :: Phage: "[pre_phage2_name]"	[pre_phage2_name] and [pre_num_phage]>1 and ([abx_pth3_pxb_data_spc] c
abx_pth3_p	antibiotics_beta	yesno	[Pathogen 3] Data available against phage: "[pre_phage2_name]"?	[pre_phage y
abx_pth3_p	antibiotics_beta	radio	[Pathogen 3 synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth3_ y
abx_pth3_p	antibiotics_beta	notes	[Pathogen 3] Additional phage-antibiotic-pathogen synergy notes against pha	([abx_pth3_ y
abx_pth3_p	antibiotics_beta	descripti	[Pathogen 3] :: Phage: "[pre_phage3_name]"	[pre_phage3_name] and [pre_num_phage]>2 and ([abx_pth3_pxb_data_spc] c
abx_pth3_p	antibiotics_beta	yesno	[Pathogen 3] Data available against phage: "[pre_phage3_name]"?	[pre_phage y
abx_pth3_p	antibiotics_beta	radio	[Pathogen 3 synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth3_ y
abx_pth3_p	antibiotics_beta	notes	[Pathogen 3] Additional phage-antibiotic-pathogen synergy notes against pha	([abx_pth3_ y
abx_pth3_p	antibiotics_beta	descripti	[Pathogen 3] :: Phage: "[pre_phage4_name]"	[pre_phage4_name] and [pre_num_phage]>3 and ([abx_pth3_pxb_data_spc] c
abx_pth3_p	antibiotics_beta	yesno	[Pathogen 3] Data available against phage: "[pre_phage4_name]"?	[pre_phage y
abx_pth3_p	antibiotics_beta	radio	[Pathogen 3 synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth3_ y
abx_pth3_p	antibiotics_beta	notes	[Pathogen 3] Additional phage-antibiotic-pathogen synergy notes against pha	([abx_pth3_ y
abx_pth3_p	antibiotics_beta	descripti	[Pathogen 3] :: Phage: "[pre_phage5_name]"	[pre_phage5_name] and [pre_num_phage]>4 and ([abx_pth3_pxb_data_spc] c
abx_pth3_p	antibiotics_beta	yesno	[Pathogen 3] Data available against phage: "[pre_phage5_name]"?	[pre_phage y
abx_pth3_p	antibiotics_beta	radio	[Pathogen 3 synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth3_ y
abx_pth3_p	antibiotics_beta	notes	[Pathogen 3] Additional phage-antibiotic-pathogen synergy notes against pha	([abx_pth3_ y
abx_pth4_c	antibiotics_beta	descripti	Pathogen 4	[sc_meets_inclusion] = "1" and [pre_num_target_pathogen] > 3
abx_pth4_p	antibiotics_beta	yesno	[Pathogen 4] Is phage-antibiotic synergy testing data available for [abx_name]	[abx_name y
abx_pth4_p	antibiotics_beta	yesno	[Pathogen 4] Is phage-antibiotic synergy testing data available for [abx_name]	[abx_name y
abx_pth4_p	antibiotics_beta	descripti	[Pathogen 4] :: Phage: "[pre_phage1_name]"	[pre_phage1_name] and [pre_num_phage]>0 and ([abx_pth4_pxb_data_spc] c
abx_pth4_p	antibiotics_beta	yesno	[Pathogen 4] Data available against phage: "[pre_phage1_name]"?	[pre_phage y
abx_pth4_p	antibiotics_beta	radio	[Pathogen 4 synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth4_ y

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abx_pth4_p	antibiotics_beta	notes	[Pathogen 4] Additional phage-antibiotic-pathogen synergy notes against pha	([abx_pth4_ y
abx_pth4_p	antibiotics_beta	descripti	[Pathogen 4] :: Phage: "[pre_phage2_name]"	[pre_phage2_name] and [pre_num_phage]>1 and ([abx_pth4_pxb_data_spc] c
abx_pth4_p	antibiotics_beta	yesno	[Pathogen 4] Data available against phage: "[pre_phage2_name]"?	[pre_phage y
abx_pth4_p	antibiotics_beta	radio	[Pathogen 4 synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth4_ y
abx_pth4_p	antibiotics_beta	notes	[Pathogen 4] Additional phage-antibiotic-pathogen synergy notes against pha	([abx_pth4_ y
abx_pth4_p	antibiotics_beta	descripti	[Pathogen 4] :: Phage: "[pre_phage3_name]"	[pre_phage3_name] and [pre_num_phage]>2 and ([abx_pth4_pxb_data_spc] c
abx_pth4_p	antibiotics_beta	yesno	[Pathogen 4] Data available against phage: "[pre_phage3_name]"?	[pre_phage y
abx_pth4_p	antibiotics_beta	radio	[Pathogen 4 synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth4_ y
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PROTOCOL

Standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy

Short title: Standardised Treatment and Monitoring of Phage therapy (STAMP)

Version: 1

Date: 20/12/2021

For peer review only

CONFIDENTIAL

This document is confidential and the property of the Phage Australia Network. No part of it may be transmitted, reproduced, published, or used without prior written authorisation from the institution.

Statement of Compliance

This document is a protocol for a research project. This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

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ADMINISTRATIVE INFORMATION

1. TITLE

Standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy

Short title: Standardised Treatment and Monitoring of Phage therapy (STAMP)

2. TRIAL REGISTRATION

2A REGISTRY

anzctr.org:

2B DATA SET

Data Category	**Information**
Primary registry and study identifying number	anzctr.org
Date of registration in primary registry	
Secondary identifying numbers	WHO UTN: U1111-1269-6000
Source(s) of monetary or material support	Medical Research Futures Fund (Australia) Frontiers Stage 1 (RFRHPI000017; Iredell) National Health and Medical Research Council (Australia) Investigator Grant (APP1197534; Iredell)
Primary Sponsor	Western Sydney Local Health District
Contact for public queries	Ameneh Khatami (ameneh.khatami@health.nsw.gov.au)
Contact for scientific queries	Ameneh Khatami (ameneh.khatami@health.nsw.gov.au)
Public title	Standardised Treatment and Monitoring of Phage therapy (STAMP)
Scientific title	Standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy
Countries of recruitment	Australia

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Data Category	Information
Health condition(s) or problem(s) studied	Any infectious syndrome requiring bacteriophage therapy
Intervention(s)	A standardised treatment and monitoring protocol for bacteriophage therapy
Key inclusion and exclusion criteria	**Inclusion criteria (all must be present):** 1) Patient with confirmed bacterial infection, for whom at least **two** appropriately qualified clinical specialists, including at least one specialist in infection management and one with experience of phage therapy, have agreed that available anti-infective therapy and source control has been optimised and that adjunctive phage therapy should be offered. 2) A suitable phage(s) product is available that complies with all relevant regulatory requirements for therapeutic administration, including at least Therapeutic Goods Administration (TGA) Special Access Scheme (SAS) notification **Exclusion criteria:** 1) Participant or person responsible has not provided informed consent 2) Participant unable or unlikely to adhere to schedule of monitoring and follow-up
Study type	Open-label, single arm trial of a standardised treatment and monitoring protocol
Date of first enrolment	January 2022
Target sample size	50-100 participants over 5 years
Primary outcome	Safety and tolerability of phage therapy (defined as absence serious adverse events attributable to phage therapy) assessed 2 weeks after completion of therapy

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Data Category	Information
Key secondary outcomes	1) Long-term safety and tolerability of phage therapy (defined as absence of serious adverse events, or any adverse events attributable to phage therapy) assessed 6 months after completion of phage therapy. 2) Feasibility of a standardised protocol as assessed by the proportion of participants with >80% of Minimum Data Requirements available for analysis. **Exploratory outcomes (assessed across the total cohort and subgroups of participants):** 1) Clinical response to phage therapy assessed 2 weeks after completion of therapy 2) Patient satisfaction of outcome assessed at multiple time-points during and after completion of therapy 3) Microbiological clearance of target pathogen(s), as defined by bacterial cultures of relevant sites a. Proportion with documented clearance and time to clearance b. Emergence of anti-phage resistance on treatment 4) Laboratory markers of phage and host responses, including: a. Phage pharmacokinetics b. Antibody development c. Host immune responses 5) Changes in microbiome assessed by metagenomics during and after completion of therapy

3. Protocol Version

Issue Date:	**Version 1, 30 September 2021**
Protocol amendment number:	**N/A**
Author(s):	**Ameneh Khatami** **Jonathan Iredell**

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	Steven Tong **Morgyn Warner** **Anton Peleg** **Thomas Snelling** **Elizabeth Barnes (independent statistician)** **Phage Australia Clinical Stream Committee members**

Revision Chronology:

Date of change (N/A)	Summary of changes (N/A)

4. Funding

Initial set-up costs for the trial, including database design and development and project management, are funded by a Medical Research Futures Fund (MRFF) Frontiers Stage 1 grant (RFRHPI000017; PHAGE AUSTRALIA: Integrating Australian Phage Biobanking and Therapeutic Networks and Delivering Solutions for Antimicrobial Resistance, CIA Iredell).

Local phage product development including Good Manufacturing Practice (GMP)-grade therapeutic products, and development of companion diagnostics are supported by the MRFF Frontiers Stage 1 grant, and a National Health and Medical Research Council Investigator Grant (GNT1197534: Positive Solutions for Critical Infection, CIA Iredell).

Phage and companion diagnostics support may come from research and professional partners, provided they are fit for purpose and satisfy all national, state and local institutional requirements as determined by authorities responsible for clinical and research governance and for regulating the provision and quality control of diagnostic and therapeutic goods.

Patients included in this trial may receive therapeutic phage products sourced from industry partners/commercial suppliers provided on “compassionate grounds”.

All investigators provide their time and expertise as in-kind contributions without payment. Local Health Districts (LHDs) and Health Networks cover the costs of inpatient and outpatient care of patients according to usual standards.

5. Roles and Responsibilities

5a Contributorship

AK and JI conceived the study. AK, JI, ST and MW initiated the study design and protocol development. JI is a grant holder. TS and EZ provided statistical expertise. All authors contributed to refinement of the study protocol.

5b Sponsor Contact Information

Study Sponsor	Western Sydney Local Health District
Contact name	Sharon Lee
Address	WSLHD Research and Education Network, Clinical Trials Support Unit, Westmead Hospital, Hawkesbury Road, Westmead NSW 2145
Telephone	02 8890 9942,

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Study Sponsor	Western Sydney Local Health District
Email	WSLHD-ClinicalTrialsSupportUnit@health.nsw.gov.au

5C Sponsor and Funder

The study Sponsor delegates responsibility for study design; collection, management, analysis, and interpretation of data; writing of the report and the decision to submit the report for publication to the CPI and the Trial Steering Committee (TSC). Any funding body involved in the trial will not have any role in these responsibilities.

5D Committees

1. Investigator Group
    a. Co-ordinating Principal Investigator: Jonathan Iredell
    b. Principal Investigators (PIs) for clinical recruitment sites
        i. Westmead Hospital: Jonathan Iredell
        ii. Sydney Children's Hospitals Network: Ameneh Khatami
        iii. The Alfred Hospital: Anton Peleg
        iv. Royal Melbourne Hospital: Steven Tong
        v. Central Adelaide Local Health Network: Morgyn Warner
        vi. Royal Brisbane and Women's Hospital: David Paterson
        vii. Queensland Children's Hospital: Adam Irwin
        viii. Fiona Stanley Hospital, Murdoch: Christopher Heath
        ix. Perth Children's Hospital: Stephen Stick
    c. Principal Investigators (PIs) for research institutes and laboratories where participant samples may be processed
        i. Westmead Institute for Medical Research: Jonathan Iredell
        ii. Monash Centre to Impact Antimicrobial Resistance: Anton Peleg
        iii. Telethon Kid's Institute: Stephen Stick
        iv. The Doherty Institute: Deborah Williamson

2. The TSC will be the Clinical Stream Steering Committee of Phage Australia, a multidisciplinary group that, collectively, have experience/expertise in the management of patients with condition(s) relevant to the study, pathways for use of phage therapy, anticipated adverse events, and in the conduct and monitoring of randomised clinical trials. Co-conveners are Steven Tong (Victoria), Ameneh Khatami (New South Wales [NSW], paediatrics), Morgyn Warner (South Australia). The committee also includes members with statistical expertise and stakeholder representatives including consumer representatives and NSW Ministry of Health representatives. Details of membership and specified roles and responsibilities are outlined in the Terms of Reference for this Committee.

3. A Data Safety Monitoring Board will include a chair with management experience in clinical trials and 5 additional members, of whom at least 1 will be paediatrician, at least 1 will be an adult physician and at least 1 will have established clinical expertise in the delivery of phage therapy. Additional details of membership and specified roles and responsibilities are outlined in the Terms of Reference for the DSMB. The DSMB will have access to all safety data available at the time of each meeting. They will be asked to review the data and make a recommendation to the CPI and site PIs within 4 weeks of the meeting. Review of the safety data may result in a recommendation for:

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- Cessation of the trial for all participants or for a subgroup (e.g. only paediatric participants, participants treated for a specific indication, or participants from a given site)
- Interim suspension while reviewing the data in more detail
- Modification of the trial
- Continuation of the trial

INTRODUCTION

6. BACKGROUND AND RATIONALE

Antibiotics are now failing due to growing antimicrobial resistance (AMR) which at least doubles mortality and health care costs of infection. Without novel solutions, AMR infections are predicted to be the leading cause of death by 2050, cost US$30 billion annually in lost productivity of the global economy, and threaten many advances in medicine(*1*). A key unmet need is for new strategies to manage difficult-to-treat infections, including chronic infections in cystic fibrosis (CF), other infections that respond poorly to antibiotics (e.g. prosthetic device infections) and highly drug resistant infections.

Bacteriophages (phages) are viruses that naturally infect and kill bacteria. Phages prey equally well on antibiotic-sensitive and -resistant bacteria and offer a novel (non-antibiotic) approach to treat infections. Unlike antibiotics that kill both disease-causing and beneficial bacteria leaving the patient vulnerable to other pathogens(*2*), the highly selective bacterial killing by phages reduces their impact on our healthy microbiome(*3*), as well as the risk of further increasing drug resistance. Phages do not attack human cells and phage therapy has a proven safety record, offering hope for people with highly drug resistant infections(*4-10*). Other critical advantages over antibiotics include the ability of phages to kill bacteria in biofilms (bacteria that hide away in a layer of slime, often on artificial surfaces) when antibiotics typically cannot(*11*), since phages are unaffected by the mechanisms that shield bacteria in biofilms from antibiotics(*12*). Biofilms are present in a wide variety of human infections and are usual in CF and on infected prosthetic devices and artificial heart valves(*13*).

Phages can be used in combination with antibiotics or substitute for them when antibiotics fail and can even be used to restore the potency of failing antibiotics(*14-16*). **Currently, phage therapy is not in wide use because there is no experience outside of a few centres in the world; standardised therapeutic protocols are lacking; there is a paucity of rigorous clinical trial data assessing efficacy and phages are generally not readily available in sufficiently purified form for use.** We and others(*5*) have built on a century of international experience to prove the value of phage therapy after antibiotic failure in severe sepsis(*6, 8*), bladder(*9*) and bone infection(*10*), and in CF [manuscript in preparation]. Our group were the first in the world to use intravenous (IV) phages in a systematic trial in severe infection in adults and thus gained new insights into dosing, disposition in the body (kinetics of distribution and clearance) and effects on the immune system(*8*). In parallel, we have established a program for compassionate access to phage therapy for children at Sydney Children's Hospitals Network (SCHN) and this protocol represents a national expansion of this programme for adults and children, providing a standardised treatment and monitoring protocol, and linked to a national database to facilitate standardised data collection. This will allow rapid and efficient data generation without wastage of a currently "scarce" resource, and will strengthen the evidence base, including for dosing and monitoring, required to establish phage therapy in the national formulary.

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A standardised treatment and monitoring protocol for Australian adult and paediatric patients receiving bacteriophage therapy is proposed, with no comparator arm. Patients included are those who have exhausted other therapeutic options for control of their infection and are being treated with phage products according to the special access scheme (SAS) as determined by the Australian Therapeutic Goods Administration (TGA) – so-called "compassionate access". Patients who are assessed to be suitable for phage therapy will receive this as outlined in this protocol, as an adjunct to routine clinical care. **The purpose of the study is to standardise therapeutic management and data collection, including safety and tolerability, in this setting and to assess the feasibility of such a standardised protocol.**

7. Study Objectives

a. **Primary Objective**: To determine the short-term safety and tolerability of phage therapy in adults and children with bacterial infections

b. **Secondary Objectives**:

   i. To determine the long-term safety and tolerability of phage therapy in adults and children with bacterial infections

   ii. To assess the feasibility of a standardised protocol used for the administration and monitoring of phage therapy in adults and children

c. **Exploratory Objectives:**

   i. To describe proportions of patients with good clinical response to phage therapy, assessed 2 weeks after completion of therapy, across the cohort of participants and according to clinical indication

   ii. To describe patient-reported quality-of-life indicators during and after phage therapy across the cohort of participants and according to clinical indication using a validated Patient Reported Outcome Measures (PROMs) tool (EQ-5D-5L/EQ-5D-Y)

   iii. To describe proportions of patients with microbiological clearance, and time to clearance, across the cohort of participants and according to clinical indication

   iv. To describe the rate of phage resistance emergence while on therapy

   v. To explore pharmacokinetics (distribution and clearance kinetics) of phages administered via different routes and according to different dosing schedules

   vi. To explore innate and adaptive immune responses to phage therapy (include age-related differences) administered via different routes and for different clinical indications

   vii. To explore optimal dosing schedules and durations for phage products used according to different routes of administration (IV, oral, nebulised/aerosolised, topical) for different clinical indications

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viii. To explore key biomarkers that can be used as diagnostic surrogates of clinical efficacy

ix. To explore significant differences between different phage products used for the same clinical indication with respect to phage pharmacokinetics, innate and adaptive immune responses, safety and tolerability and clinical efficacy

x. To explore microbiome changes as assessed by non-human metagenomics of available clinical samples during and after completion of phage therapy.

8. Study Design

Open-label, single-arm trial investigating a standardised treatment and monitoring protocol for phage therapy, with multiple subgroups stratified according to clinical indication and route of administration of phages (see section 11A – Interventions).

Methods: Participants, Interventions, Outcomes

9. Study Setting

Participants can be recruited from any hospital (public or private) in Australia, where ethics and site-specific approval has been gained. Participants can be treated as inpatients or outpatients.

9.1 Study sites

Study sites will be selected based on:

1) Access to appropriate facilities and staff to undertake the full treatment and monitoring protocol according to all regulatory approvals (e.g. physical containment [PC] level 2 facilities for use of a GMO phage, if applicable)
2) An identified site PI with experience in phage therapy or infection management.
3) A site feasibility survey is completed and approved by the Trial Steering Committee

10. Eligibility Criteria

10.1 **Inclusion Criteria for Participants** (all must be present):

1. Patient with confirmed bacterial infection, for whom at least **two** appropriately qualified clinical specialists, including at least one specialist in infection management and one with experience of phage therapy, have agreed that available anti-infective therapy and source control has been optimised and that adjunctive phage therapy should be offered (see section 11.2 below). The assessment of the need for/suitability for phage therapy will be based on clinical criteria and will not constitute a research activity.
2. Suitable phage(s) product (with lytic activity against the target pathogen/s) is available that complies with all relevant regulatory requirements for therapeutic administration. These requirements may include:
   i. Local hospital/network drug committee and/or Executive board approval (or equivalent), as applicable
   ii. Therapeutic Goods Administration (TGA) special access scheme (SAS) notification **(required)**
   iii. Bicon Permit from the Department of Agriculture for importation of phage products from international suppliers, if applicable

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iv. Material Transfer Agreement (MTA) that may be required from third-party suppliers of phage products, if applicable
v. Licence to handle and administer genetically modified organisms (GMOs) from the Office of the Gene Technology Regulator, if applicable
vi. Any other local requirements as determined by the primary medical professional caring for the patient (Primary Clinician) or hospital/network Executive board

Selection and sourcing of the phage product to be administered will be based on clinical criteria and will not constitute a research activity.

10.2 **Exclusion criteria for Participants:**

1. Participant, parent or guardian or person responsible has not provided informed consent.
2. Participant unable or unlikely to adhere to schedule of monitoring and follow-up

11. INTERVENTIONS

11A INTERVENTIONS

11.1 Summary of research activities

This protocol will be embedded within standard clinical care. The following table provides a summary of research activities and standard clinical activities that will be occurring simultaneously.

Table 1: Summary research and clinical activities that occur during phage therapy

Clinical activities	**Research activities**
Decision to access phage therapy	Confirming eligibility of patients to participate, including ensuring suitable phage(s) product (with lytic activity against the target pathogen/s) is available.
Choice of appropriate phage to be administered Route and duration of phage therapy*	Route and duration of phage therapy* Dosing schedule and dose adjustments
Regulatory oversight including TGA SAS notification, hospital drug committee/executive approval (see section 10.1)	Human research ethics committee (HREC) and site-specific approvals
All other healthcare decisions including adjunctive antibiotics, other medications, investigations for underlying health conditions, allied health interventions and standard of care for monitoring investigations for infections.	Schedule of monitoring **relevant to phage therapy**
Frequency of follow-up visits and ongoing monitoring.	Collection of data regarding adverse events during phage therapy and follow-up
	Systematic collection of data to create a registry of phage use in Australia

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* Route and duration of phage therapy will be a joint decision between the site PI (research activity) and the Primary Clinician (standard clinical activity)

11.2 Participant identification and referral pathway

Patients for whom phage therapy may be suitable can be identified by any medical professional caring for the patient (Primary Clinician). Each case must be discussed with and approved by at least one infectious diseases specialist who is relevantly clinically privileged at that recruitment site, and who must ensure optimised anti-infective therapy and infection source control. This "approval" can be by consultation with an infectious diseases specialist or **can** be undertaken by the Primary Clinician if they are so qualified. A second specialist (site PI) must approve and take responsibility for the phage therapy administered according to this protocol. If the available site PI is operating outside their usual professional scope of practice (for example, non-infectious disease specialist) and cannot reasonably take that clinical responsibility, the case should be referred to a suitably experienced PI operating within their normal scope of practice, including by telemedicine consultation, according to the normal rules that govern such consultations. If the site PI is the Primary Clinician, the case must be discussed with one other infectious disease specialist at the site, or at a referral centre. If all inclusion criteria can be met for the patient to be included, the following data should be obtained and entered on the study REDCap database (electronic case report form; eCRF). *Minimum Data Requirements.

11.2.1 Screening logs

Site PIs should maintain a record of all patients referred for inclusion in the trial including the outcome of assessment for eligibility. Screening for eligibility will occur prior to obtaining consent to participate (see also section 10 above). For patients who are not included in the trial, the reason for this should be clearly documented in a screening log:

i) Antibiotic therapy sub-optimal to date/viable alternative antibiotic therapy available
ii) Source control sub-optimal
iii) Polymicrobial infection (>2 key pathogens)
iv) Pathogen driving infectious syndrome not appropriately confirmed
v) Phage product identified unsuitable
    1. Phage activity against target pathogen(s) limited/undocumented
    2. Formulation not safe for clinical use
    3. Regulatory approvals not completed
vi) Patient/parent or guardian/responsible person unable or unlikely to adhere to schedule of treatment and monitoring
vii) Other (specify)

11.3 Pre-treatment work-up/data

11.3.1 Clinical

i) Primary infectious diagnosis (site of infection, confirmed or potential pathogens, presence of prosthetic material etc.)*

ii) Current/planned/ongoing adjunctive antibiotics*

iii) Other interventions performed to control the infection (source control)

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iv) Additional medical or surgical conditions that directly impact management of the infection (e.g. CF in a patient with lung infection)*

v) Immune suppressive conditions or therapies*

vi) Indication for phage therapy as assessed by clinical team*
   (1) Intolerance of standard therapy due to side effects, and/or
   (2) Failure of standard therapy, and/or
   (3) Extensive drug resistance profile of target pathogen(s), and/or
   (4) Other (to be specified)

11.3.2 Microbiology

i) Culture confirmation from site of infection. If the site of infection is not directly accessible, alternative sites may be sampled if it is reasonable to assume these represent pathogen(s) at the site of infection (e.g. blood culture)*

ii) Phage-bacteria matching (degree of lytic activity between selected phage(s) and target pathogen(s)*. This can be performed at the study site if this service is available within an appropriately accredited laboratory, or within Phage Australia partner sites (e.g. at the Westmead Institute for Medical Research, NSW, the Doherty Institute, Victoria, or the Department of Infectious Diseases laboratory at the Alfred Hospital, Victoria), or by third party phage suppliers (including commercial suppliers, either in Australia or internationally). This may be facilitated by external partners such as Phage Directory (https://phage.directory) and will be confirmed by an appropriately accredited Australian laboratory.

iii) Whole genome sequencing (WGS) of main pathogen(s) according to laboratory standard operating procedures (SOP), and identification of prophages.

iv) WGS of phage(s) to be used

v) Phage-bacteria-antibiotic synergy testing according to laboratory SOP. Lytic activity of suitable phage(s) to be tested against the pathogen of interest in the presence of adjunctive antibiotics as determined through consultation between the Primary Clinician and infectious disease specialists with whom the case has been discussed (see section 11.1 and 11.2 above). This can be performed at the study site if this service is available within an appropriately accredited laboratory, or within Phage Australia partner sites (e.g. at the Westmead Institute for Medical Research, NSW, the Doherty Institute, Victoria, or the Department of Infectious Diseases laboratory at the Alfred Hospital, Victoria).

11.4 Treatment and Monitoring Protocols

The specific phage product to be administered will be determined jointly by the Primary Clinician and Infectious Disease(s) specialist involved in the care of the patient, including consultation with the site PI responsible for oversight of phage therapy according to this protocol (see sections 10.1 and 11.2).

The optimal duration and route of administration of phage will be determined individually for each patient by the PI involved (see section 11.2 above) and will depend on the site of infection, confirmed or suspected pathogens, patient factors (e.g. immune compromise, IV access) and availability of phage products (e.g. formulation, purification).

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For intravenously administered phage, the dose will be determined by the endotoxin level of the phage product, keeping below accepted human pyrogenic threshold of 5 EU/kg per dose set by the United States Food and Drug Administration (FDA). Within this limit, the aim is to administer at least 10^9 plaque forming units (pfu) of the phage at each dose. 10^9 pfu/dose is aimed to achieve a multiplicity of infection (MOI; number of phage virions per bacterial target) of 10-100 per bacterium in the bloodstream for common bacteraemias.

If multiple routes of administration are used, the total dose administered at the same time must not exceed the endotoxin limit outlined above. For enteral, aerosolised/nebulised or topical administration of phage a dose limit has not been determined but is likely to be considerably higher. If a non-intravenous route is selected as the primary route of administration (not just as an adjunct to IV administration), the aim is to administer at least 10^{10} pfu/dose.

All other care, including adjunctive antibiotics or other medications to be administered, investigations (radiology, laboratory or other), allied health interventions, etc., will be according to routine clinical care and will be determined by the Primary Clinician and the Infectious Disease specialist(s) directly involved in the care of the patient.

11.4.1 Clinical monitoring:

- Full physical examination within 24 hours prior to starting phage therapy (any route of administration)
- Measurement of "vitals" (heart rate [HR], respiratory rate [RR], blood pressure [BP], oxygen saturation, temperature) within 15 minutes prior to, and then 15 and 30 minutes after each dose of phage administered. For patients receiving only topical or nebulised/aerosolised phage products where minimal systemic absorption is expected, only one set of vital signs are required 30 minutes after administration of the phage product.
- Additional clinical monitoring will be according to routine clinical care.

11.4.2 Timing of phage doses:

Frequency of phage doses to be administered for patients receiving 14 days of phage therapy is outlined in Table 2 below. Morning doses should be administered at the same time each day, preferably between 6-10am. On days where twice daily dosing is used, these should be administered 12 hours (+/- 2 hours) apart. Multiple routes of administration may be appropriate for individual patients e.g. IV and nebulised phage therapy for lung infections. For critically unwell patients where urgent control of infection is needed, initial twice daily dosing may be used (i.e. from day 1) after discussion with the site PI. Day of treatment refers to a working day, starting at 6am. Day 0 is any time within 24 hours prior to first dose of phage.

Invasive routes of administration (e.g. intra-articular or endobronchial), should be considered additional to the primary route of administration (e.g. IV) with timing and frequency of such administration determined by the Primary Clinician and the infectious disease specialists/PI involved in the care of the patient.

For patients planned to receive phage therapy for longer than 14 days, dosing frequency will be determined taking into consideration practical limitations. For example, long-term hospital in the home administration of phage therapy may only be possible once daily.

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For patients receiving only non-systemically administered phage products where minimal systemic distribution (i.e. viremic dissemination) is expected phage(s) should be administered once daily throughout the course to facilitate outpatient setting administration. The timing of non-systemic administration will be determined by the Primary Clinician and the infectious disease specialists/PI involved in the care of the patient.

11.4.3 Laboratory monitoring:

Table 2 outlines laboratory monitoring required for the first 4 weeks in patients receiving 14 days of intravenous phage therapy (majority of participants). Patients receiving oral/enteral therapy should also follow this protocol. Each of the tests listed are included in the Minimum Data Requirements for phage therapy. If it is not practical to obtain samples according to this protocol (e.g. difficult to access site of infection, difficult venous access in young children) this should be discussed with the site PI and reasons documented in the eCRF.

If abnormalities are detected (including worsening of prior abnormalities) on any blood sample that were not present at baseline, these should be followed-up beyond the intervention period (day 0-29) until resolution with frequency of monitoring determined by the Primary Clinician and the infectious disease specialists involved in the care of the patient.

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Table 2: Treatment and laboratory monitoring protocol for standard two-week intravenous/oral phage therapy

Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	29
Phage doses		OD	OD	BD	BD	BD	BD	BD	BD	BD	BD	BD	BD	BD	BD		
CRP	X		X		X				X							X	X
ESR	X				X				X							X	X
Procalcitonin (if available)	X		X		X				X							X	
FBC	X		X		X				X			X				X	X
Lymphocyte subsets	X		X		If lymphopenic[£]				If lymphopenic			If lymphopenic				If lymphopenic	If lymphopenic
LFTs	X		X		X				X							X	X
UECs	X		X		X				X							X	X
Phage antibodies*	X											X				X	X
Total IgG	X															X	X
C3, C4, CH50	X															X	X
Cultures**	X				X				X							X	X
Phage susceptibility***	X				X				X							X	X
Kinetics****			X		X				X			X				X	X
Transcriptomics and metagenomics	X		X		X				X			X				X	X

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Day 0 – up to 24 hours prior to first dose of phage; OD – once daily; BD – twice daily; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; FBC – full blood count; LFTs – liver function tests; EUCs – electrolytes, urea, creatinine; IgG – total immunoglobulin G; C3, C4, CH50 – complement levels.

Tests in bold are those available in routine clinical laboratories and considered standard of care for monitoring treatment of infections. Although the timing for these tests has been specified according to this protocol to enable standardisation of data collection and analysis, the tests can and should be performed in an appropriately accredited clinical laboratory linked to the recruitment site, as per usual care.

* Phage antibodies - antibodies against relevant therapeutic phages, measured in order to define risk of antibody-mediated neutralisation and/or immune responses. This can be performed at the study site if this service is available within an appropriately accredited laboratory according to SOP, or within Phage Australia partner sites (e.g. at the Westmead Institute for Medical Research, NSW, the Doherty Institute, Victoria, or the Department of Infectious Diseases laboratory at the Alfred Hospital, Victoria), or by third party phage suppliers (including commercial suppliers, either in Australia or internationally).

** For invasive samples baseline (day 0) and post-treatment (day 15) samples are sufficient for monitoring. For patients known or suspected to be bacteraemic at the start of phage therapy, blood cultures should be obtained daily until bacteraemia resolves.

*** All positive cultures of the target pathogen(s) that are isolated after day 1 should be reassessed for ongoing phage-susceptibility, and should have whole genome sequencing performed according to lab SOP.

**** Kinetics - see details in Table 4 and section 11.4.6

[£] Lymphopenia will be defined as <1.0 x 10^9/L in individuals aged >12 years, <1.5 x10^9/L in children aged 1-12 years, <4.0 x10^9/L for infants aged 1-12 months, and <3.0 x10^9/L for neonates <1 month.

11.4.4 Ongoing monitoring for long-term systemic phage therapy

For patients planned to receive long-term phage therapy (longer than 14 days), ongoing monitoring will be performed on a monthly basis until 1 month after the end of phage therapy. The following samples and tests will be required for ongoing monthly monitoring for patients receiving >14 days of phage therapy.

- **C-reactive protein**
- **Full blood count**
- **Liver function tests**
- **Urea, creatinine and electrolytes**
- **Total IgG**
- **Complement levels: C3, C4, CH50**
- **Relevant microbiological cultures**
- Phage susceptibility of ongoing positive cultures - All positive cultures of the target pathogen(s) that are isolated after day 1 should be reassessed for ongoing phage-susceptibility, and should have whole genome sequencing performed according to lab SOP.
- Kinetics - see details in Table 4 and section 11.4.6
- Transcriptomics and metagenomics

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- Anti-phage antibodies – measured according to lab SOP.

Tests in bold are those available in routine clinical laboratories and considered standard of care for monitoring treatment of infections. These tests can and should be performed in an appropriately accredited clinical laboratory linked to the recruitment site, as per usual care.

11.4.5 Laboratory monitoring for non-systemic therapy

For patients receiving only non-systemically administered phage products where minimal systemic distribution is expected (e.g. topical administration to a wound, or nebulised/aerosolised therapy), Table 3 outlines the laboratory monitoring required for the first 4 weeks. Each of the tests listed are included in the Minimum Data Requirements for phage therapy. If it is not practical to obtain samples according to this protocol (e.g. difficult to access site of infection, difficult venous access in young children) this should be discussed with the site PI and reasons documented in the eCRF.

Table 3: Treatment and laboratory monitoring protocol for standard two-week non-systemic phage therapy

Day	0	1	2	3	4	5-7	8	9-14	15	29
Phage doses		OD	OD	OD	OD	OD	OD	OD		
CRP	X		X		X		X		X	
FBC	X		X		X		X		X	X
LFTs	X						X		X	
UECs	X						X		X	
Phage antibodies	X								X	X
Cultures*	X						X		X	X
Phage susceptibility**	X						X		X	X

OD – once daily; CRP – C-reactive protein; FBC – full blood count; LFTs – liver function tests; EUCs – electrolytes, urea, creatinine.

* For invasive samples baseline (day 0) and post-treatment (day 15) samples are sufficient for monitoring.

** All positive cultures of the target pathogen(s) that are isolated after day 1 should be reassessed for ongoing phage-susceptibility, and should have whole genome sequencing performed according to lab SOP.

Tests in bold are those available in routine clinical laboratories and considered standard of care for monitoring treatment of infections. These tests can and should be performed in an appropriately accredited clinical laboratory linked to the recruitment site, as per usual care.

For patients planned to receive long-term phage therapy (>14 days), ongoing monitoring will be performed on a monthly basis until 1 month after the end of phage therapy. The following samples and tests will be required for ongoing monthly monitoring for patients receiving >14 days of non-systemic phage therapy:

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- Full blood count - should be performed in an appropriately accredited clinical laboratory linked to the recruitment site, as per usual care.
- Relevant microbiological cultures and phage susceptibility of ongoing positive cultures - All positive cultures of the target pathogen(s) that are isolated after day 1 should be reassessed for ongoing phage-susceptibility, and should have whole genome sequencing performed according to lab SOP.

11.4.6 Timing of blood samples:

All blood samples should be collected in the morning, prior to the first dose of phage, unless otherwise specified (e.g. post-dose samples for kinetics).

"Kinetics bloods" refers to quantification of phage and bacterial loads in patient blood/serum for patients receiving systemic therapy. These should be determined according to SOP by plaque assay (phage) and quantitative polymerase chain reaction (qPCR; phage and bacteria). The timing of kinetics bloods is outlined in Table 4.

Table 4: Timing of blood samples for quantification of phage and bacterial loads ("kinetics bloods") during phage therapy

	Immediately prior to phage dose	30-60 minutes after phage dose	2-3 hours after phage dose
Phage (plaque assay)	X		X
Phage (qPCR)	X	X	X
Bacteria (qPCR)	X	X	X

All 3 time-points (prior to dose, 30 minutes and 2 hours post-dose) should be drawn for "kinetics" on days 2, 4, 8 and 11. On days 15 and 29, only a single blood draw in the morning is required as no further phage doses will be administered.

11.4.7 Microbiological surveillance

Bacterial cultures should be obtained from the site of infection (or representative site) as outlined above. This may include cultures from blood, urine, sputum, swabs or other clinical specimens. For invasive samples other than blood or routine endotracheal aspirates (e.g. bronchoalveolar lavage or surgical biopsies) baseline (day 0) and post-treatment (day 15) samples are sufficient for monitoring. For patients known or suspected to be bacteraemic at the start of phage therapy, blood cultures should be obtained daily until bacteraemia resolves.

Metagenomics will be performed on clinical samples including blood (as well as sputum, urine, faeces or other samples that may have been collected) to investigate changes in the microbiome during treatment. The analysis pipeline will be restricted to non-human genetic material and will only be used to determine the microbiome of various clinical specimens during and after phage therapy, including endogenous phages.

11.4.8 Quality-of life questionnaire

A quality-of-life questionnaire will be sent to participants via a survey link in REDCap on days 0 (baseline) and 29, 2 weeks after completion of the 14-day course of phage therapy, and again at 3 and

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6 months (from start of phage therapy). For patients receiving longer than 3 months of phage therapy, the survey link will also be sent out at 12 months.

A validated PROMs tool (EQ-5D-5L/EQ-5D-Y) will be used as the basis of the questionnaire (see section 30 in Appendices) and will ask participants to grade various indicators for quality of life before receiving phage therapy, during and after completion of the course of treatment. Responses to the quality-of life- questionnaires will be reviewed by the site PI within 2 weeks of completion for each participant.

11.4.9 RNA samples

Whole blood should be obtained for analysis of human transcriptome according to SOP, using a panel that includes both innate and adaptive immune response markers. Analysis will be restricted to immune response genes only.

11.4.10 Long-term follow-up

All participants will be followed-up by the Primary Clinician for a minimum of 6 months after completion of phage therapy. Frequency of follow-up visits will be determined by the Primary Clinician based on the underlying clinical condition (according to routine clinical care). As a minimum, patients should be reviewed clinically, with additional investigations (laboratory or radiology) also determined by the Primary Clinician based on the underlying clinical condition (according to routine clinical care).

11B MODIFICATIONS

11.5 Criteria for modifying phage dose:

Evidence of severe immune-related phenomena after infusion may be criteria for cessation of therapy, as for any severe adverse reaction (see section 20 – Adverse Events Monitoring). Decisions regarding cessation of phage therapy will be made by the Primary Clinician in consultation with the PI based on clinical judgement. The reason for cessation of therapy will be documented in the eCRF. Early cessation of phage therapy will not constitute a withdrawal criterion from the trial for a participant (see 11.6 below) and every effort should be made by the PI to continue all other monitoring of the patient as per the protocol to ensure data integrity and safety monitoring.

Phage levels in the blood prior to re-dosing may be used to determine dosage adjustments(*10*). Doses may be adjusted on the basis of qPCR results for bacteria and phage, or plaque assay for phage, in consultation with the PI. Dose adjustment should be considered in the following scenarios, but should also take into consideration clinical response to treatment at the time.

Table 5: Criteria for consideration of changes to phage doses administered daily

Current dosing schedule	Pre-dose serum phage level by plaque assay	Adjustment
Once daily	$<10^2$ pfu/mL	Increase to twice daily dosing
Once daily	$\geq 10^2$ pfu/mL	Continue once daily dosing
Twice daily	$<10^2$ pfu/mL	Continue twice daily dosing
Twice daily	$\geq 10^2$ pfu/mL	Reduce to once daily dosing

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For patients receiving a cocktail of more than one phage, dose adjustments of the whole cocktail should be based on results obtained for the phage with the lowest detectable level of circulating viable phage.

11.6 Criteria for withdrawal of participants:

- Withdrawal of consent – a participant or their parent/guardian/person responsible may withdraw consent to participate in the trial at any point. Any data obtained prior to withdrawal of consent will be retained and the reason for withdrawal recorded in the eCRF. Routine clinical care of the patient will continue, and may include ongoing use of phage for clinical purposes. They will be given the options of:
    - Withdrawing from all subsequent monitoring samples and subsequent collection of clinical data
    - Withdrawing from all subsequent monitoring samples but allowing continued collection of clinical data
- Loss to follow-up – if a non-admitted patient is unable to be contacted (e.g. during the period of follow-up) after multiple attempts to contact them, including at least 3 phone calls and a letter mailed to their last known address, they will be assumed to be lost to follow-up. Any data collected up to that time will remain part of the study data.
- Cessation or dose-modification of phage therapy for medical reasons will not be a criterion for withdrawal from the trial and ongoing monitoring of the participant should continue as per the protocol (see section 11.5 above).

11c Ensuring Adherence to the Interventions

The first two weeks of intravenous phage therapy will be administered in hospital by clinical staff (nursing, pharmacy, medical) and monitored as per SOP and good clinical practice (as outlined in section 11a – Interventions). If phage therapy is planned for longer than two weeks, further treatment can be administered via "Hospital in the Home"-like services. Purely topical, aerosolised or oral/enteral administration of phage can occur in the outpatient setting but must be administered by qualified clinical staff (nursing, pharmacy, medical).

All doses of phage therapy administered will be prescribed by a suitably qualified doctor, dispensed from the hospital pharmacy and recorded in standard medical records (electronic or paper). Additionally, this information will be recorded on the eCRF, including modifications to the dosing schedule or early cessation of therapy.

11d Concomitant Care

Normal optimal anti-infective therapy, including optimised antibiotic and surgical therapy (e.g. source control), vouched for and managed by the responsible/consulting ID physician, is a condition of enrolment and should be recorded on the eCRF. Antibiotic synergy and antagonism (with phage/s) will be tested *in vitro* as soon as feasible. *In vitro* findings of antagonistic phage-antibiotic combinations will be notified to the responsible clinical team and will necessitate review of phage and/or antibiotic therapy.

All other care, including other medications to be administered, investigations (radiology, laboratory or other), allied health interventions, etc., will be according to routine clinical care and will be determined by the Primary Clinician and the infectious disease specialists directly involved in the care of the patient.

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12. Outcomes and Endpoints

Primary outcome: Short-term Safety

We have previously reported the safe use of bacteriophages in severe sepsis and septic shock(*8*) but phage therapy is still classified as experimental. Although there is 100 years of safety data, there are very few definitive randomised clinical trials (RCTs) and previously undetected adverse events may be uncovered by a more rigorous measurement regime, such as we define herein.

Safety and tolerability will be assessed through adverse events (AEs), vital signs, and clinical laboratory assessments. All AEs will be assessed for severity, causality, and seriousness and will be elicited and assessed from the first dosing until 6 months after the last dose of phage. The PI and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or serious AE (SAE) and remain responsible for following up SAEs that are considered related to the phage therapy or study procedures. The PI is responsible for reporting all SAEs that are observed or reported during the trial, regardless of their clinical significance or relatedness to the administered phage.

Safety will be defined by the absence of serious adverse events (SAEs) attributable to study material (phage). As phages do not attack or integrate into mammalian cells, AEs related to phage therapy are predominantly expected during active administration or shortly thereafter. As such the **primary endpoint** for safety assessments will be any SAE attributable to phage therapy occurring from day 1 (first dose of phage administered) until 2 weeks after completion of therapy (day 29 for patients receiving 14 days of therapy).

Further details regarding assessing and reporting AEs is provided in section 20 – Adverse Events Monitoring.

Secondary outcomes

1) *Additional safety outcomes*

During the follow-up period (2 weeks-6 months after the last dose of phage) only non-serious AEs considered by the investigator to be related to phage therapy, or any SAEs will be reported. These will be ascertained through discussion with the Primary Clinician undertaking the 6-month follow-up and/or review of medical records 6 months following the last dose of phage administered.

Secondary safety endpoints will thus be any SAE OR any AE attributable to phage therapy occurring from day 1 (first dose of phage administered) until 6 months after completion of phage therapy.

2) *Feasibility*

Feasibility of using a standardised treatment and monitoring protocol will be assessed as the proportion of participants with >80% of Minimum Data Requirements available for analysis. Minimum Data Requirements are outlined in section 11 above and will vary according to course of phage therapy administered. The **feasibility endpoint** will be assessed at least 2 weeks after completion of phage therapy.

Exploratory outcomes

We have previously demonstrated eradication of pathogens in settings in which it was unexpected and this can be used as a surrogate for clinical efficacy. The heterogeneity of the casemix and the lack

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of a control arm (in this non-comparative study design) makes clinical efficacy difficult to assess. The data we develop here will allow the best quality design of formal RCTs and help to inform regulatory reviews.

1) Clinical response to phage therapy

Defined as:

1) Cure – no evidence of ongoing infection: resolution of all clinical symptoms and signs of infection, radiological and laboratory parameters of infection, and microbiological clearance of target pathogen from site of infection (excludes any symptoms, signs, or abnormal radiological and laboratory parameters associated with underlying disease)
    a. Without persisting disability
    b. With persisting disability
2) Partial response
    a. Improvement in clinical signs and symptoms, radiological or laboratory parameters of disease, but with evidence that infection is not completely resolved
    b. Stabilisation of previously documented decline in function, but without obvious improvements, and evidence that infection is not completely resolved
3) No response – evidence of ongoing infection with worsening clinical signs and symptoms, radiological or laboratory parameters of disease

Clinical endpoint: Good clinical response will be defined as all participants assessed as "cured" or with "partial response" at least 2 weeks after completion of phage therapy.

2) Quality-of-life indicators

Participants will be asked to complete a brief quality-of-life questionnaire using a validated PROMs tool (EQ-5D-5L/EQ-5D-Y) (see section 30 in Appendices). This will ask participants to grade various indicators for quality of life before receiving phage therapy, during and after completion of the course of treatment (see section 11.4.8).

Quality-of-life-endpoints: Changes in EQ-5D-5L/EQ-5D-Y results from baseline to each subsequent assessment (day 29, 3, 6 or 12 months after starting phage therapy).

3) Microbiological clearance of target pathogen(s)

As defined by bacterial cultures of relevant sites (see section 11.4.3-11.4.5 above and Tables 2 and 3). Emergence of anti-phage resistance on treatment will be assessed with all positive cultures of the target pathogen(s) that are isolated after day 1 of treatment reassessed for ongoing phage-susceptibility.

Microbiological endpoints include:

- Time to clearance - day of first negative culture, measured from first day of phage therapy, among participants with sustained clearance (at least 2 consecutive negative cultures with no further positive cultures during the intervention and follow-up period)
- Proportion of participants with sustained microbiological clearance by the end of the intervention period (including up to day 29) – defined as at least 2 consecutive negative cultures by day 29.

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4) Phage kinetics over time, antibody development, host immune responses

Dosing strategies at first assume simple clearance – that is, the initial volume of distribution is a simple function of phage delivery/penetration and the clearance is a simple function of usual mechanisms (innate effector cells, renal clearance, non-specific inactivation of viral particles in different body fluids and compartments). However, both (i) phage amplification in target bacterial populations that change over time (predator-prey dynamic that waxes and wanes in a manner that is unique to every single infection), and (ii) development of acquired immune clearance (e.g. neutralising antibodies, likely to vary with individuals) may influence phage kinetics and dose adjustments may be made in response to diagnostic data(*8, 10*). Finally, the host immune response may vary as a function of all these or be independent of them – and significant beneficial immunomodulation may occur in severe sepsis(*8*) and in chronic sepsis(*10*).

These data are observational in nature but are essential for both safety monitoring and for design of future studies. Phage kinetics and human host immune responses as assessed by transcriptomics will be assessed for patients receiving intravenous/oral phage. Anti-phage neutralising/total antibodies will be measured for all patients receiving phage in any formulation (see sections 11.4.3-11.4.5 above and Tables 2 and 3).

5) Microbiome changes

Metagenomics will be performed on any available clinical samples (blood, sputum, urine, faeces or other samples that may have been collected) to investigate changes in the microbiome during treatment. The analysis pipeline will be restricted to non-human genetic material and will only be used to determine the microbiome of various clinical specimens during and after phage therapy, including endogenous phages.

13. Participant Timeline

Figure 1: Schedule of enrolment, interventions, and assessments for each participant

	STUDY PERIOD			
	Enrolment	**Intervention**		**Follow-up**
TIMEPOINT	***-4w* to Day 0***	***Day 1-14*****	***Day 15-29***	***Day 30-210******
ENROLMENT:				
Eligibility screen	X			
Informed consent	X			
Pre-treatment work-up*	X			
Determination of duration and route of phage administration	X			
PHAGE THERAPY**		X		
MONITORING:***				
Blood and clinical sampling	X	X	X	
Quality-of-life questionnaire		X	X	X
Adverse Event Reporting		X	X	X

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* Pre-treatment work-up (as outlined in section 11.3) should be performed within 4 weeks of starting phage therapy. If there is a delay (e.g. time required to source phage, or meet legal or regulatory requirements) pre-treatment work up should be repeated within 4 weeks of starting phage therapy. Any invasive sampling or other assessments that are impractical or unsafe to repeat may be referred to the most recently available investigation.

** For some patients, the duration of phage therapy may be longer than 14 days as determined by the PI/infectious disease specialist. Details of phage therapy administration and monitoring are outlined in section 11.4 above.

*** For patients receiving longer than 14 days of phage therapy, long term follow-up will be for 6 months after completion of phage therapy. Details of phage therapy administration and monitoring are outlined in section 11.4 above.

14. Sample Size

This is an open-label, single-arm clinical trial. All eligible participants that are identified will be recruited until the trial end-date (31 December 2026). No sample-size calculation has been determined. It is estimated that in the first 2 years of the study, 1-4 participants may be recruited at each study site. In subsequent years, greater numbers of participants may be identified and additional study sites will be open for recruitment. The aim is to have 50-100 participants recruited over the 5 years of the study. A study of at least 50 participants receiving phage therapy will enable the proportion who experience an SAE attributable to phage therapy (SARs) to be estimated with a 95% confidence interval (CI) of maximum width ±15%. If the proportion is low the CI will be narrower, and if no participants in 50 experience any such SAE we can be confident that the rate is not higher than 7% (95% CI of 0-7%).

We expect the rate of SARs to be <5%. If 20% or more participants suffer an SAE attributable to the therapy (SARs) then the treatment may not be considered acceptably safe in its current form. An analysis of the first 30 participants who are followed at least one month after commencing treatment has 80% statistical power at 5% one-sided alpha to rule out a rate of 20% or higher if the true rate is 5% or lower, using an exact one-sample binomial test. If 3 or more of these 30 participants have experienced an SAE attributable to therapy (SAR) then consideration will be given to stopping or modifying the study due to safety concerns. Otherwise, recruitment will continue to the target of 50-100 participants to collect data on other outcomes.

15. Recruitment

Participants will be recruited from any hospital (private or public) which is an eligible study site and where human research ethics committee (HREC), governance and all other regulatory approvals are in place (see section 10 – Eligibility Criteria). Outpatient and inpatient healthcare settings (including hospital-in-the-home-like services) will be supported as appropriate, as defined in section 11.4 above. Regional, remote and rural settings will be supported to participate through usual referral pathways to access secondary and tertiary-level care and specialist services. Site PIs have been selected for their ability to identify potentially eligible patients, as well as their clinical expertise in overseeing phage therapy. The majority of PIs are infectious diseases specialists working in tertiary referral centres where patients with difficult-to-treat infections are referred to. This will ensure optimal recruitment of participants into the trial.

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Additional activities of the Phage Australia Network outside of this trial, in areas of continuing medical education, community education and workforce development will also ensure that as many suitable patients are screened for eligibility and recruited into the trial as possible.

Consumer co-design and involvement of Cystic Fibrosis Australia representatives in the TSC will also enable recruitment of participants from this patient group which is usually very successful.

METHODS: DATA COLLECTION, MANAGEMENT, ANALYSIS

16. DATA COLLECTION METHODS

16A DATA COLLECTION METHODS

Study data will be hosted on the REDCap platform on the University of Sydney server, secured, managed, and backed-up centrally. Data management practices will follow the principles of the Australian Code for the Responsible Conduct of Research. All data will be handled in accordance with the University of Sydney data handling guidelines. An external data officer/data architect will be contracted for REDCap database construction. Data entry on the REDCap database will be the responsibility of site PIs or a qualified designee. Overall responsibility for data management and data quality control will be with the Investigator team (site PIs).

16B RETENTION

Cessation or dose-modification of phage therapy for medical reasons will not be a criterion for withdrawal from the trial and every effort should be made to continue all other monitoring of the patient as per the protocol to ensure data integrity and safety monitoring.

If a participant or their parent/guardian/person responsible withdraws consent to participate in the trial, any data obtained prior to withdrawal of consent will be retained. The Primary Clinician is responsible to ensure at least 6 months of clinical monitoring and follow-up after the last dose of administered phage takes place. All attempts will be made to record 6-month follow-up data (for safety monitoring) if the participant provides ongoing consent for this (see section 11.6 above).

17. DATA MANAGEMENT, PROTECTION AND CONFIDENTIALITY

REDCap is a secure platform endorsed by the University of Sydney and many Australian hospitals for research data collection. The REDCap system is hosted on a server behind the University of Sydney controlled firewall, and access is restricted with multi-factor authentication and encrypted connections. Only Principal Investigators or delegates and treating clinicians will be given access to this project through REDCap. They will be able to log on to the project with their access credentials.

Clinical data will be coded but re-identifiable by treating clinicians when collected on REDCap. The 'Data access group' function on REDCap will be used to ensure that clinicians only have access to re-identifiable data for their own patients, not for patients who they are not treating. PIs will have access to re-identifiable data for all patients at their respective recruitment sites.

The 'User rights' function on REDCap will be used to ensure that all data is de-identified when exported for analysis. No user will be able to create data exports from REDCap that contain identifiable information. Scientists involved in biological investigations and data analysis will not require REDCap access; they will only access de-identified exported datasets as needed. All patient data will be de-identified for analysis and dissemination in papers, reports, or presentations.

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As part of the responsibilities assumed by participating in the trial, the PI and their delegated proxies (including site sub-investigators) agree to maintain adequate eCRFs and source documents for participants treated as part of the research under this protocol. Source documents may include laboratory and radiology reports, study site notes from medical records, etc. Data quality will be optimised through use of range checks for data values, and error messages for missing data points. Interim analyses as outlined in section 19b below will also be used to highlight errors in data collection/entry.

Most biological samples collected as part of the trial will be processed in clinical diagnostic laboratories and will be stored, processed and discarded as per routine laboratory procedures for clinical samples. Exceptions include samples obtained for measurement of human transcriptomes, metagenomic analysis, anti-phage antibody measurements and phage and bacterial kinetics (see section 11.4 above). For these non-routine assessments, if biological samples are to be shipped for processing at a laboratory external to the recruitment site or their standard diagnostic referral pathways (e.g. at a state-based referral lab for whole genome sequencing of bacterial isolates), including at non-clinical Medical Research Institutes, they will be coded (using the participant's study code + sample details such as date and time of collection, sample type) prior to shipment, storage and analysis. They will be re-identifiable to the PIs and treating clinicians only.

17A Storage

Any left-over biological samples, that have been coded and de-identified may be retained up to 15 years after the study is completed, or until the youngest participant reaches the age of 25, after which they will be destroyed according to laboratory SOP for handling and disposal of clinical waste.

Clinical data and data pertaining to biological samples will be stored on REDCap for 15 years after the trial is completed and data has been exported for analysis, or until the youngest participant reaches the age of 25. Data exported for analysis will be stored on health servers at recruiting sites and accessed via secure-access computers with password protection.

Any paper records (e.g. consent forms) will be stored in locked offices at recruiting sites and only accessible by study investigators and will be destroyed by shredding, in keeping with healthcare privacy policies. At this point, all electronic data will be completely de-identified.

18. Statistical Methods

18A Outcomes

The primary outcome of the proportion of participants who experience one or more SAEs attributable to study therapy will be presented with a 95% confidence interval. An interim analysis of safety data will be undertaken after 30 participants have been followed for at least one month after commencing treatment. A final analysis will be undertaken when the last enrolled participant has been followed up for at least 6 months after the last dose of phage.

All trial outcomes will be summarised and presented using standard descriptive statistics: frequencies and percentages for categorical data and mean, standard deviation and range or median, quartiles and range for continuous data and the Kaplan-Meier method for time-to-event variables. Results will be presented overall and by sub-groups. Participants may be sub-grouped according to clinical indication (infectious syndrome), route of administration or phage formulation used, or by patient demographics (e.g. age). Exploratory comparisons for all outcomes between subgroups (e.g. adult vs. paediatric patients; those receiving treatment targeting different groups of organisms [Gram-positive

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vs. Gram-negative organisms]; or different infectious phenotypes [acute bacteraemia vs. chronic osteoarticular infections]) will use standard statistical methods: t-test, chi-square test, log-rank test and corresponding regression models if applicable.

18B Analysis Population and Missing Data

Safety data will be reported for all participants who received any dose of phage therapy. Clinical response to therapy and microbiological clearance outcomes will be reported for participants who received at least 5 days of phage therapy (cumulative). All other outcomes will be reported for all enrolled participants based on available data with no adjustment for missing data.

Methods: Monitoring

19. Data Monitoring

19A Formal Committee

The primary outcome of interest (safety), as well as data completeness, rates of recruitment and clinical outcome assessments, will be monitored by a formal DSMB as outlined in the DSMB Terms of Reference and section 5d.

19B Interim Analyses

A review of included and excluded participants and reasons for inclusion/exclusion will be undertaken annually by the CPI and at least one of the TSC co-conveners to ensure appropriateness of patient selection. Results of this review will be available for the investigator group and the DSMB and may be used for amending the trial protocol.

An interim safety analysis for the primary outcome will be conducted after 30 participants have been followed for at least one month after commencing treatment. If 3 or more of these participants have experienced an SAE attributable to therapy (SAR) then consideration will be given to stopping or modifying the study. Study progress including data on all safety, secondary and exploratory outcomes will be regularly reviewed by the trial steering committee. Reports will be provided 6 monthly and will be available for the investigator group and the DSMB and may be used for amending the trial protocol, external reporting and publication, or early termination of the trial. Final decision to terminate the trial rests with the CPI.

Thereafter, trial results will be analysed at the end of 5 years (end of study).

20. Adverse Event Monitoring

20.1 Definitions

An AE is defined as any untoward medical occurrence in a participant enrolled into this trial regardless of its causal relationship to the administered phage product.

An SAE is defined as any event that

- results in death
- is immediately life threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

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Important medical events that may not result in death, be life threatening, or require hospitalisation may be considered SAEs when, based upon appropriate medical judgment, they may jeopardise the participant or may require medical or surgical intervention to prevent one of the outcomes listed in the definition of an SAE.

A suspected, unexpected, serious adverse reaction (SUSAR) is defined as an AE that is serious in nature (i.e. meets SAE criteria), is at least probably (probably or definitely) related to phage therapy (SAR; see section 20.2.2 below) and is an unexpected reaction based on what is known and has been reported in the literature regarding phage therapy. SUSARs will be adjudicated by site PIs.

20.2 Eliciting, Documenting and Reporting Adverse Events

In accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines, all PIs are responsible for recording and reporting adverse events (AE) observed during and after the study. AEs will be assessed from the first dose of phage until the end of the follow-up period, which is 6 months after the last dose of phage.

All AEs that occur during the intervention period (phage administration) and up to 2 weeks after the last dose of phage will be will be actively collected and reported irrespective of their seriousness or relatedness to administered phage. While patients are admitted to hospital AEs will be solicited through daily clinical reviews. If the patient is discharged home for any duration between day 15 and day 28, AEs occurring over this time will be sought on day 29. For patients receiving outpatient or hospital-in-the-home style therapy, AEs will be solicited at each outpatient appointment/home visit.

During the follow-up period (2 weeks-6 months after the last dose of phage) only non-serious AEs considered by the investigator to be related to phage therapy, or any SAEs will be reported. These will be ascertained through discussion with the Primary Clinician undertaking the 6-month follow-up and/or review of medical records 6 months following the last dose of phage administered.

All AEs and SAEs will be documented on the AE page in the eCRF.

20.2.1 Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the participant's daily activities. The intensity of the AE will be rated as mild, moderate, or severe using the following criteria:

- Mild: These events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate: These events result in a low level of inconvenience or concern. Moderate events may cause some interference with normal functioning.
- Severe: These events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

20.2.2 Assessment of Causality

The relationship of the administered phage in causing or contributing to an AE will be characterised using the following classification and criteria:

- Unrelated: There is no association between the administered phage and the reported event.

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- Unlikely: There is a temporal relationship between the administered phage and the reported event; however, it is more likely that the event could have been produced by the participant's clinical state or other treatment(s) administered.
- Possible: The administered phage caused or contributed to the AE, but it could also have been produced by other factors.
- Probable: A reasonable temporal sequence of the event with phage administration exists and, based on previously reported adverse reactions to therapeutic phage, or judgment based on the investigator's clinical experience, the association of the event with the phage seems likely.
- Definite: A definite causal relationship exists between phage administration and the AE, and other conditions (concurrent illness, progression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the phage is readministered.

20.3 Reporting Adverse Events

All AEs reported or observed during the trial will be recorded on the AE page in the eCRF. Information to be collected includes the following:

- Phage product
- Phage dose and date/time of last administration
- Event term (MedDRA preferred term)
- Date/time of onset, including day of phage therapy
- Investigator-specified assessment of severity (section 20.2.1) and relationship to the study drug (section 20.2.2)
- Date/time of resolution of the event, including day of phage therapy
- Seriousness (yes/no)
- Any required treatment or evaluations
- Outcome

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. Any medical condition that is present at the time that the participant is recruited that deteriorates at any time during the trial, should be recorded as an AE.

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs. All AEs will be followed to adequate resolution, or until the investigator deems the event to be chronic/stable or not clinically significant, or the participant is lost to follow-up.

Any abnormal laboratory test results or other safety assessments (e.g., vital signs measurements), including those that worsen from baseline, felt to be clinically significant in the medical judgment of the investigator are to be recorded as AEs or SAEs.

20.3.1 Reporting Serious Adverse Events

Any AE that meets SAE criteria (Section 20.1) must be reported by site investigators to the Sponsor within 48 hours after site personnel first learn of the event. The SAE should be reported by completing an SAE report form (template provided in section 29 of Appendices) and emailed to the Sponsor at:

WSLHD-ResearchOffice@health.nsw.gov.au

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All SUSARs should also be reported using the SAE report form and notified to the study Sponsor, the chair of the DSMB and trial CPI within 48 hours after site personnel first learn of the event:

WSLHD-ResearchOffice@health.nsw.gov.au AND

ian.seppelt@sydney.edu.au AND

jonathan.iredell@sydney.edu au

An acknowledgement of receipt of email all notifications will be made within 48 hours, with the report forwarded to the responsible HREC (see section 21 – Research Ethics Approval). If events occur over a weekend/public holiday, up to 96 hours is allowed for submitting reports and for acknowledgements. The sponsor will follow NHMRC guidance on investigating and reporting SUSARS, including reporting to the responsible HREC.

In addition, annual safety reports will be provided to the responsible HREC by the trial CPI or qualified delegate which will include a line listing of all SAEs, SARs and SUSARs.

Ethics and Dissemination

21. Research Ethics Approval

The trial protocol and all trial documents will be submitted for review by the Sydney Children's Hospitals Network (SCHN) HREC under the National Mutual Agreement (NMA). Additional HREC review may be required for sites that are not covered by the NMA (e.g. private hospitals).

22. Protocol Amendments

All major protocol amendments will be submitted for review by SCHN HREC and will only be implemented after approval is gained from HREC (for all participating sites) and local governance committees for each participating recruitment site. Protocol amendments will also be notified to the relevant trial registries, and the journal to which the protocol will be submitted for peer-review and publication.

23. Consent

In accordance with ICH GCP guidelines, written informed consent will be obtained by the PI or a qualified designee from all potential trial participants or from their person responsible for adults with diminished capacity to provide consent, or from a parent or legal guardian for patients aged younger than 18 years. Templates of the Master Participant Information Sheet and Consent Form (PICF) for adult patients (self-consenting, or by person responsible) and for patients younger than 18 (consent from parent/guardian and young person information sheet) are provided in section 28 of the Appendices. The young person participant information sheet will be provided for all young people aged over 10 years. Only HREC-approved PICF will be used to obtain written informed consent. At least 24 hours will be allowed between providing PICFs and obtaining consent for potential participants to consider the information.

24. Declaration of Interests

All financial and other competing interests for PIs and the Trial Steering Committee will be documented according to the Terms of Reference for the Clinical Stream Committee of Phage Australia.

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25. Access to Data

The final trial dataset will be made available to the Investigator group. The investigator team will have ongoing custody of data or research outputs, including any intellectual property ownership, with the CPI having overall responsibility.

26. Ancillary and Post-Trial Care

Ancillary and post-trial care will be according to routine practice and will be the responsibility of the Primary Clinician. If further episodes of infection occur, including relapses or refractory illness that require further courses of phage treatment, these will be treated as separate events and will be assessed for eligibility in the trial as for the initial course of treatment (i.e. one patient can be enrolled in the trial more than once if repeated courses of phage therapy are administered that meet all inclusion and exclusion criteria). Courses of phage therapy should be separated by at least 2 weeks to allow assessment of primary outcome to occur for each course.

26a Unexpected and Secondary Findings

Unexpected secondary findings are extremely unlikely. Whole blood obtained for analysis of human transcriptomes will only be used to investigate immunological responses to the phage therapy using a panel that includes both innate and adaptive immune response markers. No other human genetic analyses are planned and will not be undertaken unless express HREC approval is obtained via an amendment. Metagenomic analyses will be restricted to non-human genetic material used only to analyse changes in the microbiome (including endogenous phages) during treatment. In the unlikely event that abnormal immune responses are detected (e.g. limited or reduced gene expression profiles) that may suggest immune deficiency or dysregulation, the results will be fed back to the Primary Clinician and Infectious Disease specialist involved in the care of the patient so that additional clinical or diagnostic assessments can be undertaken as indicated.

27. Dissemination Policy

27a Trial Results

Following interim and final analyses, trial results will be shared with the Investigator group and may be prepared for scientific publication or presentation. Final results will be submitted for publication in a peer-reviewed scientific journal. Authorship on publications arising from the trial will be determined by the Trial Steering Committee as per the Terms of Reference for the Clinical Stream Committee of Phage Australia. A lay summary of the final trial results will be made available for participants and the public on the Phage Australia website (https://criticalinfection.com/phage-australia/). A link to the website will be provided to all study participants upon recruitment. There are no restrictions on publication rights for any data generated from the study.

As the protocol is embedded in usual clinical practice, participants may expect to be informed of test results, response to treatment etc. from their Primary Clinicians. All routinely available clinical assays will be available for clinicians to discuss with participants. For some of the more specialised tests, the results may or may not be available while the patient is being treated. For example, phage/bacterial kinetics will be available and will be used to make dosing adjustments. As the study is not blinded and non-comparative, research staff or Primary Clinicians may inform participants about these results and explain why dose adjustments are being made. Other results such as transcriptomics and metagenomics will be processed at a later stage. The results of these tests will not be reported individually to participants as they will not be clinically meaningful for individuals; however, all

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patients have a right to access their health and medical records through their usual clinical teams (Primary Clinician).

27B Reproducible Research

The trial protocol will be submitted for publication in an open-access peer-reviewed journal such as BMJ Open or Trials. Specific consent will be obtained for use of data and left-over samples for other related research and where this is granted, this will be used for research which has been approved by an appropriate HREC and upon reasonable written request to the CPI. The de-identified participant-level dataset will be provided on written request to the CPI when the final trial results are submitted for publication.

Appendices

28. Informed consent Materials

Adult Participant Information Sheet and Consent Form (see separate document)

Person Responsible Participant Information Sheet and Consent Form (see separate document)

Parent/Guardian Participant Information Sheet and Consent Form (see separate document)

Youth Participant Information Sheet (see separate document)

29. Adverse Event/Serious Adverse Event (SAE) Report Form Template

Adverse Event Reporting Form Template (data to be entered directly onto REDCap)

Date of event:

If still receiving phage therapy, specify day of therapy (day 1 = day of first dose administration):

If last dose of phage administered <72 hours prior, specify time of onset of event in hours since last dose of phage:

If last dose of phage administered at least 72 hours prior, specify time of onset of event in days since last dose of phage:

Which phages has participant received at least 1 dose of prior to onset of the event?

Event term (according MedDRA):

Details of event:

Severity: Mild / Moderate / Severe

Serious: Yes / No

If yes, select seriousness criteria (multiple can be selected):

1) resulted in death

2) was immediately life threatening

3) required inpatient hospitalisation or prolongation of existing hospitalisation

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4) resulted in persistent or significant disability/incapacity

5) congenital anomaly/birth defect

6) Other, may jeopardise the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Related: Unrelated / Unlikely / Possible / Probable / Definite

If Probable or Definite relatedness, select from related to (multiple can be selected):

1) phage(s), specify which if multiple used

2) other trial related procedure (e.g. blood draw)

If the event is Serious, confirm SAE has been reported to the Sponsor (WSLHD-ResearchOffice@health.nsw.gov.au) ☐

If the event is Serious with either Probable or Definite relatedness, confirm SAR has been discussed with site PI ☐

In the opinion of the PI, if the event is Serious with either Probable or Definite relatedness, does it qualify as a SUSAR (Suspected, Unexpected Serious Adverse Reaction)? Yes / No

If yes, confirm SUSAR has been reported to the Sponsor (WSLHD-ResearchOffice@health.nsw.gov.au) AND the chair of the DSMB (ian.seppelt@sydney.edu.au) AND the CPI (jonathan.iredell@sydney.edu.au) ☐

Any required treatments or evaluations:

Final outcome: Resolution / Stabilisation / No longer clinically significant / Participant lost to follow-up

Date of final outcome:

If AE requires reporting to the Sponsor, the chair of the DSMB or the CPI/TSC, please print out a report from REDCap and email as an attachment to the appropriate person.

30. Quality-of-Life Questionnaires

EQ-5D-5L (see separate document)

EQ-5D-Y (see separate document)

References

1. J. O'Neill, "Tackling Drug-Resistant Infections Globally: Final Report and Recommendations," (Wellcome Trust, London, 2016).
2. M. J. Blaser, Antibiotic use and its consequences for the normal microbiome. *Science* **352**, 544-545 (2016).
3. A. Petrovic Fabijan *et al.*, Phage therapy for severe bacterial infections: a narrative review. *Med J Aust*, (2019).
4. R. M. Dedrick *et al.*, Engineered bacteriophages for treatment of a patient with a disseminated drug-resistant Mycobacterium abscessus. *Nat Med* **25**, 730-733 (2019).

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5. R. T. Schooley *et al.*, Development and Use of Personalized Bacteriophage-Based Therapeutic Cocktails To Treat a Patient with a Disseminated Resistant Acinetobacter baumannii Infection. *Antimicrobial agents and chemotherapy* **61**, (2017).
6. S. Maddocks *et al.*, Bacteriophage Therapy of Ventilator-associated Pneumonia and Empyema caused by Pseudomonas aeruginosa. *American journal of respiratory and critical care medicine*, (2019).
7. T. Gilbey, J. Ho, L. A. Cooley, A. Petrovic Fabijan, J. R. Iredell, Adjunctive bacteriophage therapy for prosthetic valve endocarditis due to Staphylococcus aureus. *Med J Aust* **211**, 142-143 e141 (2019).
8. A. Petrovic Fabijan *et al.*, Safety of bacteriophage therapy in severe Staphylococcus aureus infection. *Nat Microbiol* **5**, 465-472 (2020).
9. A. Khawaldeh *et al.*, Bacteriophage therapy for refractory Pseudomonas aeruginosa urinary tract infection. *J Med Microbiol* **60**, 1697-1700 (2011).
10. A. Khatami *et al.*, Bacterial lysis, autophagy and innate immune responses during adjunctive phage therapy in a child. *EMBO Mol Med*, e13936 (2021).
11. D. Sharma, L. Misba, A. U. Khan, Antibiotics versus biofilm: an emerging battleground in microbial communities. *Antimicrob Resist Infect Control* **8**, 76 (2019).
12. R. Y. K. Chang *et al.*, Bacteriophage PEV20 and Ciprofloxacin Combination Treatment Enhances Removal of Pseudomonas aeruginosa Biofilm Isolated from Cystic Fibrosis and Wound Patients. *AAPS J* **21**, 49 (2019).
13. C. Roder, V. Gunjaca, O. Otome, S. M. Gwini, E. Athan, Cost and Outcomes of Implantable Cardiac Electronic Device Infections in Victoria, Australia. *Heart Lung Circ* **29**, e140-e146 (2020).
14. T. Morrisette, R. Kebriaei, K. L. Lev, S. Morales, M. J. Rybak, Bacteriophage Therapeutics: A Primer for Clinicians on Phage-Antibiotic Combinations. *Pharmacotherapy* **40**, 153-168 (2020).
15. A. M. Segall, D. R. Roach, S. A. Strathdee, Stronger together? Perspectives on phage-antibiotic synergy in clinical applications of phage therapy. *Curr Opin Microbiol* **51**, 46-50 (2019).
16. B. K. Chan *et al.*, Phage selection restores antibiotic sensitivity in MDR Pseudomonas aeruginosa. *Sci Rep* **6**, 26717 (2016).

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered,	2

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		name of intended registry	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2, 3, 4
Protocol version	#3	Date and version identifier	15
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 16, 17
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	16
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16, 17
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16

Introduction

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Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	n/a
Objectives	#7	Specific objectives or hypotheses	7, 8
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg,	8

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		surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-13
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	12, 13
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8, 12
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13, 14
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9

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Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a

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Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values).	13

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		Reference to where details of data management procedures can be found, if not in the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13, 14, 15
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial	12, 13

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		conduct	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	15
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	13
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of	#28	Financial and other competing interests for principal	17

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interests		investigators for the overall trial and each study site	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	8, 12
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	18
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	14

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Standardised Treatment And Monitoring Protocol to assess safety and tolerability of bacteriophage therapy for adult and paediatric patients (STAMP study): protocol for an open-label, single-arm trial

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Secondary Subject Heading:	Intensive care, Paediatrics
Keywords:	PAEDIATRICS, INFECTIOUS DISEASES, MICROBIOLOGY, GENERAL MEDICINE (see Internal Medicine), THERAPEUTICS

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Manuscripts

Standardised Treatment And Monitoring Protocol to assess safety and tolerability of bacteriophage therapy for adult and paediatric patients (STAMP study): protocol for an open-label, single-arm trial

Ameneh Khatami[1,2,3*], David A. Foley[4,5,6], Morgyn S. Warner[7,8,9], Elizabeth H. Barnes[10], Anton Y. Peleg[11,12], Jian Li[12], Stephen M. Stick[13,14,15], Nettie Burke[16], Ruby C. Y. Lin[2,3,17], Julia Warning[18], Thomas Snelling[1,19], Steven Y. C. Tong[20,21], Jonathan R. Iredell[2,3,22] for the Phage Australia Clinical Network.

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Keywords

Bacteriophage; child; adult; clinical trial; therapeutic monitoring

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Abstract

Introduction

There has been renewed interest in the therapeutic use of bacteriophages (phages); however, standardised therapeutic protocols are lacking, and there is a paucity of rigorous clinical trial data assessing efficacy.

Methods and analysis

We propose an open-label, single-arm trial investigating a standardised treatment and monitoring protocol for phage therapy. Patients included will have exhausted other therapeutic options for control of their infection and phage therapy will be administered under Australia's Therapeutic Goods Administration Special Access Scheme. A phage product with high *in vitro* activity against the targeted pathogen(s) must be available in line with relevant regulatory requirements. We aim to recruit 50-100 patients over five years, from any public or private hospitals in Australia. The standardised protocol will specify clinical assessments and biologic sampling at scheduled time points. The primary outcome is safety at day 29, assessed by the frequency of adverse events, and overseen by an independent Data Safety Monitoring Board. Secondary outcomes include long-term safety (frequency of adverse events until at least 6 months following phage therapy), and feasibility, measured as the proportion of participants with >80% of minimum data available for analysis. Additional endpoints assessed include clinical response, patient/guardian reported quality of life measures, phage pharmacokinetics, human host immune responses, and microbiome analysis. All trial outcomes will be summarised and presented using standard descriptive statistics.

Ethics and dissemination

Participant inclusion will be dependent on obtaining written informed consent from the patient or guardian. The trial protocol was approved by the Sydney Children's Hospitals Network Human Research Ethics Committee in December 2021 (Reference 2021/ETH11861). In addition to publication in a peer-reviewed scientific journal, a lay summary of study outcomes will be made available for participants and the public on the Phage Australia website (https://www.phageaustralia.org/).

Trial registration number

Registered on ANZCTR, 10 November 2021 (ACTRN12621001526864; WHO Universal Trial Number: U1111-1269-6000).

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Strengths and limitations of this study

- This protocol builds on an existing phage therapy program, expanding it to a national scale, co-designed with key stakeholders including government and the public.
- The trial has been endorsed by adult and paediatric infectious diseases specialists throughout Australia, optimising potential for participant recruitment.
- The trial is designed to be embedded into routine clinical practice and is both pragmatic and inclusive.
- The protocol promotes standardisation of therapy and outcome assessment, enabling credible inference about risks and benefits.
- Heterogeneity in disease syndromes and phage products used will limit inference about any particular syndromes or products.

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Introduction

There has been renewed interest in the therapeutic use of bacteriophages (phages), driven by emerging challenges in the medical landscape (1). Growing antimicrobial resistance (AMR) has fuelled a crisis in medicine, contributing to a significant rise in mortality, morbidity and associated healthcare costs (2). Without novel solutions, AMR infections are predicted to be the leading cause of death by 2050, to cost US$30 billion annually in lost productivity, and to threaten many advances in medicine (2). Similarly, there is an unmet need for new strategies to manage complex infections in individuals with chronic conditions, including cystic fibrosis, and infections that respond poorly to antibiotics, such as prosthetic device-related infections (1). Phage therapy (PT) has the potential to meet these needs.

Phages are viruses that selectively kill bacteria (3). PT uses this characteristic to provide a novel, non-antibiotic approach to treating infections (3), with effectiveness independent of antimicrobial susceptibility (3). PT has a proven safety record (4-11) and can be used as monotherapy or in conjunction with antibiotics (3). PT can also alter the bacterial antimicrobial susceptibility profile. Bacterial reversion to susceptible phenotypes has been observed with PT, restoring the efficacy of antibiotics to pathogens that were previously testing non-susceptible (12, 13).

PT has several other potential advantages over standard care. Phages are highly selective, targeting a narrow range of bacteria. This specificity reduces their impact on the microbiome and sidesteps the associated risk of the emergence of AMR and *Clostridioides difficile* infection (14). Biofilm formation is increasingly recognised to play a role in a broad range of conditions beyond the traditionally recognised prosthetic device-related infections (15). In these difficult-to-treat infections, biofilms protect bacteria from the human immune response and reduce antibiotic efficacy (15). Due to their mechanism of action, many phages remain effective in killing bacteria present in biofilms (15, 16).

There are increasing reports underlining the value of PT in severe sepsis, bladder infections and osteomyelitis (6, 7, 9-11). Despite these potential benefits, PT is not routinely used currently. Numerous barriers to widespread adoption remain. Experience with PT is restricted to a handful of centres worldwide. Standardised therapeutic protocols are lacking, and there is a paucity of rigorous clinical trial data assessing efficacy. Furthermore, due to limitations in production, sufficiently purified phages from licensed Good Manufacturing Practice (GMP) facilities, are generally not readily available (17).

Since 2007, a program for compassionate access to PT for adults and children has been in operation at Westmead Hospital and Sydney Children's Hospitals Network. This protocol aims to enable a national expansion of this program to both adults and children, providing a standardised treatment and monitoring protocol linked to a national database to ensure systematic data collection. This protocol will allow rapid and efficient data capture to strengthen the evidence base, including the dosing and monitoring data required to establish PT on the national formulary.

Objectives

This research aims to determine the safety and tolerability of PT in adults and children with bacterial infections in both the short and long term; and to assess the feasibility of a standardised protocol used for the administration and monitoring of PT. A range of other exploratory objectives will also be investigated, including to:

a. Report the clinical response to PT 15 days following completion
b. Describe changes to patient-reported quality-of-life indicators during and after PT
c. Describe proportions of patients achieving microbiological clearance, and time to clearance, by phage product and clinical indication, as well as the frequency of emergence of *in vitro* phage resistance

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d. Identify biomarker(s) that correlate with clinical efficacy
e. Explore pharmacokinetics/pharmacodynamics of different phage preparations to guide optimal dosing schedules and durations of treatment according to various routes of administration
f. Characterise immune responses to PT, including age-related differences
g. Explore microbiome changes as assessed by non-human metagenomics during and after completion of PT.

Methods and analysis

This is an open-label, single-arm trial investigating a standardised treatment and monitoring protocol for PT. The trial is open for enrolment with the first participant recruited 01/04/2022. Fifty participants are expected to be enrolled by 31/12/2025. This trial will include multiple subgroups based on clinical indication and route of PT administration. We used the SPIRIT checklist when writing our report (18).

Participant recruitment and eligibility

Study participants of all ages will be recruited through existing infectious diseases networks from any public or private hospitals in Australia where site-specific approval is obtained. Eligibility will be limited to patients assessed as having exhausted other therapeutic options to control their infection, and where the clinical syndrome is linked directly to the aetiologic bacteria targeted. This assessment will be performed by two appropriately qualified clinical specialists and must include a specialist in infection management and a specialist with prior PT experience or from within a defined clinical working group of the Phage Australia consortium (Trial Steering Committee, TSC).

Inclusion will be dependent on obtaining written informed consent from the patient or guardian and identification of a suitable phage product. Consent must be obtained by the site Principal Investigator (PI) or their qualified designee such as the primary clinician (Supplement A). A phage product must demonstrate high *in vitro* activity (by plaquing in solid or semi-solid media and/or growth inhibition in broth media (19)) against the targeted pathogen(s) to be considered suitable. Similarly, the phage product must comply with all relevant local and national regulatory requirements for therapeutic administration, according to the special access scheme (SAS) for unregistered medicines as determined by the Australian Therapeutic Goods Administration (TGA) (20) or equivalent relevant authority in European (European Medicines Agency) or United States (Food and Drug Administration) jurisdictions (21, 22). Examples of therapeutic phage product quality control documents are provided in Supplement B. Participants unable or unlikely to adhere to the schedule of monitoring and follow-up will be excluded.

Sample size

Sample size was based on logistical considerations and the ability to estimate the proportion of participants with PT-related serious adverse events (SAE). A sample size of at least 50 participants will enable the proportion to be estimated with a 95% confidence interval of maximum width ±15%. If no SAE is observed in 50 participants, this would be consistent with a true rate of SAEs which is no higher than 7% (i.e. 95% CI of 0-7%). In line with this calculation, we aim to recruit 50-100 participants over the five years of the study.

Interventions

The schedule of enrolment, interventions and assessments for each participant is outlined in Table 1. At enrolment, demographic and clinical data will be collected, including primary infection diagnosis and previous and current antimicrobial treatments. Culture confirmation of infection and phage matching of isolated bacteria will be performed. The specific phage product, duration and route of administration will be determined individually for each patient by the clinical team in discussion with the site PI, dependent on the site of infection, bacterial pathogens, patient factors (e.g., immune compromise, intravenous [IV] access) and

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availability of phage products (e.g. formulation, purification). All other care, including adjunctive antibiotics and interventions during the trial, as well as post-trial care, will be as per the treating clinical team.

Repeat episodes of infection, including relapse or refractory illness, will be assessed for eligibility for re-enrolment in the trial, following a separation of at least 15 days to allow assessment of the primary outcome. The first episode per patient will be used for primary analyses, with additional courses described.

Table 1: Schedule of enrolment, interventions, and assessments for each participant

PERIOD	Enrolment	Intervention		Follow-up
TIME POINT	*-4 weeks* to Day 0*	*Day 1-14***	*Day 15-29*	*Day 30-210****
ENROLMENT:				
Eligibility screen	X			
Informed consent	X			
Pre-treatment work-up*	X			
Determination of duration and route of phage administration	X			
PHAGE THERAPY**		X		
MONITORING***				
Blood and clinical sampling	X	X	X	
Quality-of-life questionnaire		X	X	X
Adverse Event Reporting		X	X	X

* Pre-treatment work-up should be performed within four weeks of starting phage therapy.
** The duration of phage therapy may be longer than 14 days, as determined by the Principal Investigator/infectious disease specialist.
*** For patients receiving longer than 14 days of phage therapy follow-up continues for six months after completion of phage therapy

Phage therapy

Duration

Where appropriate, a standard 14-day course will be used for IV/oral PT (Table 2) and non-systemic PT as the default option (Table 3). For critically unwell patients needing urgent infection management, initial twice-daily dosing may be used (i.e., from day 1). The dosing frequency will be guided by practical limitations in patients receiving outpatient treatment or PT for longer than 14 days.

Adherence will be ensured with the first 14 days of IV PT administered in hospital, which may include transition to suitably staffed Hospital Outreach/Hospital in the Home services after the first dose/s are administered. Topical, aerosolised or oral administration can occur in the outpatient setting. All administered doses of phage will be prescribed by a suitably qualified doctor, dispensed from the hospital pharmacy and recorded in standard medical records.

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Table 2: Treatment and laboratory monitoring protocol for standard 14-day intravenous/oral phage therapy

Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	29
Phage doses		OD	OD	BD	BD	BD	BD	BD	BD	BD	BD	BD	BD	BD	BD		
CRP	X		X		X				X							X	X
ESR	X				X				X							X	X
Procalcitonin (if available)	X		X		X				X							X	
FBC	X		X		X				X			X				X	X
Lymphocyte subsets	X		X		£				£			£				£	£
LFTs	X		X		X				X							X	X
UECs	X		X		X				X							X	X
Phage antibodies*	X											X				X	X
Total IgG	X															X	X
C3, C4, CH50	X															X	X
Microbiology sampling**	X				X				X							X	X
Phage susceptibility***	X				X				X							X	X
Kinetic blood sample			X		X				X			X				X	X
Transcriptomics and metagenomics	X		X		X				X			X				X	X

Day 0 – up to 24 hours prior to the first dose of phage; OD – once daily; BD – twice daily; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; FBC – full blood count; LFTs – liver function tests; EUCs – electrolytes, urea, creatinine; IgG – total immunoglobulin G; C3, C4, CH50 – complement levels.

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* Phage antibodies - antibodies against relevant therapeutic phages, measured in order to define risk of antibody-mediated neutralisation and/or immune responses.
** For invasive samples, baseline (day 0) and post-treatment (day 15) microbiology samples are sufficient for monitoring. For patients bacteraemia at the start of phage therapy, blood cultures should be obtained daily until bacteraemia resolves.
*** All positive cultures of the target pathogen(s) that are isolated after day one should be reassessed for ongoing phage-susceptibility
£ Lymphocyte subsets should be performed at these time points if lymphopaenic. Lymphopenia is defined as <1.0 x 10^9/L in individuals aged >12 years, <1.5 x10^9/L in children aged 1-12 years, <4.0 x10^9/L for infants aged 1-12 months, and <3.0 x10^9/L for neonates <1 month.

Table 3: Treatment and laboratory monitoring protocol for standard 14-day non-systemic phage therapy

Day(s)	0	1	2	3	4	5-7	8	9-14	15	29
Phage doses		OD	OD	OD	OD	OD	OD	OD		
CRP	X		X		X		X		X	
FBC	X		X		X		X		X	X
LFTs	X						X		X	
UECs	X						X		X	
Phage antibodies	X								X	X
Microbiology sampling*	X						X		X	X
Phage susceptibility**	X						X		X	X

OD – once daily; CRP – C-reactive protein; FBC – full blood count; LFTs – liver function tests; EUCs – electrolytes, urea, creatinine.
*For invasive samples baseline (day 0) and post-treatment (day 15) samples are sufficient for monitoring.
**All positive cultures of the target pathogen(s) that are isolated after day 1 should be reassessed for ongoing phage-susceptibility.

Dosage

For intravenously administered phage, the dose will be limited by the endotoxin level of the phage product, keeping below the accepted human pyrogenic threshold of 5 EU/kg per dose set by the United States Food and Drug Administration (FDA), aiming to administer approximately 10^9 plaque-forming units (pfu) of phage at each dose. For non-intravenous routes of administration, approximately 10^{10} pfu/dose will be administered. For multiple routes of administration, the total dose administered will not exceed the 5 EU/kg endotoxin limit.

Dosing strategies at initiation will be guided by distribution volume and clearance by non-specific mechanisms (innate effector cells, renal clearance and non-specific inactivation of viral particles). However, the kinetics of subsequent PT doses can be more dynamic (23). Phage amplification in targeted bacterial populations can change over time. Acquired immune clearance (e.g., the development of neutralising antibodies) can increase phage clearance. Thus, phage kinetics is ideally monitored and assessed during PT (Table 2). Phage quantification in blood will be determined by plaque assay and quantitative polymerase chain reaction (qPCR). The timing of blood sampling is outlined in Table 4. Subsequent phage dosing intervals may be adjusted guided by these results (once to twice daily), aiming for a

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trough level of approximately 10^2 pfu/mL (11) . The dose may be adjusted accordingly, at the physician's discretion.

Table 4: Timing of blood samples for quantification of phage and bacterial loads

	Immediately prior to phage dose	30-60 minutes after phage dose	2-3 hours after phage dose
Phage (plaque assay)	X		X
Phage (qPCR)	X	X	X
Bacteria (qPCR)	X	X	X

All three time-points (prior to dose, 30-minutes, and 2 hours post-dose) should be drawn on days 2, 4, 8 and 11. On days 15 and 29, only a single blood draw in the morning is required as no further phage doses will be administered.

Clinical monitoring

A complete physical examination will be performed within 24 hours before starting PT. Vitals (heart rate, respiratory rate, blood pressure, oxygen saturation, temperature) will be measured within 15 minutes prior to, and at 15 and 30 minutes after, each dose of phage. For patients receiving only topical or nebulised/aerosolised phage products, vital signs are only required 30 minutes after administration. Additional clinical monitoring will be performed according to routine clinical care.

Laboratory monitoring

Laboratory monitoring for the first 29 days in patients receiving IV/oral PT and non-systemic PT is outlined in Tables 2 and 3. It is expected that essential monitoring is performed in laboratories subject to regular accreditation by a national regulatory authority which ensures compliance with ISO15189 (Requirements for Quality Management in Medical Laboratories) while some applications such as transcriptomics may be available only in research laboratories, using methods such as those previously described (9, 11). If abnormalities are detected (including worsening of prior abnormalities) that were not present at baseline, these will be followed up beyond the intervention period until resolution. Bacterial cultures will be obtained from the site of infection or representative site if not practical. Blood cultures should be obtained daily for patients with bacteraemia at the commencement of PT, continuing until resolution of the bacteraemia has been documented, consistent with Good Clinical Practice (GCP) (24). For invasive samples other than blood or endotracheal aspirates (e.g., bronchoalveolar lavage or surgical biopsies), baseline (day 0) and post-treatment (day 15) samples are sufficient for monitoring where practical. Bacterial target populations will be quantified by qPCR as genome copies/mL in whole blood at the same time-points outlined for phage kinetics (Table 4).

Measurement of anti-phage antibodies (total or neutralising antibodies (25)), and gene expression profiling of immune responses will characterise the human host's innate and adaptive immune responses following a set schedule in those receiving IV/oral PT (Table 2) and non-systemic PT (Table 3), as available.

Quality-of-life assessments

Participants will complete a brief quality-of-life questionnaire using a validated age-appropriate patient reported outcome measures (PROMs) tool (EQ-5D-5L/EQ-5D-Y) during the study from baseline until 12 months following the completion of PT.

Safety and tolerability

Safety and tolerability will be measured through adverse events (AEs), vital signs, and clinical laboratory assessments. An AE is defined as any untoward medical occurrence in a participant regardless of its causal relationship to the administered phage product. All AEs will be evaluated for severity, causality, and seriousness and will be elicited and assessed from the first dose until 15 days after the last dose of phage. From 15 days to 6 months following the

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completion of PT, only adverse reactions (ARs; AEs that are at least probably [probably or definitely] related to PT), will be collected. An SAE is defined as any event that results in death, is immediately life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity or congenital anomaly. A serious adverse reaction (SAR) is an SAE that is at least probably related to PT. A suspected, unexpected, serious adverse reaction (SUSAR) is defined as an AE that is serious in nature (i.e., meets SAE criteria), is at least probably related to PT and is an unexpected reaction based on what is known and has been reported in the literature. SUSARs will be adjudicated by site PIs. Evidence of severe immune-related phenomena after infusion may occur and may be criteria for cessation of therapy. For any severe adverse reaction, decisions regarding cessation of PT will be made by the primary clinician in consultation with the site PI. Early cessation of PT will not constitute a withdrawal criterion from the trial. The PI should make every effort to continue all other patient monitoring as per the protocol to ensure data integrity and safety monitoring.

Data collection and management

Data will be collected using a Research Electronic Data Capture (REDCap) database hosted by the University of Sydney on a controlled, protected server that requires multi-factor authentication and encrypted connections. Clinical data will be coded but re-identifiable by clinicians for their patients. PIs will only have access to re-identifiable data for patients at their respective recruitment sites. De-identified data will be used for analysis. Data quality will be optimised using range checks for data values and error messages for missing data points. The data fields and the associated data dictionary are included in Supplement C. Any data obtained prior to withdrawal of consent from a participant will be retained.

Most biological samples collected as part of the trial will be processed in clinical diagnostic laboratories and stored, processed, and discarded as per routine laboratory procedures. For non-routine assessments, samples may be processed in research laboratories and will be coded prior to shipment, storage and analysis, and re-identifiable to PIs and treating clinicians at the site only. De-identified data and left-over biological samples may be retained up to 15 years after the study is completed, or until the youngest participant reaches 25 years old, whichever is later. Residual samples may be used for additional research, if specific consent for this is obtained.

Primary and secondary safety outcomes

Safety will be defined by the absence of SAEs attributable to study material (phage). AEs related to PT are predominantly expected during active administration or shortly thereafter. The primary endpoint for safety assessments will be any SAE attributable to PT (SARs) occurring from day 1 (first dose of phage administered) until 15 days after completion of therapy (i.e., day 29 for patients receiving 14 days of therapy). The primary outcome of the proportion of participants who experience one or more SAEs attributable to study therapy will be presented with a 95% confidence interval. Secondary safety endpoints will be any AR occurring from day 1 (first dose of phage administered) until six months after completion of PT.

Secondary and exploratory outcomes

Feasibility

The feasibility of using a national standardised treatment and monitoring protocol will be measured as the proportion of participants with >80% of minimum data available for analysis entered in the REDCap dataset. The feasibility endpoint will be assessed at least 15 days after completion of PT.

This protocol includes a range of exploratory outcomes. The data we develop here will allow the best quality design of formal clinical trials and help to inform regulatory reviews.

Clinical response

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Clinical response will be assessed 15 days following completion of PT. "Cure" will be defined as no evidence of ongoing infection (including clinical signs and symptoms, laboratory and radiological abnormalities, and microbiological evidence of infection), with or without persisting disability. Clinical response will be considered "partial" if there are improvements in clinical, radiological or laboratory parameters, or stabilisation of previously documented decline in function, but with evidence of ongoing infection. Worsening clinical signs and symptoms, radiological or laboratory parameters, and evidence of ongoing infection will be defined as "no response". For analysis, cure and partial response will be grouped and termed "good clinical response".

Quality-of-life indicators

Patient-reported quality-of-life indicators will be measured during and after PT. A carer will complete this report for individuals unable. Changes in the quality-of-life questionnaire will be assessed using a validated PROMs tool (EQ-5D-5L/EQ-5D-Y), and results from baseline will be compared to each subsequent assessment (day 29, 3, 6 or 12 months after starting PT).

Microbiological clearance

Microbiological clearance will be evaluated using time to clearance and the proportion with sustained clearance at the end of the intervention period (day 29). Time to clearance will be measured for each infected site from the first day of PT to the first negative culture among participants with sustained clearance. Sustained clearance is defined as at least two consecutive negative cultures with no other positive cultures during the intervention and follow-up.

Phage resistance can emerge during PT, contributing to poor microbiological clearance. To identify phage resistance, all positive culture(s) of the target pathogen(s) isolated after day 1 of treatment will be reassessed for ongoing phage susceptibility.

Pharmacokinetics and immune response

The pharmacokinetics of different phage preparations will be assessed using the results of qPCR and plaque assays from serum. These data will guide optimal dosing schedules and durations for phage products used according to different routes of administration (IV, oral, nebulised/aerosolised, topical).

Immune responses to PT will be assessed by examining and comparing gene expression profiles coupled with the level of anti-phage neutralising or total antibodies at different time points during and after PT, and between age groups. Gene expression profiling will be restricted to genes belonging to the innate and adaptive immune response regulatory pathways only.

Microbiome changes

Metagenomics will be performed on any available clinical samples (blood, sputum, urine, faeces or other samples that may have been collected) to investigate changes in the microbiome during treatment. The analysis pipeline will be restricted to non-human genetic material and will only be used to determine the microbiome of various clinical specimens during and after PT, including endogenous phages.

Monitoring and analysis

A review of included and excluded participants and reasons for inclusion/exclusion will be undertaken annually to ensure the appropriateness of patient selection. Interim safety analysis for the primary outcome will be conducted after 30 participants have been followed at 29 days after commencement of treatment. The expected attributable SAE rate is <5%. If 20% or more participants suffer an SAR, the treatment may not be considered acceptable in its current form. An analysis of the first 30 participants who are followed at least one month after commencing treatment has 80% statistical power at 5% one-sided alpha to rule out a rate of 20% or higher

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if the true rate is 5% or lower, using an exact one-sample binomial test. If three or more of these 30 participants have experienced an SAR, then consideration will be given to stopping or modifying the study due to safety concerns. Otherwise, recruitment will continue to the target of 50-100 participants to collect data on other outcomes.

The TSC will regularly review study progress, including data on all safety, secondary and exploratory outcomes. Reports will be provided 6-monthly and may be used for amending the trial protocol, external reporting and publication, or early trial termination. A final analysis will be undertaken when the last enrolled participant has been followed up for at least six months after the last dose of phage.

All trial outcomes will be summarised and presented using standard descriptive statistics: frequencies and percentages for categorical data and mean, standard deviation and range or median, quartiles and range for continuous data and the Kaplan-Meier method for time-to-event variables. Results will be presented overall and by sub-groups. Participants may be sub-grouped according to clinical indication (infectious syndrome), route of administration or phage formulation used, or patient demographics (e.g., age). Exploratory comparisons of outcomes between subgroups, including those receiving treatment targeting different groups of organisms, and clinical phenotypes [acute bacteraemia vs. chronic osteoarticular infections]) will use standard statistical methods: t-test, chi-square test, log-rank test, and corresponding regression models.

Safety data will be reported for all participants who receive at least one dose of phage therapy. Clinical response to therapy and microbiological clearance outcomes will be reported for participants who receive at least 5 days of phage therapy (cumulative). All other outcomes will be reported for all enrolled participants based on available data with no adjustment for missing data.

Patient and public involvement

The protocol has been shaped by reviews and comments from stakeholder and consumer representatives including from the cystic fibrosis community and the New South Wales Ministry of Health.

Ethics and dissemination

This trial protocol (version 1.1, 29/05/2022; Supplement D) was assessed and approved by the Sydney Children's Hospitals Network Human Research Ethics Committee (HREC) in May 2022 (version 1 approved December 2021; Reference 2021/ETH11861). All major protocol amendments will only be implemented after approval is gained from the HREC and governance committees for participating sites. Amendments will also be notified to the trial registry, and the journal in which the protocol is published.

Following interim and final analyses, trial results will be shared with the investigator group who will have ongoing custody of the data, and will be prepared for scientific publication or presentation. The final results will be submitted for publication in a peer-reviewed scientific journal. A lay summary of the final trial results will be made available for participants and the public on the Phage Australia website (https://www.phageaustralia.org/). Upon recruitment, a link to the website will be provided to all study participants.

As the protocol is embedded in usual clinical practice, participants may expect to be informed of test results and response to treatment. All routinely available clinical assays will be available for clinicians to discuss with participants. The results may or may not be available during treatment for more specialised tests. Some results such as for transcriptomic and metagenomic analyses will not be reported individually to participants.

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Data availability

The full trial protocol (Standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy Protocol, version 1.1, 29/05/2022; Supplement D)); the database data fields and associated data dictionary, and the participant information sheets and consent forms are made available via supplementary materials submitted with this manuscript and/or via the trial registry.

De-identified individual participant data will be made available for all primary, secondary and exploratory endpoints immediately following publication of trial results. Data will only be made available to researchers who provide a methodologically sound proposal, where the use is not for commercial gain. Access is subject to approvals by Principal Investigators via email (jonathan.iredell@sydney.edu.au or ameneh.khatami@health.nsw.gov.au).

Sponsor information

Sponsor: Western Sydney Local Health District, Research and Education Network Clinical Trial Support Unit, Westmead Hospital, Hawkesbury Road, Westmead, NSW 2145, Australia (WSLHD-ClinicalTrialsSupportUnit@health.nsw.gov.au)

No trial funding is provided by the sponsor. Representatives from the sponsor were involved in the development of the protocol with respect to safety monitoring and reporting procedures. The sponsor will not be involved in collection, management or interpretation of data, writing the study report or the decision to submit the report for publication.

Trial committees

The TSC includes a multidisciplinary group that, collectively, have experience/expertise in the management of patients with condition(s) relevant to the study, pathways for use of phage therapy, and in the conduct and monitoring of randomised clinical trials. Co-conveners are ST, AK and MW and the committee includes JI. JI and AK are physicians with prior PT experience. The committee also includes members with statistical expertise and stakeholder representatives.

The independent Data Safety Monitoring Board (DSMB) includes a chair with management experience in clinical trials and 5 additional members, of whom at least 1 will be a paediatrician, at least 1 will be an adult physician and at least 1 will have established clinical expertise in the delivery of phage therapy. The DSMB will have access to all safety data available at the time of each meeting and will make a recommendation to the co-ordinating PI and site PIs within 4 weeks regarding:

- Cessation of the trial for all participants or for a subgroup
- Interim suspension while reviewing the data in more detail
- Modification of the trial
- Continuation of the trial

Discussion

PT is a promising therapeutic option with evidence of clinical efficacy. However, heterogenous reports, limited clinician experience outside specialist centres and restricted access to suitable phage products has undermined its widespread adoption. This protocol builds on an established PT program, expanding it to a national scale, co-designed with key stakeholders including government and the public. The protocol promotes standardisation of PT administration and outcome assessments, enabling credible inference about risks and benefits. The aim is to standardise the process of administration and monitoring of PT, once that therapy has been approved by the relevant authorities. Although specific phage products are not under direct investigation, and heterogeneity in disease syndromes and phage

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products used within the trial will limit inference about any particular syndromes or products, insights from this trial will allow the design of future controlled trials that can both measure, and validate diagnostic surrogates of clinical efficacy. Importantly, eligibility will be limited to patients assessed as having exhausted other therapeutic options to control their infection, and where the clinical syndrome is linked directly to the aetiologic bacteria targeted, as assessed by two appropriately qualified clinical specialists including a specialist in infection management and a specialist with prior PT experience.

The trial is designed to be embedded into routine clinical practice and is both pragmatic and inclusive, with many interventions determined by standard clinical and laboratory practice of treating physicians and recruitment sites. These methodological strengths will ensure that the data obtained in this trial will help define the safety profile of PT in all age groups and establish the feasibility of a standardised treatment protocol. Downstream effects include overcoming unfamiliarity and increasing both consumer and clinician confidence by collating standardised objective data. Due to the inherent challenges in traditional trial designs for PT, large patient registries collating standardised data, such as this one, will allow rapid and efficient data generation to strengthen the PT evidence base, including the dosing and monitoring data required to inform regulatory frameworks.

Contributors

AK and JI conceived the study. AK, JI, ST and MW initiated the study design and protocol development. AP, TS, JL, SS and RL contributed to refinement of the study protocol. NB provided input into the protocol development in her role as an advocate for the cystic fibrosis community; and JW provided input in her role as the Principal Policy Officer for Advanced Therapeutics at the Office for Health and Medical Research, New South Wales Ministry of Health. JI and AK are grant holders. TS and EB provided statistical expertise. DF and AK drafted the initial manuscript for publication. All authors reviewed and approved the final manuscript for submission.

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Local phage production and development of companion diagnostics are supported by the MRFF Frontiers Stage 1 grant, and a National Health and Medical Research Council Investigator Grant (1197534: Positive Solutions for Critical Infection, CIA Iredell).

Funding bodies do not have any role in the study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

Competing interests

All authors declare no financial or non-financial competing interests with respect to the STAMP protocol.

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References

1. Suh GA, Lodise TP, Tamma PD, et al. Considerations for the Use of Phage Therapy in Clinical Practice. Antimicrob Agents Chemother. 2022:AAC. 02071-21.
2. O'Neill J. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. London: Wellcome Trust; 2016.
3. Lin DM, Koskella B, Lin HC. Phage therapy: An alternative to antibiotics in the age of multi-drug resistance. World J Gastrointest Pharmacol Ther. 2017;8(3):162-73.
4. Jault P, Leclerc T, Jennes S, et al. Efficacy and tolerability of a cocktail of bacteriophages to treat burn wounds infected by Pseudomonas aeruginosa (PhagoBurn): a randomised, controlled, double-blind phase 1/2 trial. Lancet Infect Dis. 2019;19(1):35-45.
5. Dedrick RM, Guerrero-Bustamante CA, Garlena RA, et al. Engineered bacteriophages for treatment of a patient with a disseminated drug-resistant Mycobacterium abscessus. Nat Med. 2019;25(5):730-3.
6. Schooley RT, Biswas B, Gill JJ, et al. Development and Use of Personalized Bacteriophage-Based Therapeutic Cocktails To Treat a Patient with a Disseminated Resistant Acinetobacter baumannii Infection. Antimicrob Agents Chemother. 2017;61(10).
7. Maddocks S, Fabijan AP, Ho J, et al. Bacteriophage Therapy of Ventilator-associated Pneumonia and Empyema Caused by Pseudomonas aeruginosa. Am J Respir Crit Care Med. 2019;200(9):1179-81.
8. Gilbey T, Ho J, Cooley LA, et al. Adjunctive bacteriophage therapy for prosthetic valve endocarditis due to Staphylococcus aureus. Med J Aust. 2019;211(3):142-3 e1.
9. Petrovic Fabijan A, Lin RCY, Ho J, et al. Safety of bacteriophage therapy in severe Staphylococcus aureus infection. Nat Microbiol. 2020;5(3):465-72.
10. Khawaldeh A, Morales S, Dillon B, et al. Bacteriophage therapy for refractory Pseudomonas aeruginosa urinary tract infection. J Med Microbiol. 2011;60(Pt 11):1697-700.
11. Khatami A, Lin RCY, Petrovic-Fabijan A, et al. Bacterial lysis, autophagy and innate immune responses during adjunctive phage therapy in a child. EMBO Mol Med. 2021;13(9):e13936.
12. Gordillo Altamirano F, Forsyth JH, Patwa R, et al. Bacteriophage-resistant Acinetobacter baumannii are resensitized to antimicrobials. Nat Microbiol. 2021;6(2):157-61.
13. Duplessis C, Biswas B, Hanisch B, et al. Refractory Pseudomonas Bacteremia in a 2-Year-Old Sterilized by Bacteriophage Therapy. J Pediatric Infect Dis Soc. 2018;7(3):253-6.
14. Petrovic Fabijan A, Khalid A, Maddocks S, et al. Phage therapy for severe bacterial infections: a narrative review. Med J Aust. 2020;212(6):279-85.
15. Sharma D, Misba L, Khan AU. Antibiotics versus biofilm: an emerging battleground in microbial communities. Antimicrob Resist Infect Control. 2019;8(1):76.

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16. Chang RYK, Das T, Manos J, et al. Bacteriophage PEV20 and Ciprofloxacin Combination Treatment Enhances Removal of Pseudomonas aeruginosa Biofilm Isolated from Cystic Fibrosis and Wound Patients. AAPS J. 2019;21(3):49.
17. Lin RC, Sacher JC, Ceyssens PJ, et al. Phage Biobank: Present Challenges and Future Perspectives. Curr Opin Biotechnol. 2021;68:221-30.
18. Chan AW, Tetzlaff JM, Gotzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ. 2013;346:e7586.
19. Glonti T, Pirnay JP. In Vitro Techniques and Measurements of Phage Characteristics That Are Important for Phage Therapy Success. Viruses. 2022;14(7):1490.
20. Therapeutic Goods Administration. Special access scheme 2022 [updated 28th March 2022]. Available from: https://www.tga.gov.au/form/special-access-scheme.
21. Pirnay JP, Ferry T, Resch G. Recent progress toward the implementation of phage therapy in Western medicine. FEMS Microbiol Rev. 2022;46(1).
22. Food and Drug Administration. Science and Regulation of Bacteriophage Therapy Workshop: Research Gaps. 2021 1st September 2021. https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/science-and-regulation-bacteriophage-therapy-workshop-08302021
23. Dabrowska K. Phage therapy: What factors shape phage pharmacokinetics and bioavailability? Systematic and critical review. Med Res Rev. 2019;39(5):2000-25.
24. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015;36(44):3075-128.
25. Nick JA, Dedrick RM, Gray AL, et al. Host and pathogen response to bacteriophage engineered against Mycobacterium abscessus lung infection. Cell. 2022;185(11):1860-74 e12.

Supplementary Material

Supplementary Material A: Master copies of participant information sheets and consent forms, version 1, dated 08/12/2021.

Supplementary Material B: Examples of endpoint quality control documents for locally produced therapeutic phage products submitted to institutional drug committees prior to participant enrolment.

Supplementary Material C: Research Electronic Data Capture (REDCap) data fields and associated data dictionary.

Supplementary Material D: Standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy Protocol, version 1.1, dated 29/05/2022.

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Executive Summary of the

Participant Information Sheet/Consent Form - Adult

Standardised Treatment and Monitoring of Phage Therapy (STAMP)

[Local Chief Investigator]

You are invited to participate in the above research study because you have a bacterial infection that your doctor has determined would benefit from Phage Therapy and your doctor believes this could be a suitable treatment option for you. A detailed Information Statement about the study is attached and this is a summary of the essential information about the trial and where to find the relevant detailed information later in the Information Statement. You should read the Information Statement in full and discuss it with your family and medical practitioners before deciding to participate in this study. You may contact the study staff *[or provide a name]* to discuss or asks questions about the study on [phone number] or by email [email address].

This study aims to look at how Phage Therapy can be given to patients in a standardised way that will help better understand how the treatment affects you and other patients. If you agree you will receive a specific Phage Therapy product that is suitable for you as decided by your doctor. For a full description of the purpose and rationale for this research see pages 2-4.

Participation in this study is voluntary and refusal to participate or withdrawal from the study at a later stage will not affect the treatment you receive at *[department/hospital]*

If you decide to participate in this study you will be required to receive Phage Therapy as directed by your doctor. How long you will need to take the Phage Therapy for will be decided by your doctor by taking into consideration your medical history and the type of infection you have. During your treatment information about your background medical condition, your infection, the reason for Phage Therapy and your response to treatment will be collected. You will have blood and other samples (swabs, sputum samples etc.) collected. The schedule for study visits and a full list of all tests and procedures is on pages 3-4. After the study treatment has finished you will be followed by your primary doctor for at least 6 months and asked to complete a questionnaire after treatment.

The most common risks to participants from Phage Therapy is a brief inflammatory reaction (fever, headache, muscle aches). A full list of the side-effects from Phage Therapy and other risks associated with the study procedures are on page 6.

There is additional information about what information will be collected about you during the study, how that information will be used, and your privacy protected on pages 8-9. Your rights and additional regulatory information that we are obligated to provide on pages 9-10.

Please make sure you have completely understood what the study involves before you decide to participate.

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Participant Information Sheet/Consent Form - Adult

Standardised Treatment and Monitoring of Phage therapy (STAMP) *Adult providing own consent*

Title	Standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy
Short Title	Standardised Treatment and Monitoring of Phage therapy (STAMP)
Project Sponsor	Western Sydney Local Health District
Coordinating Principal Investigator	Prof Jonathan Iredell
Site Principal Investigator	*[Site PI name]*
Location	*[Location]*

What does my participation involve?

1 Introduction

You are invited to take part in this research project because you have a bacterial infection that your doctor has determined would benefit from Phage Therapy. The research project is investigating the best way to provide Phage Therapy to patients, including how doctors should monitor the treatment.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your doctors.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
• Understand what you have read
• Consent to take part in the research project
• Consent to have the tests and treatments that are described
• Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information Sheet and Consent Form to keep.

2 What is the purpose of this research?

Phage Therapy is an experimental treatment. This means that it is not an approved treatment for bacterial infections in Australia. You will be receiving this treatment under the Special Access Scheme (SAS) of the Australian Therapeutic Goods Administration (TGA) which is sometimes referred to as "compassionate access". The decision to provide Phage Therapy to you and the specific phage product you will receive, has been decided by your doctors and is not part of this research project. This research will investigate how the treatment can be given to you in a standardised way so that we can better understand how the treatment affects you and other patients.

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This research has been initiated by the study doctors, Professor Iredell, Associate Professor Steven Tong and Dr's Ameneh Khatami and Morgyn Warner. It has been funded by the National Health and Medical Research Council (NHMRC) and the Medical Research Future Fund (MRFF) of Australia. It is being conducted by the Phage Australia Network of researchers (https://criticalinfection.com/phage-australia/).

3 What does participation in this research involve?

Once your doctor has determined that you may benefit from Phage Therapy, and a suitable phage product has been found, they will refer you to one of the study doctors. The study doctors will confirm that you are eligible to be enrolled in this research. This will include checking that all of the approvals that are required from Government agencies and other local hospital approvals that may be required have been obtained by your doctor. You will then be asked to sign a consent form before you can participate in the study.

The dose and duration of treatment with Phage Therapy, and the way in which it will be given to you (e.g. intravenously, by mouth, nebulised or topically) will be decided by one of the study doctors, after discussion with your primary (referring) doctor, taking into consideration your background medical conditions and the specific infection you have. Most patients will receive Phage Therapy for 2 weeks, given intravenously (through a drip, in a vein), and this will be provided to you in hospital. For some patients, if the Phage Therapy is required for a longer duration, this may be given to you in your home or an outpatient clinic. For other patients who only need Phage Therapy topically (e.g. onto a wound) or by a nebuliser (to be breathed into your lungs), this may also be given to you in your home or an outpatient clinic. In any circumstance, Phage Therapy will be given by qualified doctors and nurses, and prescribed to you in the same way as other medications.

For most people receiving 2 weeks of Phage Therapy intravenously (through a drip), this will be given once daily, in the morning for the first 2 days, and then twice a day (morning and evening) for the next 12 days. It is possible that you have once daily treatment for longer than 2 days during the 2 weeks, based on blood levels of the phage that will be measured throughout the treatment. Your doctors and nurses will also monitor your heart rate, breathing rate, blood pressure and temperature before and after each dose of phage.

Information regarding your background medical condition, your infection, the reason for Phage Therapy and your response to treatment will be collected in a standardised database. We will also collect blood and other samples that might be relevant for your specific infection (e.g. swabs or sputum samples). These samples will be collected at specified time-points before, during and after completion of the treatment to investigate how effective the treatment has been at clearing your infection, how it has affected your body in other ways, such as your kidneys and liver, and how your immune system has responded to the treatment.

For most people receiving 2 weeks of Phage Therapy intravenously (through a drip), blood samples will be collected the day before starting Phage Therapy (day 0), and again, 1, 3, 7, 10 and 14 days **after** your first dose (day 1). 4 weeks after your first dose of phage, which is about 2 weeks after your last dose of phage, you will have a follow-up visit with more blood tests and collection of relevant samples. On some days you will be asked to provide a blood sample 3 times: once before the morning dose of phage, and then 30-60 minutes, and 2-3 hours after the dose. This will help the study doctors understand how quickly phage is cleared from the body, and will also help determine whether you should receive once or twice daily treatment. The table below shows what days you will have blood tests compared to the first and last dose of phage you receive, and how many blood samples are needed each time.

Day	**0**	**1**	**2**	**4**	**8**	**11**	**14**	**15**	**29**
Number of blood samples	x1	First dose of phage	x3	x3	x3	x3	Last dose of phage	x1	x1

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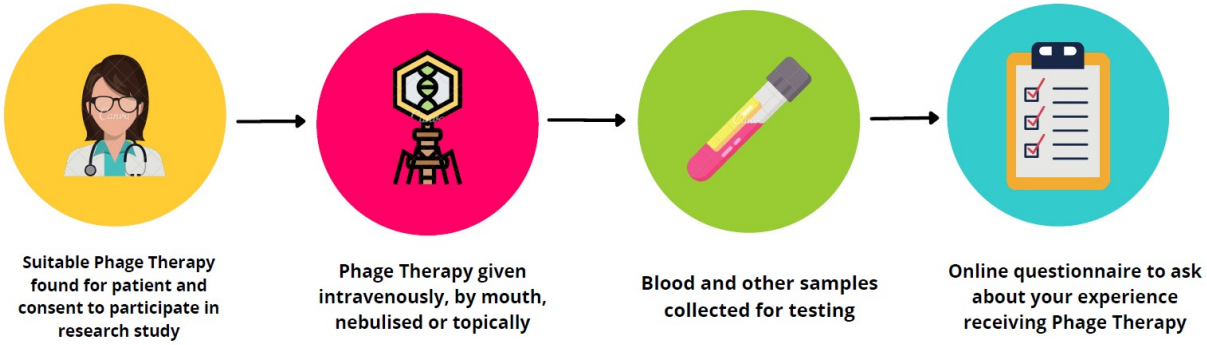
Patients who do not receive any Phage Therapy through a drip in the vein, or by mouth, will have fewer blood tests. They will not have any blood tests on day 11, and on each day will only have a single set of blood samples taken.

Day	0	1	2	4	8	14	15	29
Number of blood samples	x1	First dose of phage	x1	x1	x1	Last dose of phage	x1	x1

Patients who have longer courses of Phage Therapy will continue to have blood tests to monitor their treatment every month. All blood samples will be collected by qualified health professionals (e.g. doctors, nurses or blood collectors).

Before starting Phage Therapy, at the end of the course and again 3 and 6 months after your treatment you will also be asked to complete an online questionnaire. This will ask you questions about your experience of the Phage Therapy and how it may have affected your quality of life. It will take 10 minutes to complete. Although we would like you to complete the entire questionnaire, you can skip any questions that you do not wish to answer.



For most patients, your main involvement in the study will be for 1 month. This includes the 2 weeks of Phage Therapy and the follow-up visit 2 weeks after completing Phage Therapy. During this time, in addition to the tests described above, you will be asked about any symptoms and health events that may have occurred so that study doctors can determine the safety of Phage Therapy. For some patients who are receiving longer courses of Phage Therapy, their involvement in the study will be determined by the duration of Phage Therapy that has been recommended for them. Once the Phage Therapy has finished, you will be followed up by your primary doctor for at least 6 months. The frequency of follow-up visits will be determined by your doctor, based on any underlying medical conditions. During this follow-up period you will also continue to receive invitations to complete the quality-of-life questionnaire at 3 and 6 months after your initial course of treatment.

There are no additional costs associated with participating in this research project, nor will you be paid. All medication, tests and medical care required as part of the research project will be provided to you free of charge.

It is desirable that your local (family) doctor be advised of your decision to participate in this research project. If you have a local doctor, we strongly recommend that you inform them of your participation in this research project.

4 What do I have to do?

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions. It is

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important that administration of phage (including any dose changes) and all of the monitoring tests are done in a standardised way as written in the study protocol. It is also important that all of the information is collected in a standardised way so that the data from all participants in the study can be collated and analysed together. This includes answers you provide in the quality-of-life questionnaire. However, there will be no other restrictions on you with respect to diet, exercise or other activities, or other medications you may need. All of your other routine health care will continue as normal, and as determined by your doctor(s).

5 Other relevant information about the research project

This research is being conducted at multiple hospitals around Australia and will continue for 5 years. We are aiming to recruit 50-100 participants in the study during this time. At *[Location where the research will be conducted]* we expect around 2-3 participants to be recruited each year. The research is a collaboration between multiple hospitals, universities and research institutes working together.

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information Sheet and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with *[Institution]*.

7 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this hospital. If you choose not to participate in this research, your doctor(s) may still decide to offer you Phage Therapy but it may not be monitored in the way outlined in this research. This includes having access to some of the special tests that are not available in routine hospital or community labs. Your study doctor will discuss these options with you before you decide whether or not to take part in this research project. You can also discuss the options with your primary or local doctor.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research; however, possible benefits may include clearance of your infection, or stabilisation or improvement in your symptoms. In addition, your treatment will be overseen and monitored by a group of study doctors which include specialists in infectious diseases and Phage Therapy from around Australia and internationally. Importantly, the information that we collect in this research will help us and other researchers determine the best way to provide Phage Therapy to patients in the future. It may also help us be able to make Phage Therapy more widely available in Australia.

9 What are the possible risks and disadvantages of taking part?

Any medical treatment can cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

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The specific phage product you will receive will be determined by your own doctor. This will be discussed with one of the study doctors, but this decision is not included in the research. Your doctor can provide you with specific information about the phage product you will receive, including where it has been sourced from and how it has been manufactured. Below is some general information about possible risks that might occur for patients receiving Phage Therapy.

Phage Therapy general information and risks

Phages are viruses that infect and kill bacterial cells, but they do not attack human cells. For this reason, phage therapy is considered very safe. It has been used for over 100 years to treat patients with bacterial infections. When phages are well purified to remove contaminants, they cause very few side effects. Only phage products that meet regulatory requirements regarding purification standards will be used in this research.

Sometimes a brief inflammatory reaction is seen after the initial doses of phage. This is mostly due to the phage attacking and killing the bacteria causing your infection. It is usually a good sign that the phages are doing their job but it may be uncomfortable for you. You may have a fever or feel unwell in other ways (chills, headache, muscle aches). Depending on the site of your bacterial infection, you may also experience pain at the site. Usually this inflammatory response is brief, lasting a few hours and can be managed with simple medication like paracetamol or ibuprofen. Rarely, there may be a severe reaction which may mean that further doses of phage are delayed or not given.

Other side effects that may occur during your treatment include abnormalities in results of tests of your liver or kidney function, blood cells and immune responses. If such abnormalities are seen, they will be monitored until they return to their baseline value. In our experience of treating patients in Australia, as well as reports from patients treated in other countries, these abnormalities in lab tests are usually not severe and resolve after a few weeks of stopping the Phage Therapy.

Unknown risks of Phage Therapy

There may also be side effects that we do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you experience. Sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you. Any side effects that may occur during your treatment will be managed or treated by the study doctors and your own doctors according to usual health care practice.

Risks of Phage Therapy of pregnancy and breastfeeding

Since phages do not attack human cells, we do not believe there are any additional risks of using Phage Therapy during pregnancy. However, if you are pregnant or breastfeeding, or you are trying to conceive a child and you have concerns about receiving Phage Therapy, please speak to your study doctors. You will not need to avoid pregnancy, breastfeeding, sperm or egg donation as a result of your participation in this research.

Risks of taking part in this research project

There are very few risks or disadvantages to taking part in this research because the study is mainly investigating how Phage Therapy should be given and monitored. As part of the research, you will be asked to provide blood and other samples at specific timepoints, and the phage will be given to you at specific times of the day, for most patients injected through an intravenous drip. Having a treatment injected or blood samples taken may cause some discomfort, bruising, minor infection or bleeding. If this happens, it can be easily treated.

If you become upset or distressed as a result of your participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who are not members of the research project team. This counselling will be provided free of charge.

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10 What will happen to my test samples?

Most of the tests that will be performed to monitor your treatment are the same routine lab tests used by doctors to monitor infections. These tests will be performed at the usual labs where patient samples from *[Location where the research will be conducted]* are always processed. Once the testing is completed in these labs, the samples will be discarded and destroyed in the same way as other patient samples are handled by labs.

Some of the tests are specific to the Phage Therapy, including tests to determine the levels of phage in your blood, tests to look at how your immune system is responding to the Phage Therapy and tests that will investigate your microbiome (the collection of bacteria and other microorganisms, including viruses, which live in your body). Your blood and other samples (e.g. urine, sputum, faeces) for these tests may need to be sent to another lab in Australia that specialises in Phage Therapy. If this is the case, the samples will be sent in an anonymised way, using only a study code that will be assigned to you for the research project. No personal or identifiable information will be sent outside of *[Location where the research will be conducted]*. Only study doctors from *[Location where the research will be conducted]* and your clinical team will be able to re-identify these samples as yours, using your specific study code.

These tests are all required as part of your participation in the research. Once testing on these samples is completed, any remaining samples will be stored in the external lab in case further testing is required in the future (for this research project). We will also ask your permission to use these stored samples in other related research projects in the future, however this is optional. You can still take part in this research if you do not wish to have your samples used in other projects. Any leftover samples will be destroyed 15 years after the end of the study in the usual safe way that human samples are discarded and destroyed and according to law.

Genetic tests that will be performed in this research will be:
1) to investigate your microbiome which includes all of the bacteria, fungi and viruses that normally live in our bodies, and how these might change during Phage Therapy. This test will not look at any human genetic material, only at the genetic material of microorganisms.
2) to investigate the genes responsible for your immune system and how it responds to the Phage Therapy. This test will not look at any of your other genes so it is unlikely that it will identify any genetic disorders. There is a small chance that we may find that your immune system is not responding as well to infections as in other people. If that is the case, study doctors would let your doctor know the results so that they can discuss these with you and arrange any other investigations that might be needed.

11 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue.

12 Can I have other treatments during this research project?

Participating in this research project will not affect your ability to take other medications or treatments for your condition or for other reasons. However, it is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including

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over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project.

13 What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional information from or about you, although information already collected will be kept as part of the research to ensure that the results of the research can be measured properly and to comply with law. This information will only ever be used in an anonymised way and no personal or identifiable information about you will be used for research purposes. You should be aware that data collected by the sponsor up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell the study team before you join the research project.

14 Could this research project be stopped unexpectedly?

Although unlikely, this research project may be stopped unexpectedly for a variety of reasons, including unacceptable side effects or safety concerns.

15 What happens when the research project ends?

Once you have completed your course of Phage Therapy for your infection, no further ongoing access to Phage Therapy will be required. If further episodes of infection occur, including relapses or recurrence of the same infection, that require further courses of Phage Therapy, these future episodes will be treated as separate events and will be assessed for eligibility for you to be re-enrolled in the research project in the same way as for the initial course of treatment.

All other health care that may be required by you after the end of Phage Therapy will be according to routine practice and will be managed by your primary or local doctor.

After the project is completed in 5 years' time, the results of the research will be published in a scientific journal or may be presented at scientific meetings. A summary of publications and presentations will be made available for participants and the public on the Phage Australia website (https://criticalinfection.com/phage-australia/).

Part 2 How is the research project being conducted?

16 What will happen to information about me?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal and health information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential and securely stored. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research (e.g. results of lab tests or scans). By signing the consent form you agree to the study team accessing health records if they are relevant to your participation in this research project.

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All study information will be entered into a web-based database called REDCap. This is hosted by the University of Sydney and is protected so that only the study team can access the information. Within this database you would be assigned a study code. Your personal and identifiable information would only be available to the clinical team looking after you and the study team at *[Location where the research will be conducted]* so that they can discuss the best possible way to provide Phage Therapy to you, including any changes that might be needed in the dose of phage you are receiving. The rest of the research team would only have access to non-personal information through your anonymised study code.

Any of your blood or other samples that need to be sent to external labs will also only be identified with your study code and none of your personal or identifiable information will be sent outside of *[Location where the research will be conducted]*. It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission. All personal and identifiable information will be removed from the data when it is analysed and reported.

Paper documents, including copies of signed consent forms that include any personal or identifiable information will be stored in locked cupboards in offices at *[Location where the research will be conducted]*. All research data will be stored for 15 years after completion of the project, at which point all electronic documents with any identifiable information will be destroyed by permanent deletion and all paper files will be destroyed by shredding.

We will ask your permission to use your anonymised information in other related research projects in the future, however this is optional. You can still take part in this research if you do not wish to have your information used in other projects. Only anonymised information would be used for other future research projects and your personal or identifiable information will not be shared with anyone outside of the clinical team looking after you and the study team at *[Location where the research will be conducted]* without your permission.

Your health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives of the Sponsor, Western Sydney Local Health District, the institution relevant to this Participant Information Sheet, Sydney Children's Hospitals Network Human Research Ethics Committee, or as required by law. By signing the consent form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

In accordance with relevant Australian and *[Name of state/territory]* privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

17 Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

18 Who is organising and funding the research?

This research has been funded by the National Health and Medical Research Council (NHMRC) and the Medical Research Future Fund (MRFF) of Australia. It is being conducted by the Phage

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Australia Network of researchers (https://criticalinfection.com/phage-australia/), including *[Name of local PI and relevant study staff]*.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

19 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Sydney Children's Hospitals Network.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor *[Name of local PI]* on *[phone number]* or any of the following people:

Clinical contact person

Name	During normal working hours: *[Site PI name]* After hours or if unable to contact *[Site PI name]*: Infectious diseases registrar or consultant on call
Position	*[Title/position/department of Site PI]*
Telephone	During normal working hours: *[Site PI contact number]* After hours: Infectious diseases registrar or consultant on call via *[Hospital switch/on call Phone number]*
Email	*[Site PI Email address]*

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Sydney Children's Hospital Network
HREC Executive Officer	Clare Bayram
Telephone	(02) 9845 3066
Email	SCHN-Ethics@health.nsw.gov.au

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Consent Form - Adult providing own consent

Title	Standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy
Short Title	Standardised Treatment and Monitoring of Phage therapy (STAMP)
Project Sponsor	Western Sydney Local Health District
Coordinating Principal Investigator	Prof Jonathan Iredell
Site Principal Investigator	*[Site PI name]*
Location	*[Location]*

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to *[Name of Institution]* concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

I consent to the storage and use of blood and tissue samples taken from me for use, as described in the relevant section of the Participant Information Sheet, for:

- This specific research project only
- This research project and other research that is closely related to this research project

Strike out one option above and initial next to your choice.

I consent to the storage and use of my de-identified (anonymous) information, as described in the relevant section of the Participant Information Sheet, for:

- This specific research project only
- This research project and other research that is closely related to this research project

Strike out one option above and initial next to your choice.

I agree to the use of my samples for genetic testing, as outlined in the relevant Section of the Participant Information Sheet.

Name of Participant (please print) _____

Signature _____ Date _____

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If the person providing consent is unable to read, an impartial witness should be present during the entire informed consent discussion

Name of Witness* to
Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

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Form for Withdrawal of Participation - Adult

Title	Standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy
Short Title	Standardised Treatment and Monitoring of Phage therapy (STAMP)
Project Sponsor	Western Sydney Local Health District
Coordinating Principal Investigator	Prof Jonathan Iredell
Site Principal Investigator	*[Site PI name]*
Location	*[Location]*

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with *[Institution]*.

- I wish to withdraw from any further collection of samples and clinical data for this research
- I wish to withdraw from any further collection of samples but I am allowing continued collection of my clinical data for this research

Strike out one option above and initial next to your choice.

Name of Participant (please print) _____

Signature _____ Date _____

In the event that the participant's decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.

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Insert Header with institution's name or institution's letterhead

Executive Summary of the

Participant Information Sheet/Consent Form – Parent/Guardian

Standardised Treatment and Monitoring of Phage Therapy (STAMP)

[Local Chief Investigator]

Your child is invited to participate in the above research study because they have a bacterial infection that their doctor has determined would benefit from Phage Therapy and their doctor believes this could be a suitable treatment option for your child. A detailed Information Statement about the study is attached and this is a summary of the essential information about the trial and where to find the relevant detailed information later in the Information Statement. You should read the Information Statement in full and discuss it with your family and medical practitioners before deciding to consent to your child participating in this study. You may contact the study staff *[or provide a name]* to discuss or asks questions about the study on [phone number] or by email [email address].

This study aims to look at how Phage Therapy can be given to patients in a standardised way that will help better understand how the treatment affects them and other patients. If you agree your child will receive a specific Phage Therapy product that is suitable for them as decided by their doctor. For a full description of the purpose and rationale for this research see pages 2-4.

Participation in this study is voluntary and refusal to participate or withdrawal from the study at a later stage will not affect the treatment your child receives at *[department/hospital]*

If you decide to participate in this study your child will be required to receive Phage Therapy as directed by their doctor. How long they will need to take the Phage Therapy for will be decided by their doctor by taking into consideration medical history and the type of infection they have. During your treatment information about your child's background medical condition infection, the reason for Phage Therapy and their response to treatment will be collected. They will have blood and other samples (swabs, sputum samples etc.) collected. The schedule for study visits and a full list of all tests and procedures is on page 4. After the study treatment has finished your child will be followed by their primary doctor for at least 6 months and asked to complete a questionnaire after treatment.

The most common risks to participants from Phage Therapy is a brief inflammatory reaction (fever, headache, muscle aches). A full list of the side-effects from Phage Therapy and other risks associated with the study procedures are on page 6.

There is additional information about what information will be collected about your child during the study, how that information will be used, and their privacy protected on pages 8-9. Your rights and additional regulatory information that we are obligated to provide on pages 9-10.

Please make sure you have completely understood what the study involves before you decide to participate.

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Participant Information Sheet/Consent Form – Parent/Guardian

Standardised Treatment and Monitoring of Phage therapy (STAMP)
Parent/Guardian consenting on behalf of participant

Title	Standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy
Short Title	Standardised Treatment and Monitoring of Phage therapy (STAMP)
Project Sponsor	Western Sydney Local Health District
Coordinating Principal Investigator	Prof Jonathan Iredell
Site Principal Investigator	*[Site PI name]*
Location	*[Location]*

Part 1 What does my child's participation involve?

1 Introduction

Your child is invited to take part in this research project because they have a bacterial infection that their doctor has determined would benefit from Phage Therapy. The research project is investigating the best way to provide Phage Therapy to patients, including how doctors should monitor the treatment.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want your child to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not your child should take part, you might want to talk about it with a relative, friend or your doctors.

Participation in this research is voluntary. If you don't wish for your child to take part, they don't have to. They will receive the best possible care whether or not they take part.

If you decide you want your child to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
• Understand what you have read
• Consent for your child to take part in the research project
• Consent for your child to have the tests and treatments that are described
• Consent to the use of your child's personal and health information as described.

You will be given a copy of this Participant Information Sheet and Consent Form to keep.

2 What is the purpose of this research?

Phage Therapy is an experimental treatment. This means that it is not an approved treatment for bacterial infections in Australia. Your child will be receiving this treatment under the Special Access Scheme (SAS) of the Australian Therapeutic Goods Administration (TGA) which is sometimes referred to as "compassionate access". The decision to provide Phage Therapy to your child and the specific phage product they will receive, has been decided by their doctors and is not part of this research project. This research will investigate how the treatment can be

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given to your child in a standardised way so that we can better understand how the treatment affects your child and other patients.

This research has been initiated by the study doctors, Professor Iredell, Associate Professor Steven Tong and Dr's Ameneh Khatami and Morgyn Warner. It has been funded by the National Health and Medical Research Council (NHMRC) and the Medical Research Future Fund (MRFF) of Australia. It is being conducted by the Phage Australia Network of researchers (https://criticalinfection.com/phage-australia/).

3 What does participation in this research involve?

Once your doctor has determined that your child may benefit from Phage Therapy, and a suitable phage product has been found, they will refer your child to one of the study doctors. The study doctors will confirm that they are eligible to be enrolled in this research. This will include checking that all of the approvals that are required from Government agencies and other local hospital approvals that may be required have been obtained by their doctor. You will then be asked to sign a consent form before your child can participate in the study.

The dose and duration of treatment with Phage Therapy, and the way in which it will be given to your child (e.g. intravenously, by mouth, nebulised or topically) will be decided by one of the study doctors, after discussion with your child's primary (referring) doctor, taking into consideration your child's background medical conditions and the specific infection they have. Most patients will receive Phage Therapy for 2 weeks, given intravenously (through a drip, in a vein), and this will be provided to your child in hospital. For some patients, if the Phage Therapy is required for a longer duration, this may be given to your child in your home or an outpatient clinic. For other patients who only need Phage Therapy topically (e.g. onto a wound) or by a nebuliser (to be breathed into your lungs), this may also be given to your child in your home or an outpatient clinic. In any circumstance, Phage Therapy will be given by qualified doctors and nurses, and prescribed to your child in the same way as other medications.

For most people receiving 2 weeks of Phage Therapy intravenously (through a drip), this will be given once daily, in the morning for the first 2 days, and then twice a day (morning and evening) for the next 12 days. It is possible that your child may have once daily treatment for longer than 2 days during the 2 weeks, based on blood levels of the phage that will be measured throughout the treatment. Your child's doctors and nurses will also monitor their heart rate, breathing rate, blood pressure and temperature before and after each dose of phage.

Information regarding your child's background medical condition, their infection, the reason for Phage Therapy and their response to treatment will be collected in a standardised database. We will also collect blood and other samples that might be relevant for your child's specific infection (e.g. swabs or sputum samples). These samples will be collected at specified time-points before, during and after completion of the treatment to investigate how effective the treatment has been at clearing your child's infection, how it has affected their body in other ways, such as their kidneys and liver, and how their immune system has responded to the treatment.

For most people receiving 2 weeks of Phage Therapy intravenously (through a drip), blood samples will be collected the day before starting Phage Therapy (day 0), and again, 1, 3, 7, 10 and 14 days **after** their first dose (day 1). 4 weeks after your child's first dose of phage, which is about 2 weeks after their last dose of phage, your child will have a follow-up visit with more blood tests and collection of relevant samples. On some days your child will be asked to provide a blood sample 3 times: once before the morning dose of phage, and then 30-60 minutes, and 2-3 hours after the dose. This will help the study doctors understand how quickly phage is cleared from the body, and will also help determine whether they should receive once or twice daily treatment. The table below shows what days your child will have blood tests compared to the first and last dose of Phage Therapy they get, and how many blood samples are needed each time.

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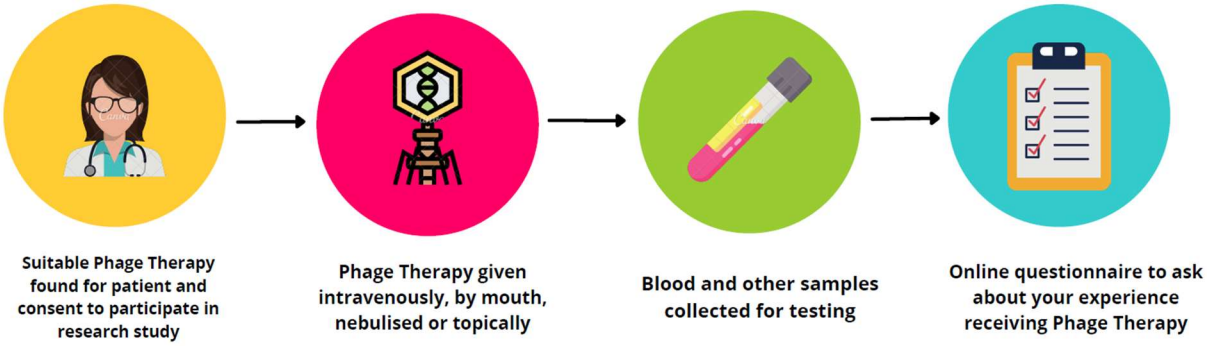
Day	0	1	2	4	8	11	14	15	29
Number of blood samples	x1	First dose of phage	x3	x3	x3	x3	Last dose of phage	x1	x1

Patients who do not receive any Phage Therapy through a drip in the vein, or by mouth, will have fewer blood tests. They will not have any blood tests on day 11, and on each day will only have a single set of blood samples taken.

Day	0	1	2	4	8	14	15	29
Number of blood samples	x1	First dose of phage	x1	x1	x1	Last dose of phage	x1	x1

Patients who have longer courses of Phage Therapy will continue to have blood tests to monitor their treatment every month. All blood samples will be collected by qualified health professionals (e.g. doctors, nurses or blood collectors).

Before starting Phage Therapy, at the end of the course and again 3 and 6 months after your child's treatment patients enrolled in the research who are at least 5 years old will also be asked to complete an online questionnaire. This will ask questions about their experience of the Phage Therapy and how it may have affected their quality of life. It will take 10 minutes to complete. We would ask that you help your child complete these questionnaires. Although we would like your child to complete the entire questionnaire, they and you can skip any questions that you do not wish to answer.



For most patients, their main involvement in the study will be for 1 month. This includes the 2 weeks of Phage Therapy and the follow-up visit 2 weeks after completing Phage Therapy. During this time, in addition to the tests described above, you and your child will be asked about any symptoms and health events that may have occurred so that study doctors can determine the safety of Phage Therapy. For some patients who are receiving longer courses of Phage Therapy, their involvement in the study will be determined by the duration of Phage Therapy that has been recommended for them. Once the Phage Therapy has finished, your child will be followed up by your child's primary doctor for at least 6 months. The frequency of follow-up visits will be determined by your child's doctor, based on any underlying medical conditions. During this follow-up period, if your child is at least 5 years old, they will also continue to receive invitations to complete the quality-of-life questionnaire at 3 and 6 months after their initial course of treatment.

There are no additional costs associated with participating in this research project, nor will you or your child be paid. All medication, tests and medical care required as part of the research project will be provided to your child free of charge.

It is desirable that your local (family) doctor be advised of your decision to participate in this research project. If you have a local doctor, we strongly recommend that you inform them of your child's participation in this research project.

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4 What does my child have to do?

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions. It is important that administration of phage (including any dose changes) and all of the monitoring tests are done in a standardised way as written in the study protocol. It is also important that all of the information is collected in a standardised way so that the data from all participants in the study can be collated and analysed together. This includes answers you and your child provide in the quality-of-life questionnaires. However, there will be no other restrictions on your child with respect to diet, exercise or other activities, or other medications they may need. All of your child's other routine health care will continue as normal, and as determined by their doctor(s).

5 Other relevant information about the research project

This research is being conducted at multiple hospitals around Australia and will continue for 5 years. We are aiming to recruit 50-100 participants in the study during this time (including adults and children). At *[Location where the research will be conducted]* we expect around 2-3 participants to be recruited each year. The research is a collaboration between multiple hospitals, universities and research institutes working together.

6 Does my child have to take part in this research project?

Participation in any research project is voluntary. If you do not wish for your child to take part, they do not have to. If you decide to take part and later change your mind, you are free to withdraw your child from the project at any stage.

If you do decide to take part, you will be given this Participant Information Sheet and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your child's routine treatment, you or your child's relationship with those treating your child or you or your child's relationship with *[Institution]*.

7 What are the alternatives to participation?

Your child does not have to take part in this research project to receive treatment at this hospital. If you choose not to participate in this research, your child's doctor(s) may still decide to offer them Phage Therapy but it may not be monitored in the way outlined in this research. This includes having access to some of the special tests that are not available in routine hospital or community labs. Your child's study doctor will discuss these options with you before you decide whether or not you want your child to take part in this research project. You can also discuss the options with your child's primary or local doctor.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that your child will receive any benefits from this research; however, possible benefits may include clearance of their infection, or stabilisation or improvement in their symptoms. In addition, your child's treatment will be overseen and monitored by a group of study doctors which include specialists in infectious diseases and Phage Therapy from around Australia and internationally. Importantly, the information that we collect in this research will help us and other researchers determine the best way to provide Phage Therapy to patients in the future. It may also help us be able to make Phage Therapy more widely available in Australia.

9 What are the possible risks and disadvantages of taking part?

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Any medical treatment can cause side effects. Your child may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If your child has any of these side effects, or you are worried about them, talk with your child's study doctor. Your child's study doctor will also be looking out for side effects.

The specific phage product your child will receive will be determined by their own doctor. This will be discussed with one of the study doctors, but this decision is not included in the research. Your child's doctor can provide you with specific information about the phage product your child will receive, including where it has been sourced from and how it has been manufactured. Below is some general information about possible risks that might occur for patients receiving Phage Therapy.

Phage Therapy general information and risks

Phages are viruses that infect and kill bacterial cells, but they do not attack human cells. For this reason, phage therapy is considered very safe. It has been used for over 100 years to treat patients with bacterial infections. When phages are well purified to remove contaminants, they cause very few side effects. Only phage products that meet regulatory requirements regarding purification standards will be used in this research.

Sometimes a brief inflammatory reaction is seen after the initial doses of phage. This is mostly due to the phage attacking and killing the bacteria causing your child's infection. It is usually a good sign that the phages are doing their job but it may be uncomfortable for your child. They may have a fever or feel unwell in other ways (chills, headache, muscle aches). Depending on the site of your child's bacterial infection, they may also experience pain at the site. Usually this inflammatory response is brief, lasting a few hours and can be managed with simple medication like paracetamol or ibuprofen. Rarely, there may be a severe reaction which may mean that further doses of phage are delayed or not given.

Other side effects that may occur during your child's treatment include abnormalities in results of tests of their liver or kidney function, blood cells and immune responses. If such abnormalities are seen, they will be monitored until they return to their baseline value. In our experience of treating patients in Australia, as well as reports from patients treated in other countries, these abnormalities in lab tests are usually not severe and resolve after a few weeks of stopping the Phage Therapy.

Unknown risks of Phage Therapy

There may also be side effects that we do not expect or do not know about and that may be serious. Tell your child's study doctor immediately about any new or unusual symptoms that your child experiences. Sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your child's study doctor may need to stop your treatment. Your child's study doctor will discuss the best way of managing any side effects with you. Any side effects that may occur during your treatment will be managed or treated by the study doctors and your child's own doctors according to usual health care practice.

Risks of taking part in this research project

There are very few risks or disadvantages to taking part in this research because the study is mainly investigating how Phage Therapy should be given and monitored. As part of the research, your child will be asked to provide blood and other samples at specific timepoints, and the phage will be given to your child at specific times of the day, for most patients injected through an intravenous drip. Having a treatment injected or blood samples taken may cause some discomfort, bruising, minor infection or bleeding. If this happens, it can be easily treated.

If your child becomes upset or distressed as a result of their participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who are not members of the research project team. This counselling will be provided free of charge.

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10 What will happen to my child's test samples?

Most of the tests that will be performed to monitor your child's treatment are the same routine lab tests used by doctors to monitor infections. These tests will be performed at the usual labs where patient samples from *[Location where the research will be conducted]* are always processed. Once the testing is completed in these labs, the samples will be discarded and destroyed in the same way as other patient samples are handled by labs.

Some of the tests are specific to the Phage Therapy, including tests to determine the levels of phage in your child's blood, tests to look at how your child's immune system is responding to the Phage Therapy and tests that will investigate your child's microbiome (the collection of bacteria and other microorganisms, including viruses, which live in your body). Your child's blood and other samples (e.g. urine, sputum, faeces) for these tests may need to be sent to another lab in Australia that specialises in Phage Therapy. If this is the case, the samples will be sent in an anonymised way, using only a study code that will be assigned to your child for the research project. No personal or identifiable information will be sent outside of *[Location where the research will be conducted]*. Only study doctors from *[Location where the research will be conducted]* and your child's clinical team will be able to re-identify these samples as belonging to your child, using their specific study code.

These tests are all required as part of your child's participation in the research. Once testing on these samples is completed, any remaining samples will be stored in the external lab in case further testing is required in the future (for this research project). We will also ask your permission to use these stored samples in other related research projects in the future, however this is optional. Your child can still take part in this research if you do not wish to have their samples used in other projects. Any leftover samples will be destroyed 15 years after the end of the study in the usual safe way that human samples are discarded and destroyed and according to law.

Genetic tests that will be performed in this research will be:
1) to investigate your child's microbiome which includes all of the bacteria, fungi and viruses that normally live in our bodies, and how these might change during Phage Therapy. This test will not look at any human genetic material, only at the genetic material of microorganisms.
2) to investigate the genes responsible for your child's immune system and how it responds to the Phage Therapy. This test will not look at any of your child's other genes so it is unlikely that it will identify any genetic disorders. There is a small chance that we may find that your child's immune system is not responding as well to infections as in other people. If that is the case, study doctors would let your child's doctor know the results so that they can discuss these with you and arrange any other investigations that might be needed.

11 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your child's study doctor will tell you about it and discuss with you whether you want your child to continue in the research project. If you decide to withdraw, your child's study doctor will make arrangements for your child's regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, your child's study doctor might consider it to be in your child's best interests to withdraw them from the research project. If this happens, he/ she will explain the reasons and arrange for your child's regular health care to continue.

12 Can my child have other treatments during this research project?

Participating in this research project will not affect your child's ability to take other medications or treatments for their condition or for other reasons. However, it is important to tell your child's

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study doctor and the study staff about any treatments or medications they may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your child's study doctor about any changes to these during your child's participation in the research project.

13 What if I withdraw my child from this research project?

If you decide to withdraw your child from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional information from or about your child, although information already collected will be kept as part of the research to ensure that the results of the research can be measured properly and to comply with law. This information will only ever be used in an anonymised way and no personal or identifiable information about your child will be used for research purposes. You should be aware that data collected by the sponsor up to the time you withdraw your child will form part of the research project results. If you do not want them to do this, you must tell the study team before your child joins the research project.

14 Could this research project be stopped unexpectedly?

Although unlikely, this research project may be stopped unexpectedly for a variety of reasons, including unacceptable side effects or safety concerns.

15 What happens when the research project ends?

Once your child has completed their course of Phage Therapy for their infection, no further ongoing access to Phage Therapy will be required. If further episodes of infection occur, including relapses or recurrence of the same infection, that require further courses of Phage Therapy, these future episodes will be treated as separate events and will be assessed for eligibility for your child to be re-enrolled in the research project, in the same way as for the initial course of treatment.

All other health care that may be required by your child after the end of Phage Therapy will be according to routine practice and will be managed by your child's primary or local doctor.

After the project is completed in 5 years' time, the results of the research will be published in a scientific journal or may be presented at scientific meetings. A summary of publications and presentations will be made available for participants and the public on the Phage Australia website (https://criticalinfection.com/phage-australia/).

Part 2 How is the research project being conducted?

16 What will happen to information about my child?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal and health information about your child for the research project. Any information obtained in connection with this research project that can identify your child will remain confidential and securely stored. Your child's information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information about your child may be obtained from their health records held at this and other health services for the purpose of this research (e.g. results of lab tests or scans). By signing the consent form you agree to the study team accessing health records if they are relevant to your child's participation in this research project.

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All study information will be entered into a web-based database called REDCap. This is hosted by the University of Sydney and is protected so that only the study team can access the information. Within this database your child would be assigned a study code. Your child's personal and identifiable information would only be available to the clinical team looking after your child and the study team at *[Location where the research will be conducted]* so that they can discuss the best possible way to provide Phage Therapy to your child, including any changes that might be needed in the dose of phage they are receiving. The rest of the research team would only have access to non-personal information through your child's anonymised study code.

Any of your child's blood or other samples that need to be sent to external labs will also only be identified with their study code and none of your child's personal or identifiable information will be sent outside of *[Location where the research will be conducted]*. It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that your child cannot be identified, except with your permission. All personal and identifiable information will be removed from the data when it is analysed and reported.

Paper documents, including copies of signed consent forms that include any personal or identifiable information will be stored in locked cupboards in offices at *[Location where the research will be conducted]*. All research data will be stored for 15 years after completion of the project, at which point all electronic documents with any identifiable information will be destroyed by permanent deletion and all paper files will be destroyed by shredding.

We will ask your permission to use your child's anonymised information in other related research projects in the future, however this is optional. Your child can still take part in this research if you do not wish to have their information used in other projects. Only anonymised information would be used for other future research projects and your child's personal or identifiable information will not be shared with anyone outside of the clinical team looking after your child and the study team at *[Location where the research will be conducted]* without your permission.

Your child's health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives of the Sponsor, Western Sydney Local Health District, the institution relevant to this Participant Information Sheet, Sydney Children's Hospitals Network Human Research Ethics Committee, or as required by law. By signing the consent form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

In accordance with relevant Australian and *[Name of state/territory]* privacy and other relevant laws, you have the right to request access to your child's information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your child's information.

17 Complaints and Compensation

If your child suffers any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If your child is eligible for Medicare, they can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

18 Who is organising and funding the research?

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This research has been funded by the National Health and Medical Research Council (NHMRC) and the Medical Research Future Fund (MRFF) of Australia. It is being conducted by the Phage Australia Network of researchers (https://criticalinfection.com/phage-australia/), including *[Name of local PI and relevant study staff]*.

No member of the research team will receive a personal financial benefit from your child's involvement in this research project (other than their ordinary wages).

19 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Sydney Children's Hospitals Network.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if your child has any medical problems which may be related to their involvement in the project (for example, any side effects), you can contact the principal study doctor *[Name of local PI]* on *[phone number]* or any of the following people:

Clinical contact person

Name	During normal working hours: *[Site PI name]* After hours or if unable to contact *[Site PI name]*: Infectious diseases registrar or consultant on call
Position	*[Title/position/department of Site PI]*
Telephone	During normal working hours: *[Site PI contact number]* After hours: Infectious diseases registrar or consultant on call via *[Hospital switch/on call Phone number]*
Email	*[Site PI Email address]*

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Sydney Children's Hospital Network
HREC Executive Officer	Clare Bayram
Telephone	(02) 9845 3066
Email	SCHN-Ethics@health.nsw.gov.au

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Consent Form – Parent/Guardian

Title	Standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy
Short Title	Standardised Treatment and Monitoring of Phage therapy (STAMP)
Project Sponsor	Western Sydney Local Health District
Coordinating Principal Investigator	Prof Jonathan Iredell
Site Principal Investigator	*[Site PI name]*
Location	*[Location]*

Declaration by Parent/Guardian

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my child's doctors, other health professionals, hospitals or laboratories outside this hospital to release information to *[Name of Institution]* concerning my child's disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to have my child participate in this research project as described and understand that I am free to withdraw my child at any time during the study without affecting their future health care.

I understand that I will be given a signed copy of this document to keep.

I consent to the storage and use of blood and tissue samples taken from my child for use, as described in the relevant section of the Participant Information Sheet, for:

- This specific research project only
- This research project and other research that is closely related to this research project

Strike out one option above and initial next to your choice.

I consent to the storage and use of my child's de-identified (anonymous) information, as described in the relevant section of the Participant Information Sheet, for:

- This specific research project only
- This research project and other research that is closely related to this research project

Strike out one option above and initial next to your choice.

I agree to the use of my child's samples for genetic testing, as outlined in the relevant Section of the Participant Information Sheet.

Name of Child (please print) _____

Signature of Child _____ Date _____

Name of Parent/Guardian (please print)

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Signature of Parent/Guardian _____ Date _____

If the person providing consent is unable to read, an impartial witness should be present during the entire informed consent discussion

Name of Witness* to Parent/Guardian's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the parent/guardian has understood that explanation.

Name of Study Doctor/ Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

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Form for Withdrawal of Participation – Parent/Guardian

Title	Standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy
Short Title	Standardised Treatment and Monitoring of Phage therapy (STAMP)
Project Sponsor	Western Sydney Local Health District
Coordinating Principal Investigator	Prof Jonathan Iredell
Site Principal Investigator	*[Site PI name]*
Location	*[Location]*

Declaration by Parent/Guardian

I wish to withdraw my child from participation in the above research project and understand that such withdrawal will not affect my child's routine treatment, our relationship with those treating my child or our relationship with *[Institution]*.

- I wish to withdraw my child from any further collection of samples and clinical data for this research
- I wish to withdraw my child from any further collection of samples but I am allowing continued collection of my child's clinical data for this research

Strike out one option above and initial next to your choice.

Name of Child (please print) _____

Name of Parent/Guardian (please print) _____

Signature of Parent/Guardian _____ Date_____

In the event that the parent/guardian's decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the parent/guardian has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.

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Insert Header with institution's name or institution's letterhead

Executive Summary of the
Participant Information Sheet/Consent Form – Person Responsible

Standardised Treatment and Monitoring of Phage Therapy (STAMP)

[Local Chief Investigator]

The participant is invited to participate in the above research study because they have a bacterial infection that their doctor has determined would benefit from Phage Therapy and their doctor believes this could be a suitable treatment option. A detailed Information Statement about the study is attached and this is a summary of the essential information about the trial and where to find the relevant detailed information later in the Information Statement. You should read the Information Statement in full and discuss it with your family and medical practitioners before deciding to agree to participation of the person you are responsible for in this study. You may contact the study staff *[or provide a name]* to discuss or asks questions about the study on [phone number] or by email [email address].

This study aims to look at how Phage Therapy can be given to patients in a standardised way that will help better understand how the treatment affects them and other patients. If you agree, the person you are responsible for will receive a specific Phage Therapy product that is suitable for them as decided by their doctor. For a full description of the purpose and rationale for this research see pages 2-4.

Participation in this study is voluntary and refusal to participate or withdrawal from the study at a later stage will not affect the treatment they receive at *[department/hospital]*

If you decide the person you are responsible for should participate in this study they will be required to receive Phage Therapy as directed by their doctor. How long they will need to take the Phage Therapy for will be decided by their doctor, taking into consideration medical history and the type of infection they have. During treatment information about the participant's background medical condition, infection, the reason for Phage Therapy and response to treatment will be collected. They will have blood and other samples (swabs, sputum samples etc.) collected. The schedule for study visits and a full list of all tests and procedures is on page 4. After the study treatment has finished they will be followed by their primary doctor for at least 6 months and asked to complete a questionnaire after treatment.

The most common risks to participants from Phage Therapy is a brief inflammatory reaction (fever, headache, muscle aches). A full list of the side-effects from Phage Therapy and other risks associated with the study procedures are on page 6.

There is additional information about what information will be collected about the participant during the study, how that information will be used, and their privacy protected on pages 8-9. Their rights and additional regulatory information that we are obligated to provide on pages 9-10.

Please make sure you have completely understood what the study involves before you decide to consent to participation on behalf of the person you are responsible for.

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Participant Information Sheet/Consent Form – Person Responsible

Standardised Treatment and Monitoring of Phage therapy (STAMP)
Person responsible consenting on behalf of participant

Title	Standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy
Short Title	Standardised Treatment and Monitoring of Phage therapy (STAMP)
Project Sponsor	Western Sydney Local Health District
Coordinating Principal Investigator	Prof Jonathan Iredell
Site Principal Investigator	*[Site PI name]*
Location	*[Location]*

Part 1 What does participation involve?

1 Introduction

The participant is invited to take part in this research project because they have a bacterial infection that their doctor has determined would benefit from Phage Therapy. The research project is investigating the best way to provide Phage Therapy to patients, including how doctors should monitor the treatment.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want the participant to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not the participant should take part, you might want to talk about it with a relative, friend or your doctors.

Participation in this research is voluntary. If you don't wish for the participant to take part, they don't have to. They will receive the best possible care whether or not they take part.

If you decide you want the participant to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
• Understand what you have read
• Consent for the participant to take part in the research project
• Consent for the participant to have the tests and treatments that are described
• Consent to the use of the participant's personal and health information as described.

You will be given a copy of this Participant Information Sheet and Consent Form to keep.

2 What is the purpose of this research?

Phage Therapy is an experimental treatment. This means that it is not an approved treatment for bacterial infections in Australia. The participant will be receiving this treatment under the Special Access Scheme (SAS) of the Australian Therapeutic Goods Administration (TGA) which is sometimes referred to as "compassionate access". The decision to provide Phage Therapy to the participant and the specific phage product they will receive, has been decided by their

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doctors and is not part of this research project. This research will investigate how the treatment can be given to the participant in a standardised way so that we can better understand how the treatment affects the participant and other patients.

This research has been initiated by the study doctors, Professor Iredell, Associate Professor Steven Tong and Dr's Ameneh Khatami and Morgyn Warner. It has been funded by the National Health and Medical Research Council (NHMRC) and the Medical Research Future Fund (MRFF) of Australia. It is being conducted by the Phage Australia Network of researchers (https://criticalinfection.com/phage-australia/).

3 What does participation in this research involve?

Once your doctor has determined that the participant may benefit from Phage Therapy, and a suitable phage product has been found, they will refer the participant to one of the study doctors. The study doctors will confirm that they are eligible to be enrolled in this research. This will include checking that all of the approvals that are required from Government agencies and other local hospital approvals that may be required have been obtained by their doctor. You will then be asked to sign a consent form before the participant can take part in the study.

The dose and duration of treatment with Phage Therapy, and the way in which it will be given to the participant (e.g. intravenously, by mouth, nebulised or topically) will be decided by one of the study doctors, after discussion with the participant's primary (referring) doctor, taking into consideration the participant's background medical conditions and the specific infection they have. Most patients will receive Phage Therapy for 2 weeks, given intravenously (through a drip, in a vein), and this will be provided to the participant in hospital. For some patients, if the Phage Therapy is required for a longer duration, this may be given to the participant in their home or an outpatient clinic. For other patients who only need Phage Therapy topically (e.g. onto a wound) or by a nebuliser (to be breathed into your lungs), this may also be given to the participant in their home or an outpatient clinic. In any circumstance, Phage Therapy will be given by qualified doctors and nurses, and prescribed to the participant in the same way as other medications.

For most people receiving 2 weeks of Phage Therapy intravenously (through a drip), this will be given once daily, in the morning for the first 2 days, and then twice a day (morning and evening) for the next 12 days. It is possible that the participant may have once daily treatment for longer than 2 days during the 2 weeks, based on blood levels of the phage that will be measured throughout the treatment. The participant's doctors and nurses will also monitor their heart rate, breathing rate, blood pressure and temperature before and after each dose of phage.

Information regarding the participant's background medical condition, their infection, the reason for Phage Therapy and their response to treatment will be collected in a standardised database. We will also collect blood and other samples that might be relevant for the participant's specific infection (e.g. swabs or sputum samples). These samples will be collected at specified time-points before, during and after completion of the treatment to investigate how effective the treatment has been at clearing the participant's infection, how it has affected their body in other ways, such as their kidneys and liver, and how their immune system has responded to the treatment.

For most people receiving 2 weeks of Phage Therapy intravenously (through a drip), blood samples will be collected the day before starting Phage Therapy (day 0), and again, 1, 3, 7, 10 and 14 days **after** their first dose (day 1). 4 weeks after the participant's first dose of phage, which is about 2 weeks after their last dose of phage, the participant will have a follow-up visit with more blood tests and collection of relevant samples. On some days the participant will be asked to provide a blood sample 3 times: once before the morning dose of phage, and then 30-60 minutes, and 2-3 hours after the dose. This will help the study doctors understand how quickly phage is cleared from the body, and will also help determine whether they should receive once or twice daily treatment. The table below shows what days the participant will have blood tests compared to the first and last dose of phage they receive, and how many blood samples are needed each time.

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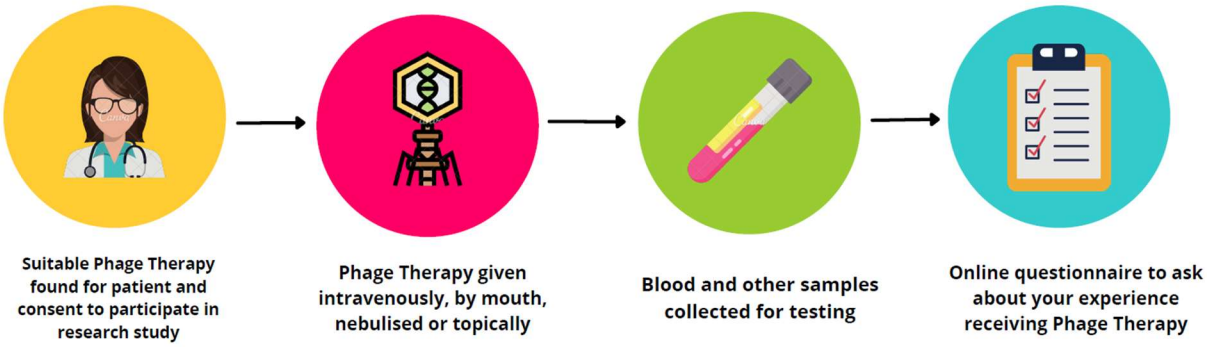
Day	0	1	2	4	8	11	14	15	29
Number of blood samples	x1	First dose of phage	x3	x3	x3	x3	Last dose of phage	x1	x1

Patients who do not receive any Phage Therapy through a drip in the vein, or by mouth, will have fewer blood tests. They will not have any blood tests on day 11, and on each day will only have a single set of blood samples taken.

Day	0	1	2	4	8	14	15	29
Number of blood samples	x1	First dose of phage	x1	x1	x1	Last dose of phage	x1	x1

Patients who have longer courses of Phage Therapy will continue to have blood tests to monitor their treatment every month. All blood samples will be collected by qualified health professionals (e.g. doctors, nurses or blood collectors).

Before starting Phage Therapy, at the end of the course and again 3 and 6 months after the participant's treatment they will also be asked to complete an online questionnaire. This will ask questions about their experience of the Phage Therapy and how it may have affected their quality of life. It will take 10 minutes to complete. We would ask that you help the participant complete these questionnaires. Although we would like the participant to complete the entire questionnaire, they and you can skip any questions that you do not wish to answer.



For most patients, their main involvement in the study will be for 1 month. This includes the 2 weeks of Phage Therapy and the follow-up visit 2 weeks after completing Phage Therapy. During this time, in addition to the tests described above, you and the participant will be asked about any symptoms and health events that may have occurred so that study doctors can determine the safety of Phage Therapy. For some patients who are receiving longer courses of Phage Therapy, their involvement in the study will be determined by the duration of Phage Therapy that has been recommended for them. Once the Phage Therapy has finished, the participant will be followed up by the participant's primary doctor for at least 6 months. The frequency of follow-up visits will be determined by the participant's doctor, based on any underlying medical conditions. During this follow-up period, they will also continue to receive invitations to complete the quality-of-life questionnaire at 3 and 6 months after their initial course of treatment.

There are no additional costs associated with participating in this research project, nor will you or the participant be paid. All medication, tests and medical care required as part of the research project will be provided to the participant free of charge.

It is desirable that your local (family) doctor be advised of your decision to participate in this research project. If you have a local doctor, we strongly recommend that you inform them of the participant's participation in this research project.

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4 What does the participant have to do?

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions. It is important that administration of phage (including any dose changes) and all of the monitoring tests are done in a standardised way as written in the study protocol. It is also important that all of the information is collected in a standardised way so that the data from all participants in the study can be collated and analysed together. This includes answers you and the participant provide in the quality-of-life questionnaires. However, there will be no other restrictions on the participant with respect to diet, exercise or other activities, or other medications they may need. All of the participant's other routine health care will continue as normal, and as determined by their doctor(s).

5 Other relevant information about the research project

This research is being conducted at multiple hospitals around Australia and will continue for 5 years. We are aiming to recruit 50-100 participants in the study during this time. At *[Location where the research will be conducted]* we expect around 2-3 participants to be recruited each year. The research is a collaboration between multiple hospitals, universities and research institutes working together.

6 Does the participant have to take part in this research project?

Participation in any research project is voluntary. If you do not wish for the participant to take part, they do not have to. If you decide to take part and later change your mind, you are free to withdraw the participant from the project at any stage.

If you do decide to take part, you will be given this Participant Information Sheet and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect the participant's routine treatment, you or the participant's relationship with those treating the participant or you or the participant's relationship with *[Institution]*.

7 What are the alternatives to participation?

The participant does not have to take part in this research project to receive treatment at this hospital. If you choose not to participate in this research, the participant's doctor(s) may still decide to offer them Phage Therapy but it may not be monitored in the way outlined in this research. This includes having access to some of the special tests that are not available in routine hospital or community labs. The study doctor will discuss these options with you before you decide whether or not you want the participant to take part in this research project. You can also discuss the options with the participant's primary or local doctor.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that the participant will receive any benefits from this research; however, possible benefits may include clearance of their infection, or stabilisation or improvement in their symptoms. In addition, the participant's treatment will be overseen and monitored by a group of study doctors which include specialists in infectious diseases and Phage Therapy from around Australia and internationally. Importantly, the information that we collect in this research will help us and other researchers determine the best way to provide Phage Therapy to patients in the future. It may also help us be able to make Phage Therapy more widely available in Australia.

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9 What are the possible risks and disadvantages of taking part?

Any medical treatment can cause side effects. The participant may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If the participant has any of these side effects, or you are worried about them, talk with the study doctor. The study doctor will also be looking out for side effects.

The specific phage product the participant will receive will be determined by their own doctor. This will be discussed with one of the study doctors, but this decision is not included in the research. The participant's doctor can provide you with specific information about the phage product the participant will receive, including where it has been sourced from and how it has been manufactured. Below is some general information about possible risks that might occur for patients receiving Phage Therapy.

Phage Therapy general information and risks
Phages are viruses that infect and kill bacterial cells, but they do not attack human cells. For this reason, phage therapy is considered very safe. It has been used for over 100 years to treat patients with bacterial infections. When phages are well purified to remove contaminants, they cause very few side effects. Only phage products that meet regulatory requirements regarding purification standards will be used in this research.

Sometimes a brief inflammatory reaction is seen after the initial doses of phage. This is mostly due to the phage attacking and killing the bacteria causing the participant's infection. It is usually a good sign that the phages are doing their job but it may be uncomfortable for the participant. They may have a fever or feel unwell in other ways (chills, headache, muscle aches). Depending on the site of the participant's bacterial infection, they may also experience pain at the site. Usually this inflammatory response is brief, lasting a few hours and can be managed with simple medication like paracetamol or ibuprofen. Rarely, there may be a severe reaction which may mean that further doses of phage are delayed or not given.

Other side effects that may occur during the participant's treatment include abnormalities in results of tests of their liver or kidney function, blood cells and immune responses. If such abnormalities are seen, they will be monitored until they return to their baseline value. In our experience of treating patients in Australia, as well as reports from patients treated in other countries, these abnormalities in lab tests are usually not severe and resolve after a few weeks of stopping the Phage Therapy.

Unknown risks of Phage Therapy
There may also be side effects that we do not expect or do not know about and that may be serious. Tell the study doctor immediately about any new or unusual symptoms that the participant experiences. Sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, the study doctor may need to stop your treatment. The study doctor will discuss the best way of managing any side effects with you. Any side effects that may occur during your treatment will be managed or treated by the study doctors and the participant's own doctors according to usual health care practice.

Risks of taking part in this research project
There are very few risks or disadvantages to taking part in this research because the study is mainly investigating how Phage Therapy should be given and monitored. As part of the research, the participant will be asked to provide blood and other samples at specific timepoints, and the phage will be given to the participant at specific times of the day, for most patients injected through an intravenous drip. Having a treatment injected or blood samples taken may cause some discomfort, bruising, minor infection or bleeding. If this happens, it can be easily treated.

If the participant becomes upset or distressed as a result of their participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any

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counselling or support will be provided by qualified staff who are not members of the research project team. This counselling will be provided free of charge.

10 What will happen to the participant's test samples?

Most of the tests that will be performed to monitor the participant's treatment are the same routine lab tests used by doctors to monitor infections. These tests will be performed at the usual labs where patient samples from *[Location where the research will be conducted]* are always processed. Once the testing is completed in these labs, the samples will be discarded and destroyed in the same way as other patient samples are handled by labs.

Some of the tests are specific to the Phage Therapy, including tests to determine the levels of phage in the participant's blood, tests to look at how the participant's immune system is responding to the Phage Therapy and tests that will investigate the participant's microbiome (the collection of bacteria and other microorganisms, including viruses, which live in your body). The participant's blood and other samples (e.g. urine, sputum, faeces) for these tests may need to be sent to another lab in Australia that specialises in Phage Therapy. If this is the case, the samples will be sent in an anonymised way, using only a study code that will be assigned to the participant for the research project. No personal or identifiable information will be sent outside of *[Location where the research will be conducted]*. Only study doctors from *[Location where the research will be conducted]* and the participant's clinical team will be able to re-identify these samples as belonging to the participant, using their specific study code.

These tests are all required for the participant to take part in the research. Once testing on these samples is completed, any remaining samples will be stored in the external lab in case further testing is required in the future (for this research project). We will also ask your permission to use these stored samples in other related research projects in the future, however this is optional. The participant can still take part in this research if you do not wish to have their samples used in other projects. Any leftover samples will be destroyed 15 years after the end of the study in the usual safe way that human samples are discarded and destroyed and according to law.

Genetic tests that will be performed in this research will be:
1) to investigate the participant's microbiome which includes all of the bacteria, fungi and viruses that normally live in our bodies, and how these might change during Phage Therapy. This test will not look at any human genetic material, only at the genetic material of microorganisms.
2) to investigate the genes responsible for the participant's immune system and how it responds to the Phage Therapy. This test will not look at any of the participant's other genes so it is unlikely that it will identify any genetic disorders. There is a small chance that we may find that the participant's immune system is not responding as well to infections as in other people. If that is the case, study doctors would let the participant's doctor know the results so that they can discuss these with you and arrange any other investigations that might be needed.

11 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, the study doctor will tell you about it and discuss with you whether you want the participant to continue in the research project. If you decide to withdraw, the study doctor will make arrangements for the participant's regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, the study doctor might consider it to be in the participant's best interests to withdraw them from the research project. If this happens, he/ she will explain the reasons and arrange for the participant's regular health care to continue.

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12 Can the participant have other treatments during this research project?

Participating in this research project will not affect the participant's ability to take other medications or treatments for their condition or for other reasons. However, it is important to tell the study doctor and the study staff about any treatments or medications they may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell the study doctor about any changes to these while the participant is taking part in the research project.

13 What if I withdraw the participant from this research project?

If you decide to withdraw the participant from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional information from or about the participant, although information already collected will be kept as part of the research to ensure that the results of the research can be measured properly and to comply with law. This information will only ever be used in an anonymised way and no personal or identifiable information about the participant will be used for research purposes. You should be aware that data collected by the sponsor up to the time you withdraw the participant will form part of the research project results. If you do not want them to do this, you must tell the study team before the participant joins the research project.

14 Could this research project be stopped unexpectedly?

Although unlikely, this research project may be stopped unexpectedly for a variety of reasons, including unacceptable side effects or safety concerns.

15 What happens when the research project ends?

Once the participant has completed their course of Phage Therapy for their infection, no further ongoing access to Phage Therapy will be required. If further episodes of infection occur, including relapses or recurrence of the same infection, that require further courses of Phage Therapy, these future episodes will be treated as separate events and will be assessed for eligibility for the participant to be re-enrolled in the research project, in the same way as for the initial course of treatment.

All other health care that may be required by the participant after the end of Phage Therapy will be according to routine practice and will be managed by the participant's primary or local doctor.

After the project is completed in 5 years' time, the results of the research will be published in a scientific journal or may be presented at scientific meetings. A summary of publications and presentations will be made available for participants and the public on the Phage Australia website (https://criticalinfection.com/phage-australia/).

Part 2 How is the research project being conducted?

16 What will happen to information about the participant?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal and health information about the participant for the research project. Any information obtained in connection with this research project that can identify the participant will remain confidential and securely stored. The participant's information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

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Information about the participant may be obtained from their health records held at this and other health services for the purpose of this research (e.g. results of lab tests or scans). By signing the consent form you agree to the study team accessing health records if they are relevant to the participant taking part in this research project.

All study information will be entered into a web-based database called REDCap. This is hosted by the University of Sydney and is protected so that only the study team can access the information. Within this database the participant would be assigned a study code. The participant's personal and identifiable information would only be available to the clinical team looking after the participant and the study team at *[Location where the research will be conducted]* so that they can discuss the best possible way to provide Phage Therapy to the participant, including any changes that might be needed in the dose of phage they are receiving. The rest of the research team would only have access to non-personal information through the participant's anonymised study code.

Any of the participant's blood or other samples that need to be sent to external labs will also only be identified with their study code and none of the participant's personal or identifiable information will be sent outside of *[Location where the research will be conducted]*. It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that the participant cannot be identified, except with your permission. All personal and identifiable information will be removed from the data when it is analysed and reported.

Paper documents, including copies of signed consent forms that include any personal or identifiable information will be stored in locked cupboards in offices at *[Location where the research will be conducted]*. All research data will be stored for 15 years after completion of the project, at which point all electronic documents with any identifiable information will be destroyed by permanent deletion and all paper files will be destroyed by shredding.

We will ask your permission to use the participant's anonymised information in other related research projects in the future, however this is optional. The participant can still take part in this research if you do not wish to have their information used in other projects. Only anonymised information would be used for other future research projects and the participant's personal or identifiable information will not be shared with anyone outside of the clinical team looking after the participant and the study team at *[Location where the research will be conducted]* without your permission.

The participant's health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives of the Sponsor, Western Sydney Local Health District, the institution relevant to this Participant Information Sheet, Sydney Children's Hospitals Network Human Research Ethics Committee, or as required by law. By signing the consent form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

In accordance with relevant Australian and *[Name of state/territory]* privacy and other relevant laws, you have the right to request access to the participant's information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access the participant's information.

17 Complaints and Compensation

If the participant suffers any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If the participant is eligible for Medicare, they can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

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18 Who is organising and funding the research?

This research has been funded by the National Health and Medical Research Council (NHMRC) and the Medical Research Future Fund (MRFF) of Australia. It is being conducted by the Phage Australia Network of researchers (https://criticalinfection.com/phage-australia/), including *[Name of local PI and relevant study staff]*.

No member of the research team will receive a personal financial benefit from the participant's involvement in this research project (other than their ordinary wages).

19 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Sydney Children's Hospitals Network.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if the participant has any medical problems which may be related to their involvement in the project (for example, any side effects), you can contact the principal study doctor *[Name of local PI]* on *[phone number]* or any of the following people:

Clinical contact person

Name	During normal working hours: *[Site PI name]* After hours or if unable to contact *[Site PI name]*: Infectious diseases registrar or consultant on call
Position	*[Title/position/department of Site PI]*
Telephone	During normal working hours: *[Site PI contact number]* After hours: Infectious diseases registrar or consultant on call via *[Hospital switch/on call Phone number]*
Email	*[Site PI Email address]*

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Sydney Children's Hospital Network
HREC Executive Officer	Clare Bayram
Telephone	(02) 9845 3066
Email	SCHN-Ethics@health.nsw.gov.au

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Consent Form – Person Responsible

Title	Standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy
Short Title	Standardised Treatment and Monitoring of Phage therapy (STAMP)
Project Sponsor	Western Sydney Local Health District
Coordinating Principal Investigator	Prof Jonathan Iredell
Site Principal Investigator	*[Site PI name]*
Location	*[Location]*

Declaration by Person Responsible

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for the participant's doctors, other health professionals, hospitals or laboratories outside this hospital to release information to *[Name of Institution]* concerning the participant's disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to the participant taking part in this research project as described and understand that I am free to withdraw the participant at any time during the study without affecting their future health care.

I understand that I will be given a signed copy of this document to keep.

I consent to the storage and use of blood and tissue samples taken from the participant for use, as described in the relevant section of the Participant Information Sheet, for:

- This specific research project only
- This research project and other research that is closely related to this research project

Strike out one option above and initial next to your choice.

I consent to the storage and use of the participant's de-identified (anonymous) information, as described in the relevant section of the Participant Information Sheet, for:

- This specific research project only
- This research project and other research that is closely related to this research project

Strike out one option above and initial next to your choice.

I agree to the use of the participant's samples for genetic testing, as outlined in the relevant Section of the Participant Information Sheet.

Name of Participant (please print) _____

Name of Person Responsible (please print) _____

Signature of Person Responsible _____ Date _____

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If the person providing consent is unable to read, an impartial witness should be present during the entire informed consent discussion

Name of Witness* to Person Responsible's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the Person Responsible has understood that explanation.

Name of Study Doctor/ Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

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Form for Withdrawal of Participation – Person Responsible

Title	Standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy
Short Title	Standardised Treatment and Monitoring of Phage therapy (STAMP)
Project Sponsor	Western Sydney Local Health District
Coordinating Principal Investigator	Prof Jonathan Iredell
Site Principal Investigator	*[Site PI name]*
Location	*[Location]*

Declaration by Person Responsible

I wish to withdraw the participant from participation in the above research project and understand that such withdrawal will not affect the participant's routine treatment, our relationship with those treating the participant or our relationship with *[Institution]*.

- I wish to withdraw the participant from any further collection of samples and clinical data for this research
- I wish to withdraw the participant from any further collection of samples but I am allowing continued collection of the participant's clinical data for this research

Strike out one option above and initial next to your choice.

Name of Participant (please print) _____

Name of Person Responsible (please print) _____

Signature of Person Responsible _____ Date_____

In the event that the person responsible's decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the Person Responsible has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.

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Insert Header with institution's name or institution's letterhead

Participant Information Sheet – Young Person

Standardised Treatment and Monitoring of Phage therapy (STAMP)

Title	Standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy
Short Title	Standardised Treatment and Monitoring of Phage therapy (STAMP)
Project Sponsor	Western Sydney Local Health District
Coordinating Principal Investigator	Prof Jonathan Iredell
Site Principal Investigator	*[Site PI name]*
Location	*[Location]*

What does my participation involve?

1 Introduction

You are invited to take part in this research project because you have an infection that your doctor thinks would benefit from Phage Therapy. The research project is investigating the best way to provide Phage Therapy to patients, including how doctors should monitor the treatment.

This Participant Information Sheet tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you should talk about it with your parents or guardians and your doctor.

Participation in this research is voluntary. If you don't want to take part, you don't have to. You will receive the best possible care whether or not you take part.

2 What is the purpose of this research?

Phage Therapy is an experimental treatment. This means that it is not an approved treatment for infections in Australia. The decision to give you Phage Therapy and the specific phage product you will get, has been decided by your doctor and is not part of this research project. This research will look at **how** the treatment should be given to you so that we can better understand how it affects you and other patients like you.

3 What does participation in this research involve?

Once your doctor has decided that Phage Therapy might be good for you, and a suitable phage product has been found for you, they will refer you to one of the study doctors. The study doctors will check that it is o.k. to enrol you in this research. Your parent or guardian will then be asked to sign a consent form before you can take part in the study.

How much of the phage you get, and for how long, and the way in which it will be given to you (through a drip in your vein, by mouth, breathed in or another way) will be decided by one of the

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study doctors, after talking with your doctor. They will make these decisions by thinking about your medical conditions and the specific infection you have. Most patients will get Phage Therapy for 2 weeks in hospital, given through a drip in a vein. For some patients, if the Phage Therapy is needed for longer, this might be given to you in your home or an outpatient clinic. Phage Therapy will always be given by doctors and nurses, and prescribed to you in the same way as other medications.

For most people who get 2 weeks of Phage Therapy through a drip, this will be given only once a day, in the morning for the first 2 days, and then twice a day (morning and evening) for the next 12 days. It is possible that you have once daily treatment for longer than 2 days during the 2 weeks, based on levels of the phage in your blood that will be measured throughout the treatment. Your doctors and nurses will also monitor your heart rate, breathing rate, blood pressure and temperature before and after each dose of phage.

Information regarding your medical condition, your infection, the reason why you are getting Phage Therapy and how your body responds to the treatment will be collected in a database. We will also collect blood and other samples that might be needed for your specific infection (such as swabs or sputum samples). These samples will be collected at specific time-points before, during and after completion of the treatment to try to understand how good the treatment has been at clearing your infection, how it has affected your body in other ways, such as your kidneys and liver, and how your immune system has responded to the treatment.

For most people who get 2 weeks of Phage Therapy through a drip, blood samples will be collected the day before starting Phage Therapy (day 0), and again, 1, 3, 7, 10 and 14 days **after** your first dose (day 1). 4 weeks after your first dose of phage, which is about 2 weeks after your last dose of phage, you will have a follow-up visit with more blood tests. On some of these days, you will be asked to give a blood sample 3 times: once before the morning dose of phage, and then 30-60 minutes, and 2-3 hours after the dose. This will help the study doctors understand how quickly the phage leaves your body, and will also help work out if you should get once or twice daily treatment. The table below shows what days you will have blood tests compared to the first and last dose of phage you get, and how many blood samples are needed each time.

Day	**0**	**1**	**2**	**4**	**8**	**11**	**14**	**15**	**29**
Number of blood samples	x1	First dose of phage	x3	x3	x3	x3	Last dose of phage	x1	x1

Patients who do not get any Phage Therapy through a drip in the vein, or by mouth, will have fewer blood tests. They will not have any blood tests on day 11, and on each day will only have a single set of blood samples taken.

Day	**0**	**1**	**2**	**4**	**8**	**14**	**15**	**29**
Number of blood samples	x1	First dose of phage	x1	x1	x1	Last dose of phage	x1	x1

Patients who have longer courses of Phage Therapy will continue to have blood tests to monitor their treatment every month. All blood samples will be collected by staff who have done lots of blood tests on children and young people, such as doctors, nurses or blood collectors.

Before starting Phage Therapy, at the end of the course and again 3 and 6 months after your treatment you will also be asked to complete an online questionnaire. This will ask you questions about your experience of the Phage Therapy and how it may have affected your quality of life. It will take 10 minutes to complete. Although we would like you to complete the entire questionnaire, you can skip any questions that you don't want to answer.

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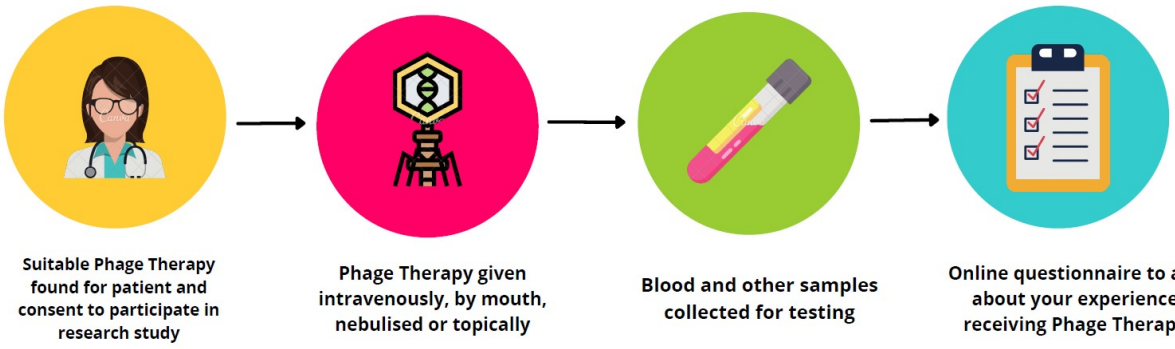

Most patients will be in the study for 1 month. This includes the 2 weeks of Phage Therapy and the follow-up visit 2 weeks after completing Phage Therapy. During this time, in addition to the tests described already, you will be asked about any symptoms and health events that may have occurred so that study doctors can work out how safe Phage Therapy is.

For some patients who are receiving longer courses of Phage Therapy, how long they are in the study will depend on how long Phage Therapy has been recommended for them. Once the Phage Therapy has finished, you will be followed up by your own doctor for at least 6 months. During this time, you will continue to receive invitations to complete the quality-of-life questionnaire at 3 and 6 months after your initial Phage Therapy treatment.

4 What do I have to do?

This research project has been designed to make sure the researchers interpret the results correctly and avoids study doctors or participants jumping to conclusions. It is important that the phage is given in the way it is written in the study protocol (study design) and all of the monitoring tests are done as written in the study protocol. It is also important that all of the information is collected accurately so that data from all patients in the study can be analysed together. This includes answers you give to the quality-of-life questionnaire. However, being part of this research will not affect you in other ways, such as what you can eat, any exercise or other activities you do, or other medications you may need. All of your other usual health care will continue as normal.

5 Other relevant information about the research project

This research is being conducted at many hospitals around Australia and will continue for 5 years. We would like to enrol 50-100 people in the study during this time. At *[Location where the research will be conducted]* we expect around 2-3 people to be enrolled each year. The research is a collaboration (teamwork) between multiple hospitals, universities and research institutes working together.

6 Do I have to take part in this research project?

Taking part in any research project is voluntary. If you do not want to take part, you do not have to. If you decide to take part and later change your mind, you can stop taking part (withdraw) at any time. Your decision to take part or not, or to take part and then later stop taking part, will not affect your usual health care, your relationship with those treating you or your relationship with *[Institution]*.

7 What are the alternatives (other options) to taking part in this research?

You do not have to take part in this research project to receive treatment at this hospital. If you choose not to take part in this research, your doctor(s) may still decide to give you Phage Therapy but it may not be monitored in the way described in this research. This includes having

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access to some of the special tests that are not available in usual hospital or community labs. Your study doctor will discuss these options with you before you decide whether or not to take part in this research project. You can also discuss the options with your own doctor and your parents or guardians.

8 What are the possible benefits of taking part?

We can't promise that you will receive any benefits from this research; however, possible benefits might be clearing your infection or improving how you feel. In addition, your treatment will be overseen and monitored by a group of study doctors which include specialists in infectious diseases and Phage Therapy from around Australia and the world. The information that we collect in this research will also help us and other researchers work out the best way to give Phage Therapy to other patients in the future. It may also help us make Phage Therapy more widely available in Australia to other patients.

9 What are the possible risks of taking part?

Any medical treatment can cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

The specific phage product you will get will be decided by your own doctor. This will be discussed with one of the study doctors, but this decision is not included in the research. Your doctor can give you information about the phage product you will get, including where it has come from and how it has been produced. Below is some general information about possible risks that might occur for patients receiving Phage Therapy.

Phage Therapy general information and risks
Phages are viruses that infect and kill bacteria, but they do not attack human cells. For this reason, phage therapy is very safe. It has been used for over 100 years to treat patients with bacterial infections. When phages are purified well, they cause very few side effects. Only phages that are highly purified will be used in this research.

Sometimes patients can have a brief reaction after the first few doses of phage. This is mostly due to the phage attacking and killing the bacteria causing your infection. It is usually a good sign that the phages are doing their job but it may be a little uncomfortable for you. You may have a fever or feel unwell in other ways (chills, headache, muscle aches). Depending on where your infection is, you may also get some pain there. Usually, this reaction only lasts a few hours and can be treated easily with simple medication like paracetamol or ibuprofen. Very occasionally, there may be a severe reaction which might mean that further doses of phage are delayed or not given.

Other side effects that might occur during your treatment include abnormalities in results of lab tests of your liver or kidneys, blood cells and immune system. If study doctors see any abnormalities on your blood tests, they will monitor them until they go back to normal for you. In our experience of treating patients in Australia, as well as reports from patients treated in other countries, these abnormalities in lab tests are usually not severe and all get better a few weeks after stopping the Phage Therapy.

Unknown risks of Phage Therapy
There might be other side effects that we do not expect or do not know about. Tell your study doctor immediately about any new or unusual symptoms that you get. Sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor might need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you. Any side effects that might occur during your treatment will

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be managed or treated by the study doctors and your own doctors according to usual health care practice.

Risks of taking part in this research project
There are very few risks to taking part in this research because the study is mainly looking at how Phage Therapy should be given and monitored. As part of the research, you will be asked to give blood and other samples at specific timepoints, and the phage will be given to you at specific times of the day, for most patients injected through a drip in the vein. Having a treatment injected or blood samples taken might be uncomfortable and might cause bruising, minor infection or bleeding. If this happens, it can be easily treated.

If any problems happen for you because you are taking part in this research project, you should contact the study team as soon as possible. They will make sure you get the help and treatment you need. If you become upset at any time because you are taking part in this research, the study doctor will be able to get counselling or other support to help you.

10 What will happen to my test samples?

Most of the tests that will be done to monitor your treatment are the same lab tests that are usually used by doctors to monitor infections. These tests will be done at the usual labs where tests for patients from *[Location where the research will be conducted]* are done. Once the testing is finished, the samples will be destroyed in the same way as other patient samples are normally handled by labs.

Some of the tests are specific to the Phage Therapy, including tests to look for the levels of phage in your blood, tests to look at how your immune system is responding to the Phage Therapy and tests that will look at your microbiome (the collection of bacteria and other microorganisms, including viruses, which live in your body). Your blood and other samples such as urine, sputum, faeces (poo) that are collected for these tests may need to be sent to another lab in Australia that specialises in Phage Therapy. If this is the case, the samples will be sent in an anonymous way, using only a study code that will be given to you for the research project. None of your personal information (such as your name or address) will be sent outside of *[Location where the research will be conducted]*. Only study doctors from *[Location where the research will be conducted]* and your clinical team will know that these samples are yours, using your specific study code.

These tests are all needed for you to take part in the research. Once testing on these samples is finished, the samples will be kept in the outside lab in case more testing is required later for this research project. We will also ask your permission to use these stored samples in other similar research projects in the future, but this is optional. You can still take part in this research if you do not want to have your samples used in other projects. Any leftover samples will be destroyed 15 years after the end of the study in the usual safe way that human samples are destroyed and according to the law.

Some genetic tests that will be performed in this research will be:
1) to look at your microbiome which includes all of the bacteria, fungi and viruses (microorganisms) that normally live in our bodies, and how these might change during Phage Therapy. This test will not look at your genes, only at the genes of these microorganisms.
2) to look at the genes responsible for your immune system and how it responds to the Phage Therapy. This test will not look at any of your other genes. There is a small chance that we may find that your immune system is not responding as well to infections as in other people. If that happens, study doctors would let your doctor know so that they can discuss these with you and your parents or guardians.

11 What if new information comes up during this research project?

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Sometimes, during a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue to take part in the research. If you decide you don't want to continue in the research, your study doctor will make sure your regular health care continues.

Also, on receiving new information, your study doctor might think it is better for you not to continue in the research project. If this happens, he/she will explain the reasons.

12 Can I have other treatments during this research project?

Taking part in this research project will not affect whether or not you can take other medications or treatments. But it is important to tell your study doctor and the study staff about any treatments or medications you are taking, including vitamins or herbal medicines. You should also tell your study doctor if any of your medications change during the time you are taking part in the research project.

13 What if I want to stop taking part in this research project?

If you decide to stop taking part in the research project, please let a member of the research team know so they can discuss with you anything that needs to happen or anything that you may need to do when you stop taking part in the research.

If you decide to stop taking part in the research project at any point, the study doctor and study staff will not collect any more information from or about you, although information already collected will be kept as part of the research to make sure that the results of the research can be measured properly.

14 Could this research project be stopped unexpectedly?

Although unlikely, this research project may be stopped unexpectedly for a variety of reasons, including unacceptable side effects or safety concerns.

15 What happens when the research project ends?

Once you have completed your course of Phage Therapy for your infection, you won't need any more Phage Therapy. If the infection comes back, gets worse or you get another infection that needs Phage Therapy again, your doctor can refer you to the study doctors again to see if you can be re-enrolled in the research project.

All other health care that you might need after the end of Phage Therapy will be according to usual practice and will be managed by your doctor.

When the project is completed in 5 years' time, the results of the research will be published in a scientific journal or may be presented at scientific meetings. A summary of publications and presentations will be made available for everyone on the Phage Australia website (https://criticalinfection.com/phage-australia/).

Part 2 How is the research project being conducted?

16 What will happen to information about me?

By agreeing to take part in this research project you agree to let the study doctor and other study staff collect and use information about you for the research project. Any information that is collected as part of this research project that can identify you (like your name or address) will be kept confidential (private) and stored securely. Your information will only be used for this

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research project and it will not be shared with anyone without your permission, except if it is required by law.

Information about you may be collected from your health records held at this and other health services (labs, clinics, hospitals) for this research (such as the results of lab tests or scans).

All study information will be entered into a web-based database called REDCap. This is provided by the University of Sydney and is protected so that only the study team can see the information. Within this database you will be given a study code. Your personal information will only be available to the team looking after you and the study team at *[Location where the research will be conducted]* so that they can discuss the best possible way to give you Phage Therapy, including any changes that might be needed in the dose of phage you are receiving. The rest of the research team would only be able to see non-personal information through your anonymous study code.

Any of your blood or other samples that need to be sent to outside labs will only have your study code and none of your personal information will be sent outside of *[Location where the research will be conducted]*. We expect to publish and/or present the results of this research project in scientific journals and meetings. In any publication and/or presentation, only anonymous information will be used so that you can't be identified, except with your permission.

Paper documents that have any of your personal information will be kept in locked cupboards in offices at *[Location where the research will be conducted]*. All research data will be stored for 15 years after the end of the project, and then everything with any personal information will be destroyed by permanently deleting electronic files and shredding any paper documents.

We will also ask your permission to use your anonymous information in other similar research projects in the future, but this is optional. You can still take part in this research if you do not want to have your information used in other projects.
According to the law in Australia and *[Name of state/territory]*, you are allowed to ask to see the information collected by the research team about you. You can also ask to have any information about you corrected if you disagree with it. Please contact the study team member named at the end of this Information Sheet if you would like to see your information.

17 Who is organising and funding the research?

Money for this research comes from the National Health and Medical Research Council (NHMRC) and the Medical Research Future Fund (MRFF) of Australia. The research is being done by the Phage Australia Network of researchers (https://criticalinfection.com/phage-australia/), including *[Name of local PI and relevant study staff]*.

No member of the research team will get any money because you are taking part in this research project (other than their normal salary/wages).

18 Who has reviewed the research project?

All research in Australia involving humans is reviewed (checked) by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Sydney Children's Hospitals Network.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This has been developed to protect people who agree to take part in research projects.

19 Further information and who to contact

The person you need to contact will depend on what your question is.

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If you want any more information about this project or if you have any medical problems which might be related to taking part in the project (for example, any side effects), you can contact the main study doctor *[Name of local PI]* on *[phone number]* or any of the following people:

Clinical (medical) contact person

Name	During normal working hours: *[Site PI name]* After hours or if unable to contact *[Site PI name]*: Infectious diseases registrar or consultant on call
Position	*[Title/position/department of Site PI]*
Telephone	During normal working hours: *[Site PI contact number]* After hours: Infectious diseases registrar or consultant on call via *[Hospital switch/on call Phone number]*
Email	*[Site PI Email address]*

If you have any complaints about the project or the way it is being done, or any questions about being part of a research project in general, you can contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Sydney Children's Hospital Network
HREC Executive Officer	Clare Bayram
Telephone	(02) 9845 3066
Email	SCHN-Ethics@health.nsw.gov.au

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THERAPEUTIC USE OF BACTERIOPHAGE PREPARATION EC184B

Phage Australia | Jon Iredell

Phage Australia Phage Safety Data Sheet v2.0

Issued	Westmead	**time**	23092022_1430
Common name	EC134B		caudovirales/ demerecviridae
PA ID	ECP00134B		
Provenance	Westmead (Iredell lab) Jan 2019		
Genomic. acc. no.	TBA		

Lysogeny markers identified[1]	None
Antibiotic resistance genes identified[2]	None
Virulence related genes identified[3]	None

Comment

EC134B is a dsDNA T5 virus of 108 Kb, with no evident virulence- or antibiotic resistance-associated genes of concern detected, using standard approaches at the time of reporting*. Its closest match in NCBI *nr* is Salmonella phage L6jm (89% coverage, 98% max identity) at the time of reporting. Extremely high coverage (>900X) was obtained to ensure absence of background contamination.

Reporting bioinformatician **Nouri BEN ZAKOUR**

Supervising pathologist **Jon IREDELL 24/09/22**

**Genome sequencing*: Whole genome sequencing (WGS) of pure phage preparation was performed at the Centre for Infectious Disease and Microbiology, Westmead Institute for Medical research. Genomic DNA was extracted using QIAGEN DNeasy Blood and Tissue Mini Kit (QIAGEN). Sequencing libraries were prepared using Illumina DNA Library Prep Kit and sequenced on a iSeq 100.

Primary genome analysis: Sequenced raw reads were subjected to an in-house quality control procedure prior to further analysis and analyzed using the in-house bz_phage_pipeline (v0.1.0). Sequencing quality assessment and filtering was performed using FastP (v0.20.1). Assembly was performed using Unicycler v0.5.0 (conservative and normal modes) and inspected using Bandage (v0.8.1). Taxonomy and sequence contamination profiling were performed using Kraken 2 (v2.1.2 – db minikraken2_v2_8GB_201904_UPDATE) and Blobtools (v1.1.1 – db ref_viruses_rep_genomes 2022-Sep-23 update). Closest match was identified using BLASTn (v2.13.0) against nr. Identification of phage-related contigs, functional annotation, lifestyle predictions, phage contigs assembly quality, and circularity were performed using the VIBRANT pipeline (v1.2.0).

Resistome analysis: Sequence data were screened using Abricate (v1.0.1) against the NCBI Bacterial Antimicrobial Resistance Reference Gene Database (2022-Sep-23 update) to identify specific resistance gene variants. Results from the VIBRANT pipeline were also used to confirm absence of resistance related genes using HMMER3 against KEGG, PFAM and pVOG.

Virulence factors analysis: Sequence data were screened using Abricate (v1.0.1) against the VFDB (2022-Sep-23 update). Results from the VIBRANT pipeline were also used to confirm absence of virulence and toxin related genes using HMMER3 against KEGG, PFAM and pVOG.

Enquiries to **Jon Iredell**

02 8890 6102/6255

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Phage Australia Bacterial Safety Data Sheet v2.0

Issued Westmead **time** 23092022_1430

Common name	BW25113	*Escherichia coli*
PA ID	BW251131-1	ST 10

Genomic. acc. no.	CP009273
prophages identified[1]	CP4-6, DLP12, e14, rac, Qin, CP4-44, CPS-53, CPZ-55, CP4-57
major plasmids identified[2]:	none
Antibiotic resistance genes identified[3]	blaEC-19
Virulence related genes identified[4]	none

Comment

The clinical risk associated with co-purified toxins and phages arising from this production strain is low.

Escherichia coli strain BW25113 is a K12 laboratory strain extensively studied and used for phage propagation, systematic phenotypic surveys and synthetic biology projects. Nine prophages are detected (mostly remnant, 10-40 Kb). Genome sequence analysis of this strain using standard approaches at the time of reporting* revealed an absence of problematic antimicrobial resistance genes, characterised toxins, plasmids, and functional CRISPR machinery. BlaEC-19 is a chromosomal class C cephalosporinase-encoding gene ("*E. coli* Amp C") commonly found in *E. coli*.

Reporting bioinformatician **Nouri BEN ZAKOUR**

Supervising pathologist **Jon IREDELL 24/09/22**

**Genome sequencing*: Whole genome sequencing (WGS) of pure cultures was performed at the Centre for Infectious Disease and Microbiology, Westmead Institute for Medical research Genomic DNA was extracted using QIAGEN DNeasy Blood and Tissue Mini Kit (QIAGEN). Sequencing libraries were prepared using Illumina DNA Library Prep Kit and sequenced on an iSeq 100.

Primary genome analysis: Sequenced raw reads were subjected to an in-house version of the Nullarbor pipeline (v1.2; https://github.com/tseemann/nullarbor). Assemblies were performed using Unicycler v0.5.0 and inspected using Bandage (v0.8.1). Taxonomy and sequence contamination profiling were performed using Kraken 2 (v2.1.2 – db minikraken2_v2_8GB_201904_UPDATE) and Blobtools (v1.1.1 – db ref_viruses_rep_genomes 2022-Sep-23 update). The WGS-based multilocus sequence type (MLST) was inferred from sequencing data using MLST 2.8 from the pipeline.

Mobile genetic elements analysis: Identification of phage-related contigs, functional annotation, lifestyle predictions, phage contigs assembly quality were performed using the VIBRANT pipeline (v1.2.0). Additional intact and remnant prophages were identified using PHASTER (https://phaster.ca/), then manually inspected.

Resistome analysis: Sequence data were screened using Abricate (v1.0.1) against the NCBI Bacterial Antimicrobial Resistance Reference Gene Database (2022-Sep-23 update) to identify specific resistance gene variants. Characteristics and mobile genetic elements and plasmid markers were inferred from sequencing data using the Plasmid Finder and plasmidMLST services (https://cge.cbs.dtu.dk/services/).

Virulence factors analysis: Sequence data were screened using Abricate (v1.0.1) against the VFDB (2022-Sep-23 update). Results from the VIBRANT pipeline were also used to confirm absence of virulence and toxin related genes using HMMER3 against KEGG, PFAM and pVOG.

Enquiries to **Jon Iredell**

+61 2 8890 6012/6255

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Phage Australia

Batch Cert. Data Sheet v2.0

Issued	WIMR	**time**	27092022_2210
Phage	Ec134B		Caudovirales/ Demerecviridae
Production strain	BW25113		*Escherichia coli*

Batch ID	**Ec134b_BW25113_270922**
Production date	**27092022**
Nominated expiry date	**25102022**
Medium	saline
Storage	4C, glass vials
Batch volume	34 x 2.0-mL vials
PFU/mL	1 x 10^9
EU/mL	6.18
Sterility	No growth at 5 days
pH	6.6
Genome sequencing*	99.7% sequence purity

Comment

Phage Ec134b was produced and purified according to Phage on Tap methodology (Bonilla et al. 2016)**. Briefly, phage was co-cultured with host strain BW25113 in 150 mL LB + 1mM $CaCl_2$ + 1mM $MgCl_2$ at 37 ºC 18 h to a final concentration of 1.1x10^{11} PFU/mL. Clarified lysate was filtered through 0.22 um to sterilize, concentrated by 50 kDa Amicon spin column, and washed with saline to remove media components. Endotoxin was depleted using octanol extraction. Octanol was removed by dialysis against 25% EtOH (2L x 3 h x 4) and then 0.15 M NaCl (2L x 3 h x 4). Endotoxin reading of concentrated lysate (measured by Charles River Limulus Amoebocyte Lysate assay using Endosafe LAL cartridge) showed 618 EU/mL. Batch was diluted 1/100 in sterile saline, aliquoted into 2 mL vials, and stored at 4 ºC. Phage titre of diluted lysate (as determined by plaque assay on BW25113) showed 1.0 x 10^9 PFU/mL. Diluted batch was used to inoculate blood culture bottles for sterility testing (1-mL inoculum; aerobic and anaerobic) and to perform pH testing. Sterility testing was performed by Institute Of Clinical Pathology And Medical Research (ICPMR), Westmead via Culture Body Fluid BC Bottle.

Batch satisfies endotoxin thresholds for safe use at up to 10^9 PFU/kg/hr intravenously based on <5 EU/kg/h acceptable limit.

Reporting scientists **Jessica SACHER**

Supervising pathologist **Jon IREDELL 04/10/22**

**Genome sequencing*: Whole genome sequencing (WGS) of pure phage preparation was performed at the Centre for Infectious Disease and Microbiology, Westmead Institute for Medical research. Genomic DNA was extracted using QIAGEN DNeasy Blood and Tissue Mini Kit (QIAGEN). Sequencing libraries were prepared using Illumina DNA Library Prep Kit and sequenced on a iSeq 100.

Primary genome analysis: Sequenced raw reads were subjected to an in-house quality control procedure prior to further analysis and analyzed using the in-house bz_phage_pipeline (v0.1.0). Sequencing quality assessment and filtering was performed using FastP (v0.20.1). Assembly was performed using Unicycler v0.5.0 (conservative and normal modes) and inspected using Bandage (v0.8.1). Taxonomy and sequence contamination profiling were performed using Kraken 2 (v2.1.2 – db

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minikraken2_v2_8GB_201904_UPDATE) and Blobtools (v1.1.1 – db ref_viruses_rep_genomes 2022-Sep-23 update). Closest match was identified using BLASTn (v2.13.0) against nr. Identification of phage-related contigs, functional annotation, lifestyle predictions, phage contigs assembly quality, and circularity were performed using the VIBRANT pipeline (v1.2.0).

Resistome analysis: Sequence data were screened using Abricate (v1.0.1) against the NCBI Bacterial Antimicrobial Resistance Reference Gene Database (2022-Sep-23 update) to identify specific resistance gene variants. Results from the VIBRANT pipeline were also used to confirm absence of resistance related genes using HMMER3 against KEGG, PFAM and pVOG.

Virulence factors analysis: Sequence data were screened using Abricate (v1.0.1) against the VFDB (2022-Sep-23 update). Results from the VIBRANT pipeline were also used to confirm absence of virulence and toxin related genes using HMMER3 against KEGG, PFAM and pVOG.

**Bonilla N, Rojas MI, Netto Flores Cruz G, Hung S, Rohwer F, Barr JJ. 2016. Phage on tap–a quick and efficient protocol for the preparation of bacteriophage laboratory stocks. PeerJ 4:e2261 https://doi.org/10.7717/peerj.2261

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Issued	Westmead	**time**	26092022_12:30
Referring doctor	Jon Iredell	Westmead Hospital, NSW	
Contact	02 8890 6012		
Received	29032021_1140		
Case ID	**WIMR_C6**		
Isolate ID	ECOL_C6_1 & ECOL_C6_2		

Clinical notes

Chronically infected thoracotomy dominated by *E. coli* pathogen, previous combined antibiotic and surgical approaches have failed.

In vitro phage susceptibility

Efficiency of plating (EOP)

Efficiency of plating (EOP) is used to determine the efficiency of a phage on a test isolate (e.g. patient isolate) compared to the phage reference strain (host strain). The EOP is determined by serially diluting a phage of interest of a known concentration and spotting the dilutions on a bacterial lawn of a reference strain (phage host strain) and on a test isolate (e.g. patient isolate). Following incubation, the titre of the phage on the respective bacterial isolates is calculated by counting the number of phage plaques, multiplied by the dilution factor and divided by the volume of phage plated. The EOP value is calculated by dividing the titre of the phage on the test isolate by the titre on the reference strain divided, this value is represented as a percentage of efficiency.

Titre of EC134b on BW25113 (EOP %): 1.1 x 10^{11} PFU/mL (100%)

Titre of EC134b on Case 6 isolate 1 (EOP %): 1.03 x 10^{11} PFU/mL (94%)

Titre of EC134b on Case 6 isolate 2 (EOP %): 0 PFU/mL (0%)

Kinetic assay

A kinetic assay is an assay used to observe the phages' ability to inhibit the bacterial growth within a liquid medium. For this assay, the patient bacterial isolate is added to wells of a 96-well microplate, followed by the addition of either control substances (broth) or phage at different concentrations, and the absorbance (OD 600nm) is read every 10 mins over an 18-hour period, by a microplate reader. Following the 18-hour assay, analysis is performed to determine whether the phage is able to inhibit the patient isolate and the optimal phage concentration to do so.

Enquiries to **Jon Iredell**

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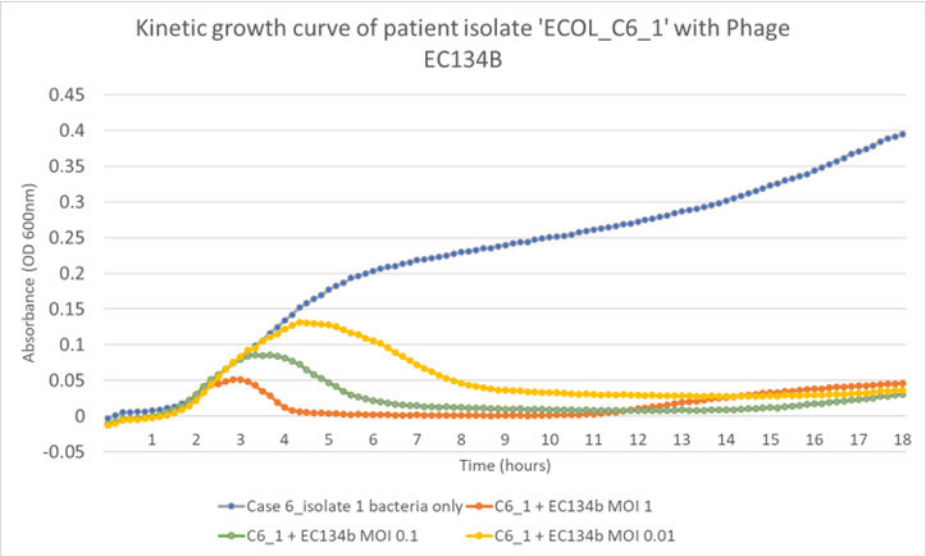

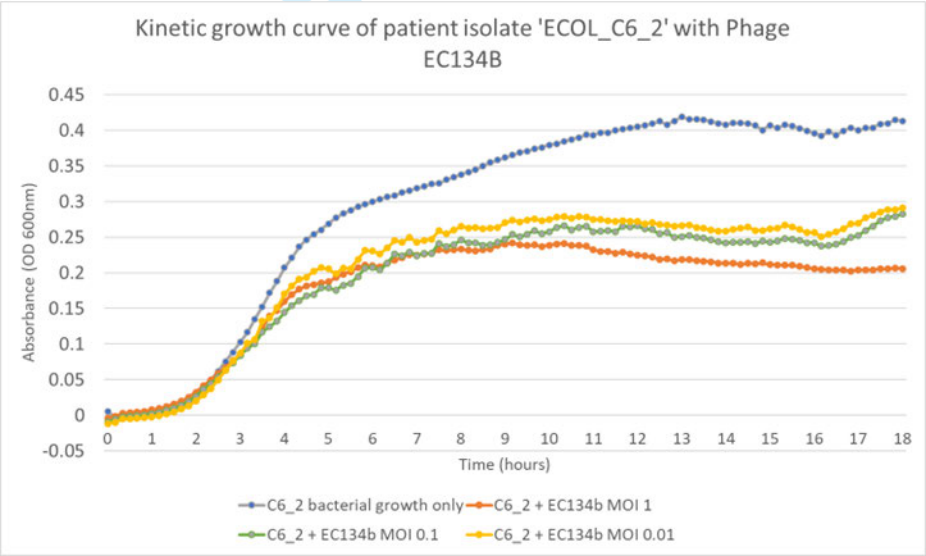

Comment

Escherichia coli ECOL_C6_1 is susceptible to EC134b with a 94% efficiency in the EOP assay and inhibits the growth of this isolate for 18 hours in the kinetic assay (Figure 1). Escherichia coli ECOL_C6_2 is not susceptible to EC134b as there is a 0% efficiency in the EOP assay, however, there is a moderate inhibitory effect of this phage-isolate combination in the kinetic assay (Figure 1).

Enquiries to **Jon Iredell**

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Recommend.
EC134b at MOI 1 (~1 x 10^9 PFU/mL) adjunct to antibiotics recommended by treating physician.

Reporting scientists **Stephanie LYNCH & Jessica SACHER**

Supervising pathologist **Jon IREDELL xx/xx/22**

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Enquiries to **Jon Iredell**

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Variable / F	Form Name	Section Hea	Field Typ	Field Label	Choices, Ca	Field Note	Text Valida	min	max	Identifier?	Branching L	Requir	Custom	Questior	Matrix Gr	Matrix Gro	Field Annotation
phage_pati	screening_log_beta		text	Phage Patient ID													
sc_date	screening_log_beta		text	Date of referral			date_dmy					y					
sc_ptp_initi	screening_log_beta		text	Patient initials		Only two letters allowed						y					@CHARLIMIT=2
sc_dob	screening_log_beta		text	DOB			date_dmy			y		y					
sc_meets_i	screening_log_beta		yesno	Meets inclusion criteria								y					
sc_exclusio	screening_log_beta		checkbox	Reason for	1, Source control sub-optimal | 2, Polymicrobial infection (>2 key						[sc_meets_	y					
sc_exclusio	screening_log_beta		checkbox	If phage pr	1, Phage activity against target pathogen(s) limited/undocumente						[sc_exclusic	y					@CHARLIMIT=100
sc_exclusio	screening_log_beta		notes	Specify other exclusion reasons							[sc_exclusic	y					
dm_no_inc	demographics_beta		descriptiv	<h3><span style="background-color: #e03e2							[sc_meets_inclusion] < 1						
dm_picf_si	demographics_beta		text	Date PICF signed			date_dmy				[sc_meets_	y					
dm_consen	demographics_beta		calc	Age at time	round(datediff([sc_dob], "today", "y"),2)						[sc_meets_	y					
dm_gender	demographics_beta		radio	Gender	m, M | f, F						[sc_meets_	y					
dm_recruit	demographics_beta		radio	Recruitmen	westmd, Westmead Hospital | schn, Sydney Children's Hospitals N						[sc_meets_	y					
pre_no_inc	pretreatment_beta		descriptiv	<h3><span style="background-color: #e03e2							[sc_meets_inclusion] < 1						
pre_primar	pretreatment_beta		radio	Primary inf	1, Endovascular infection | 2, Lung infection | 3, Musculoskeletal i						[sc_meets_	y					
pre_primar	pretreatment_beta		notes	Other prim	1, Endovascular infection | 2, Lung infection | 3, Musculoskeletal i						[sc_meets_	y					@CHARLIMIT='50'
pre_infectic	pretreatment_beta		radio	Duration of	1, Acute (< 2 weeks) | 2, Subacute (2 weeks-2 months) | 3, Chroni						[sc_meets_	y					
pre_other_	pretreatment_beta		notes	Other medical or surgical diagnoses (please list if directly relevant to infection							[sc_meets_	y					
pre_has_im	pretreatment_beta		yesno	Immune suppression							[sc_meets_	y					
pre_immu_	pretreatment_beta		radio	Primary cor	1, HIV | 2, Malignancy with or without chemotherapy | 3, SOT | 4						[sc_meets_	y					
pre_immu_	pretreatment_beta		text	Other primary condition							[sc_meets_	y					@CHARLIMIT='50'
pre_immu_	pretreatment_beta		checkbox	Acquired cc	1, HIV | 2, Malignancy with or without chemotherapy | 3, SOT | 4						[sc_meets_	y					
pre_immu_	pretreatment_beta		text	Other acquired conditions							[sc_meets_	y					@CHARLIMIT='50'
pre_has_pr	pretreatment_beta		yesno	Prosthesis involved							[sc_meets_	y					
pre_prosth	pretreatment_beta		checkbox	Types of pr	1, Prosthetic valve | 2, Vascular shunt | 3, Ventricular assist devic						[sc_meets_	y					
pre_prosth	pretreatment_beta		text	Please specify	Other endovascular prosthesis						[sc_meets_	y					@CHARLIMIT='50'
pre_prosth	pretreatment_beta		text	Please specify	Other osteoartciular prosthesis						[sc_meets_	y					@CHARLIMIT='50'
pre_prosth	pretreatment_beta		text	Please specify	Other drain						[sc_meets_	y					@CHARLIMIT='50'
pre_prosth	pretreatment_beta		text	Please specify	Other prosthesis						[sc_meets_	y					@CHARLIMIT='50'
pre_pt_indi	pretreatment_beta		checkbox	Indication f	1, Intolerance of standard therapy due to side effects | 2, Failure o						[sc_meets_	y					
pre_pt_indi	pretreatment_beta		text	Specify other indication for phage therapy							[sc_meets_	y					@CHARLIMIT='50'
pre_num_t	pretreatme	Pathogen S	radio	How many	1,1 | 2,2 | 3,3 | 4,4 | 5,5						[sc_meets_	y					
pre_pth1_d	pretreatment_beta		descriptiv	Pathogen 1							[sc_meets_inclusion] = "1" and [pre_num_target_pathogen] > 0						
pre_pth1_t	pretreatment_beta		radio	[Pathogen	1, E. coli | 2, P. aeruginosa | 3, M. abscessus | 4, S. aureus | 11, Kl						[sc_meets_	y					
pre_pth1_s	pretreatment_beta		text	[Pathogen 1] Full Genus	e.g. Salmonella enterica						[sc_meets_	y					@CHARLIMIT='50'
pre_pth1_is	pretreatment_beta		yesno	[Pathogen 1] ESBL?							[sc_meets_	y					
pre_pth1_is	pretreatment_beta		yesno	[Pathogen 1] MRSA?							[sc_meets_	y					
pre_pth1_is	pretreatment_beta		yesno	[Pathogen 1] VRE?							[sc_meets_	y					
pre_pth1_s	pretreatment_beta		radio	[Pathogen	confirmed, Confirmed (isolated from site of infection) | suspected						[sc_meets_	y					
pre_pth1_is	pretreatment_beta		checkbox	[Pathogen	1, Blood | 2, Sputum/endotracheal aspirate | 3, BAL fluid | 4, Join						[sc_meets_	y					

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pre_pth1_i	pretreatment_beta	text	[Pathogen 1] Specify Intra-operative pus site	[sc_meets_ y	@CHARLIMIT='50'
pre_pth1_i	pretreatment_beta	text	[Pathogen 1] Specify Intra-operative tissue type	[sc_meets_ y	@CHARLIMIT='50'
pre_pth1_i	pretreatment_beta	text	[Pathogen 1] Specify Non-operative swab site	[sc_meets_ y	@CHARLIMIT='50'
pre_pth1_h	pretreatment_beta	yesno	[Pathogen 1] Is WGS data available?	[sc_meets_ y	
pre_pth1_v	pretreatment_beta	notes	[Pathogen 1] Where is the WGS data stored?	[sc_meets_ y	
pre_pth1_h	pretreatment_beta	yesno	[Pathogen 1] Is the isolate available for further testing?	[sc_meets_ y	
pre_pth1_i	pretreatment_beta	notes	[Pathogen 1] Where is the isolate stored?	[sc_meets_ y	
pre_pth2_d	pretreatment_beta	descriptiv	Pathogen 2	[sc_meets_inclusion] = "1" and [pre_num_target_pathogen] > 1	
pre_pth2_t	pretreatment_beta	radio	[Pathogen 2] 1, E. coli | 2, P. aeruginosa | 3, M. abscessus | 4, S. aureus | 11, Kl	[sc_meets_ y	
pre_pth2_s	pretreatment_beta	text	[Pathogen 2] Full Genus e.g. Salmonella enterica	[sc_meets_ y	@CHARLIMIT='50'
pre_pth2_i	pretreatment_beta	yesno	[Pathogen 2] ESBL?	[sc_meets_ y	
pre_pth2_i	pretreatment_beta	yesno	[Pathogen 2] MRSA?	[sc_meets_ y	
pre_pth2_i	pretreatment_beta	yesno	[Pathogen 2] VRE?	[sc_meets_ y	
pre_pth2_s	pretreatment_beta	radio	[Pathogen 2 confirmed, Confirmed (isolated from site of infection) | suspected	[sc_meets_ y	
pre_pth2_i	pretreatment_beta	checkbox	[Pathogen 2] 1, Blood | 2, Sputum/endotracheal aspirate | 3, BAL fluid | 4, Join	[sc_meets_ y	
pre_pth2_i	pretreatment_beta	text	[Pathogen 2] Specify Intra-operative pus site	[sc_meets_ y	@CHARLIMIT='50'
pre_pth2_i	pretreatment_beta	text	[Pathogen 2] Specify Intra-operative tissue type	[sc_meets_ y	@CHARLIMIT='50'
pre_pth2_i	pretreatment_beta	text	[Pathogen 2] Specify Non-operative swab site	[sc_meets_ y	@CHARLIMIT='50'
pre_pth2_h	pretreatment_beta	yesno	[Pathogen 2] Is WGS data available?	[sc_meets_ y	
pre_pth2_v	pretreatment_beta	notes	[Pathogen 2] Where is the WGS data stored?	[sc_meets_ y	
pre_pth2_h	pretreatment_beta	yesno	[Pathogen 2] Is the isolate available for further testing?	[sc_meets_ y	
pre_pth2_i	pretreatment_beta	notes	[Pathogen 2] Where is the isolate stored?	[sc_meets_ y	
pre_pth3_d	pretreatment_beta	descriptiv	Pathogen 3	[sc_meets_inclusion] = "1" and [pre_num_target_pathogen] > 2	
pre_pth3_t	pretreatment_beta	radio	[Pathogen 3] 1, E. coli | 2, P. aeruginosa | 3, M. abscessus | 4, S. aureus | 11, Kl	[sc_meets_ y	
pre_pth3_s	pretreatment_beta	text	[Pathogen 3] Full Genus e.g. Salmonella enterica	[sc_meets_ y	@CHARLIMIT='50'
pre_pth3_i	pretreatment_beta	yesno	[Pathogen 3] ESBL?	[sc_meets_ y	
pre_pth3_i	pretreatment_beta	yesno	[Pathogen 3] MRSA?	[sc_meets_ y	
pre_pth3_i	pretreatment_beta	yesno	[Pathogen 3] VRE?	[sc_meets_ y	
pre_pth3_s	pretreatment_beta	radio	[Pathogen 3 confirmed, Confirmed (isolated from site of infection) | suspected	[sc_meets_ y	
pre_pth3_i	pretreatment_beta	checkbox	[Pathogen 3] 1, Blood | 2, Sputum/endotracheal aspirate | 3, BAL fluid | 4, Join	[sc_meets_ y	
pre_pth3_i	pretreatment_beta	text	[Pathogen 3] Specify Intra-operative pus site	[sc_meets_ y	@CHARLIMIT='50'
pre_pth3_i	pretreatment_beta	text	[Pathogen 3] Specify Intra-operative tissue type	[sc_meets_ y	@CHARLIMIT='50'
pre_pth3_i	pretreatment_beta	text	[Pathogen 3] Specify Non-operative swab site	[sc_meets_ y	@CHARLIMIT='50'
pre_pth3_h	pretreatment_beta	yesno	[Pathogen 3] Is WGS data available?	[sc_meets_ y	
pre_pth3_v	pretreatment_beta	notes	[Pathogen 3] Where is the WGS data stored?	[sc_meets_ y	
pre_pth3_h	pretreatment_beta	yesno	[Pathogen 3] Is the isolate available for further testing?	[sc_meets_ y	
pre_pth3_i	pretreatment_beta	notes	[Pathogen 3] Where is the isolate stored?	[sc_meets_ y	
pre_pth4_d	pretreatment_beta	descriptiv	Pathogen 4	[sc_meets_inclusion] = "1" and [pre_num_target_pathogen] > 3	
pre_pth4_t	pretreatment_beta	radio	[Pathogen 4] 1, E. coli | 2, P. aeruginosa | 3, M. abscessus | 4, S. aureus | 11, Kl	[sc_meets_ y	
pre_pth4_s	pretreatment_beta	text	[Pathogen 4] Full Genus e.g. Salmonella enterica	[sc_meets_ y	@CHARLIMIT='50'
pre_pth4_i	pretreatment_beta	yesno	[Pathogen 4] ESBL?	[sc_meets_ y	

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pre_pth4_i	pretreatment_beta	yesno	[Pathogen 4] MRSA?	[sc_meets_ y	
pre_pth4_i	pretreatment_beta	yesno	[Pathogen 4] VRE?	[sc_meets_ y	
pre_pth4_s	pretreatment_beta	radio	[Pathogen 4 confirmed, Confirmed (isolated from site of infection) | suspected	[sc_meets_ y	
pre_pth4_i	pretreatment_beta	checkbox	[Pathogen 4 1, Blood | 2, Sputum/endotracheal aspirate | 3, BAL fluid | 4, Join	[sc_meets_ y	
pre_pth4_i	pretreatment_beta	text	[Pathogen 4] Specify Intra-operative pus site	[sc_meets_ y	@CHARLIMIT='50'
pre_pth4_i	pretreatment_beta	text	[Pathogen 4] Specify Intra-operative tissue type	[sc_meets_ y	@CHARLIMIT='50'
pre_pth4_i	pretreatment_beta	text	[Pathogen 4] Specify Non-operative swab site	[sc_meets_ y	@CHARLIMIT='50'
pre_pth4_h	pretreatment_beta	yesno	[Pathogen 4] Is WGS data available?	[sc_meets_ y	
pre_pth4_v	pretreatment_beta	notes	[Pathogen 4] Where is the WGS data stored?	[sc_meets_ y	
pre_pth4_h	pretreatment_beta	yesno	[Pathogen 4] Is the isolate available for further testing?	[sc_meets_ y	
pre_pth4_i	pretreatment_beta	notes	[Pathogen 4] Where is the isolate stored?	[sc_meets_ y	
pre_pth5_d	pretreatment_beta	descripti	Pathogen 5	[sc_meets_inclusion] = "1" and [pre_num_target_pathogen] > 4	
pre_pth5_t	pretreatment_beta	radio	[Pathogen 5 1, E. coli | 2, P. aeruginosa | 3, M. abscessus | 4, S. aureus | 11, Kl	[sc_meets_ y	
pre_pth5_s	pretreatment_beta	text	[Pathogen 5] Full Genus e.g. Salmonella enterica	[sc_meets_ y	@CHARLIMIT='50'
pre_pth5_i	pretreatment_beta	yesno	[Pathogen 5] ESBL?	[sc_meets_ y	
pre_pth5_i	pretreatment_beta	yesno	[Pathogen 5] MRSA?	[sc_meets_ y	
pre_pth5_i	pretreatment_beta	yesno	[Pathogen 5] VRE?	[sc_meets_ y	
pre_pth5_s	pretreatment_beta	radio	[Pathogen 5 confirmed, Confirmed (isolated from site of infection) | suspected	[sc_meets_ y	
pre_pth5_i	pretreatment_beta	checkbox	[Pathogen 5 1, Blood | 2, Sputum/endotracheal aspirate | 3, BAL fluid | 4, Join	[sc_meets_ y	
pre_pth5_i	pretreatment_beta	text	[Pathogen 5] Specify Intra-operative pus site	[sc_meets_ y	@CHARLIMIT='50'
pre_pth5_i	pretreatment_beta	text	[Pathogen 5] Specify Intra-operative tissue type	[sc_meets_ y	@CHARLIMIT='50'
pre_pth5_i	pretreatment_beta	text	[Pathogen 5] Specify Non-operative swab site	[sc_meets_ y	@CHARLIMIT='50'
pre_pth5_h	pretreatment_beta	yesno	[Pathogen 5] Is WGS data available?	[sc_meets_ y	
pre_pth5_v	pretreatment_beta	notes	[Pathogen 5] Where is the WGS data stored?	[sc_meets_ y	
pre_pth5_h	pretreatment_beta	yesno	[Pathogen 5] Is the isolate available for further testing?	[sc_meets_ y	
pre_pth5_i	pretreatment_beta	notes	[Pathogen 5] Where is the isolate stored?	[sc_meets_ y	
pre_num_p	pretreatme Phages	radio	How many 1,1 | 2,2 | 3,3 | 4,4 | 5,5 | -1, Proprietary cocktail | 0, Unable to define separa	y	
pre_phage1	pretreatment_beta	descripti	Phage 1	[sc_meets_inclusion] = "1" and abs([pre_num_phage]) > 0	
pre_phage1	pretreatment_beta	text	[Phage 1] Phage 1 name or identifier	[sc_meets_ y	
pre_phage1	pretreatment_beta	radio	[Phage 1] A 1, E. coli | 2, P. aeruginosa | 3, M. abscessus | 4, S. aureus | 11, Kl	[sc_meets_ y	
pre_phage1	pretreatment_beta	text	[Phage 1] A 1, E. coli | 2 Enter both genus and species name, e.g. (Pseudomon	[sc_meets_inclusion] = "1" and abs([pre_phage1_active_	@CHARLIMIT='50'
pre_phage1	pretreatment_beta	radio	[Phage 1] E 1, >= 0.9 | 2, 0.5-0.899 | 3, 0.1-0.499 | 4, <0.1	[sc_meets_ y	
pre_phage1	pretreatment_beta	notes	[Phage 1] Source/supplier	[sc_meets_ y	
pre_phage1	pretreatment_beta	text	[Phage 1] Endotoxin level (XXXX.X E number_1dp	[sc_meets_ y	
pre_phage1	pretreatment_beta	yesno	[Phage 1] Is sequencing data for the phage available?	[sc_meets_ y	
pre_phage1	pretreatment_beta	text	[Phage 1] Where is the sequencing data stored?	[sc_meets_ y	
pre_phage2	pretreatment_beta	descripti	Phage 2	[sc_meets_inclusion] = "1" and abs([pre_num_phage]) > 1	
pre_phage2	pretreatment_beta	text	[Phage 2] Phage 2 name or identifier	[sc_meets_ y	
pre_phage2	pretreatment_beta	radio	[Phage 2] A 1, E. coli | 2, P. aeruginosa | 3, M. abscessus | 4, S. aureus | 11, Kl	[sc_meets_ y	
pre_phage2	pretreatment_beta	text	[Phage 2] A 1, E. coli | 2 Enter both genus and species name, e.g. (Pseudomon	[sc_meets_inclusion] = "1" and abs([pre_phage2_active_	@CHARLIMIT='50'
pre_phage2	pretreatment_beta	radio	[Phage 2] E 1, >= 0.9 | 2, 0.5-0.899 | 3, 0.1-0.499 | 4, <0.1	[sc_meets_ y	

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pre_phage2	pretreatment_beta	notes	[Phage 2] Source/supplier	[sc_meets_ y	
pre_phage2	pretreatment_beta	text	[Phage 2] Endotoxin level (XXXX.X E number_1dp	[sc_meets_ y	
pre_phage2	pretreatment_beta	yesno	[Phage 2] Is sequencing data for the phage available?	[sc_meets_ y	
pre_phage2	pretreatment_beta	text	[Phage 2] Where is the sequencing data stored?	[sc_meets_ y	
pre_phage3	pretreatment_beta	descriptiv	Phage 3	[sc_meets_inclusion] = "1" and abs([pre_num_phage]) > 2	
pre_phage3	pretreatment_beta	text	[Phage 3] Phage 3 name or identifier	[sc_meets_ y	
pre_phage3	pretreatment_beta	radio	[Phage 3] A 1, E. coli | 2, P. aeruginosa | 3, M. abscessus | 4, S. aureus | 11, Kl	[sc_meets_ y	
pre_phage3	pretreatment_beta	text	[Phage 3] A 1, E. coli | 2 Enter both genus and species name, e.g. (Pseudomona	[sc_meets_inclusion] = "1" and abs([pre_phage3_active_ @CHARLIMIT='50'	
pre_phage3	pretreatment_beta	radio	[Phage 3] E 1, >= 0.9 | 2, 0.5-0.899 | 3, 0.1-0.499 | 4, <0.1	[sc_meets_ y	
pre_phage3	pretreatment_beta	notes	[Phage 3] Source/supplier	[sc_meets_ y	
pre_phage3	pretreatment_beta	text	[Phage 3] Endotoxin level (XXXX.X E number_1dp	[sc_meets_ y	
pre_phage3	pretreatment_beta	yesno	[Phage 3] Is sequencing data for the phage available?	[sc_meets_ y	
pre_phage3	pretreatment_beta	text	[Phage 3] Where is the sequencing data stored?	[sc_meets_ y	
pre_phage4	pretreatment_beta	descriptiv	Phage 4	[sc_meets_inclusion] = "1" and abs([pre_num_phage]) > 3	
pre_phage4	pretreatment_beta	text	[Phage 4] Phage 4 name or identifier	[sc_meets_ y	
pre_phage4	pretreatment_beta	radio	[Phage 4] A 1, E. coli | 2, P. aeruginosa | 3, M. abscessus | 4, S. aureus | 11, Kl	[sc_meets_ y	
pre_phage4	pretreatment_beta	text	[Phage 4] A 1, E. coli | 2 Enter both genus and species name, e.g. (Pseudomona	[sc_meets_inclusion] = "1" and abs([pre_phage4_active_ @CHARLIMIT='50'	
pre_phage4	pretreatment_beta	radio	[Phage 4] E 1, >= 0.9 | 2, 0.5-0.899 | 3, 0.1-0.499 | 4, <0.1	[sc_meets_ y	
pre_phage4	pretreatment_beta	notes	[Phage 4] Source/supplier	[sc_meets_ y	
pre_phage4	pretreatment_beta	text	[Phage 4] Endotoxin level (XXXX.X E number_1dp	[sc_meets_ y	
pre_phage4	pretreatment_beta	yesno	[Phage 4] Is sequencing data for the phage available?	[sc_meets_ y	
pre_phage4	pretreatment_beta	text	[Phage 4] Where is the sequencing data stored?	[sc_meets_ y	
pre_phage5	pretreatment_beta	descriptiv	Phage 5	[sc_meets_inclusion] = "1" and abs([pre_num_phage]) > 4	
pre_phage5	pretreatment_beta	text	[Phage 5] Phage 5 name or identifier	[sc_meets_ y	
pre_phage5	pretreatment_beta	radio	[Phage 5] A 1, E. coli | 2, P. aeruginosa | 3, M. abscessus | 4, S. aureus | 11, Kl	[sc_meets_ y	
pre_phage5	pretreatment_beta	text	[Phage 5] A 1, E. coli | 2 Enter both genus and species name, e.g. (Pseudomona	[sc_meets_inclusion] = "1" and abs([pre_phage5_active_ @CHARLIMIT='50'	
pre_phage5	pretreatment_beta	radio	[Phage 5] E 1, >= 0.9 | 2, 0.5-0.899 | 3, 0.1-0.499 | 4, <0.1	[sc_meets_ y	
pre_phage5	pretreatment_beta	notes	[Phage 5] Source/supplier	[sc_meets_ y	
pre_phage5	pretreatment_beta	text	[Phage 5] Endotoxin level (XXXX.X E number_1dp	[sc_meets_ y	
pre_phage5	pretreatment_beta	yesno	[Phage 5] Is sequencing data for the phage available?	[sc_meets_ y	
pre_phage5	pretreatment_beta	text	[Phage 5] Where is the sequencing data stored?	[sc_meets_ y	
tre_no_incl	treatment_beta	descriptiv	<h3><span style="background-color: #e03e2	[sc_meets_inclusion] < 1	
tre_start_w	treatment_beta	text	Weight at start of treat XXX.X kg number_1dp	[sc_meets_ y	
tre_ph0	treatment_beta	descriptiv	Phage: "[pre_phage1_name]"	[sc_meets_inclusion] = "1" and [pre_phage1_name] and [pre_num_phage]>0	
tre_ph_0_r	treatment_beta	checkbox	[Phage: "[p aero, Aerosolised / Nebulised | instl, Instillation | iv, Intravenous (	[sc_meets_ y	
tre_ph_0_r	treatment_beta	text	[Phage: "[pre_phage1_name]"] Specify instillation site	[sc_meets_ y	@CHARLIMIT='50'
tre_ph_0_r	treatment_beta	text	[Phage: "[pre_phage1_name]"] Specify 'other'	[sc_meets_ y	@CHARLIMIT='50'
tre_ph_0_d	treatment_beta	radio	[Phage: "[p under2wks, Less than or equal to 2 weeks | over2wks, Longer tha	[sc_meets_ y	
tre_ph_0_d	treatment_beta	text	[Phage: "[pre_phage1_name]"] Dur integer	[sc_meets_ y	
tre_ph_0_d	treatment_beta	radio	[Phage: "[p days, Days | doseperapp, Doses/applications	[sc_meets_ y	
tre_ph_0_d	treatment_beta	radio	[Phage: "[p days, Days | weeks, Weeks | months, Months	[sc_meets_ y	

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tre_ph_0_d	treatment_beta	radio	[Phage: "[p	10e8, 10^8 pfu/mL | 10e9, 10^9 pfu/mL | 10e10, 10^10 pfu/mL |				[sc_meets_ y	
tre_ph_0_d	treatment_beta	text	[Phage: "[pre_phage1_	XXX.X mL	number_1dp			[sc_meets_ y	
tre_ph_0_a	treatment_beta	text	[Phage: "[pre_phage1_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_0_fi	treatment_beta	text	[Phage: "[pre_phage1_name]"] Dat		date_dmy			[sc_meets_ y	
tre_ph_0_ir	treatment_beta	text	[Phage: "[pre_phage1_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_0_iv	treatment_beta	text	[Phage: "[pre_phage1_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_0_c	treatment_beta	text	[Phage: "[pre_phage1_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_0_t	treatment_beta	text	[Phage: "[pre_phage1_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_0_c	treatment_beta	text	[Phage: "[pre_phage1_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph1	treatment_beta	descriptiv	Phage: "[pre_phage2_name]"					[sc_meets_inclusion] = "1" and [pre_phage2_name] and [pre_num_phage]>1	
tre_ph_1_r	treatment_beta	checkbox	[Phage: "[p	aero, Aerosolised / Nebulised | instl, Instillation | iv, Intravenous (				[sc_meets_ y	
tre_ph_1_r	treatment_beta	text	[Phage: "[pre_phage2_name]"] Specify instillation site					[sc_meets_ y	@CHARLIMIT='50'
tre_ph_1_r	treatment_beta	text	[Phage: "[pre_phage2_name]"] Specify 'other'					[sc_meets_ y	@CHARLIMIT='50'
tre_ph_1_d	treatment_beta	radio	[Phage: "[p	under2wks, Less than or equal to 2 weeks | over2wks, Longer tha				[sc_meets_ y	
tre_ph_1_d	treatment_beta	text	[Phage: "[pre_phage2_name]"] Dur	integer				[sc_meets_ y	
tre_ph_1_d	treatment_beta	radio	[Phage: "[p	days, Days | doseperapp, Doses/applications				[sc_meets_ y	
tre_ph_1_d	treatment_beta	radio	[Phage: "[p	days, Days | weeks, Weeks | months, Months				[sc_meets_ y	
tre_ph_1_d	treatment_beta	radio	[Phage: "[p	10e8, 10^8 pfu/mL | 10e9, 10^9 pfu/mL | 10e10, 10^10 pfu/mL |				[sc_meets_ y	
tre_ph_1_d	treatment_beta	text	[Phage: "[pre_phage2_	XXX.X mL	number_1dp			[sc_meets_ y	
tre_ph_1_a	treatment_beta	text	[Phage: "[pre_phage2_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_1_fi	treatment_beta	text	[Phage: "[pre_phage2_name]"] Dat		date_dmy			[sc_meets_ y	
tre_ph_1_ir	treatment_beta	text	[Phage: "[pre_phage2_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_1_iv	treatment_beta	text	[Phage: "[pre_phage2_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_1_c	treatment_beta	text	[Phage: "[pre_phage2_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_1_t	treatment_beta	text	[Phage: "[pre_phage2_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_1_c	treatment_beta	text	[Phage: "[pre_phage2_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph2	treatment_beta	descriptiv	Phage: "[pre_phage3_name]"					[sc_meets_inclusion] = "1" and [pre_phage3_name] and [pre_num_phage]>2	
tre_ph_2_r	treatment_beta	checkbox	[Phage: "[p	aero, Aerosolised / Nebulised | instl, Instillation | iv, Intravenous (				[sc_meets_ y	
tre_ph_2_r	treatment_beta	text	[Phage: "[pre_phage3_name]"] Specify instillation site					[sc_meets_ y	@CHARLIMIT='50'
tre_ph_2_r	treatment_beta	text	[Phage: "[pre_phage3_name]"] Specify 'other'					[sc_meets_ y	@CHARLIMIT='50'
tre_ph_2_d	treatment_beta	radio	[Phage: "[p	under2wks, Less than or equal to 2 weeks | over2wks, Longer tha				[sc_meets_ y	
tre_ph_2_d	treatment_beta	text	[Phage: "[pre_phage3_name]"] Dur	integer				[sc_meets_ y	
tre_ph_2_d	treatment_beta	radio	[Phage: "[p	days, Days | doseperapp, Doses/applications				[sc_meets_ y	
tre_ph_2_d	treatment_beta	radio	[Phage: "[p	days, Days | weeks, Weeks | months, Months				[sc_meets_ y	
tre_ph_2_d	treatment_beta	radio	[Phage: "[p	10e8, 10^8 pfu/mL | 10e9, 10^9 pfu/mL | 10e10, 10^10 pfu/mL |				[sc_meets_ y	
tre_ph_2_d	treatment_beta	text	[Phage: "[pre_phage3_	XXX.X mL	number_1dp			[sc_meets_ y	
tre_ph_2_a	treatment_beta	text	[Phage: "[pre_phage3_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_2_fi	treatment_beta	text	[Phage: "[pre_phage3_name]"] Dat		date_dmy			[sc_meets_ y	
tre_ph_2_ir	treatment_beta	text	[Phage: "[pre_phage3_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_2_iv	treatment_beta	text	[Phage: "[pre_phage3_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_2_c	treatment_beta	text	[Phage: "[pre_phage3_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	

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tre_ph_2_t	treatment_beta	text	[Phage: "[pre_phage3_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_2_c	treatment_beta	text	[Phage: "[pre_phage3_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph3	treatment_beta	descripti	Phage: "[pre_phage4_name]"					[sc_meets_inclusion] = "1" and [pre_phage4_name] and [pre_num_phage]>3	
tre_ph_3_r	treatment_beta	checkbo	[Phage: "[p	aero, Aerosolised / Nebulised | instl, Instillation | iv, Intravenous (				[sc_meets_ y	
tre_ph_3_r	treatment_beta	text	[Phage: "[pre_phage4_name]"] Specify instillation site					[sc_meets_ y	@CHARLIMIT='50'
tre_ph_3_r	treatment_beta	text	[Phage: "[pre_phage4_name]"] Specify 'other'					[sc_meets_ y	@CHARLIMIT='50'
tre_ph_3_d	treatment_beta	radio	[Phage: "[p	under2wks, Less than or equal to 2 weeks | over2wks, Longer tha				[sc_meets_ y	
tre_ph_3_d	treatment_beta	text	[Phage: "[pre_phage4_name]"] Dur	integer				[sc_meets_ y	
tre_ph_3_d	treatment_beta	radio	[Phage: "[p	days, Days | doseperapp, Doses/applications				[sc_meets_ y	
tre_ph_3_d	treatment_beta	radio	[Phage: "[p	days, Days | weeks, Weeks | months, Months				[sc_meets_ y	
tre_ph_3_d	treatment_beta	radio	[Phage: "[p	10e8, 10^8 pfu/mL | 10e9, 10^9 pfu/mL | 10e10, 10^10 pfu/mL |				[sc_meets_ y	
tre_ph_3_d	treatment_beta	text	[Phage: "[pre_phage4_	XXX.X mL	number_1dp			[sc_meets_ y	
tre_ph_3_a	treatment_beta	text	[Phage: "[pre_phage4_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_3_fi	treatment_beta	text	[Phage: "[pre_phage4_name]"] Dat	date_dmy				[sc_meets_ y	
tre_ph_3_ir	treatment_beta	text	[Phage: "[pre_phage4_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_3_iv	treatment_beta	text	[Phage: "[pre_phage4_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_3_c	treatment_beta	text	[Phage: "[pre_phage4_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_3_t	treatment_beta	text	[Phage: "[pre_phage4_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_3_c	treatment_beta	text	[Phage: "[pre_phage4_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph4	treatment_beta	descripti	Phage: "[pre_phage5_name]"					[sc_meets_inclusion] = "1" and [pre_phage5_name] and [pre_num_phage]>4	
tre_ph_4_r	treatment_beta	checkbo	[Phage: "[p	aero, Aerosolised / Nebulised | instl, Instillation | iv, Intravenous (				[sc_meets_ y	
tre_ph_4_r	treatment_beta	text	[Phage: "[pre_phage5_name]"] Specify instillation site					[sc_meets_ y	@CHARLIMIT='50'
tre_ph_4_r	treatment_beta	text	[Phage: "[pre_phage5_name]"] Specify 'other'					[sc_meets_ y	@CHARLIMIT='50'
tre_ph_4_d	treatment_beta	radio	[Phage: "[p	under2wks, Less than or equal to 2 weeks | over2wks, Longer tha				[sc_meets_ y	
tre_ph_4_d	treatment_beta	text	[Phage: "[pre_phage5_name]"] Dur	integer				[sc_meets_ y	
tre_ph_4_d	treatment_beta	radio	[Phage: "[p	days, Days | doseperapp, Doses/applications				[sc_meets_ y	
tre_ph_4_d	treatment_beta	radio	[Phage: "[p	days, Days | weeks, Weeks | months, Months				[sc_meets_ y	
tre_ph_4_d	treatment_beta	radio	[Phage: "[p	10e8, 10^8 pfu/mL | 10e9, 10^9 pfu/mL | 10e10, 10^10 pfu/mL |				[sc_meets_ y	
tre_ph_4_d	treatment_beta	text	[Phage: "[pre_phage5_	XXX.X mL	number_1dp			[sc_meets_ y	
tre_ph_4_a	treatment_beta	text	[Phage: "[pre_phage5_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_4_fi	treatment_beta	text	[Phage: "[pre_phage5_name]"] Dat	date_dmy				[sc_meets_ y	
tre_ph_4_ir	treatment_beta	text	[Phage: "[pre_phage5_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_4_iv	treatment_beta	text	[Phage: "[pre_phage5_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_4_c	treatment_beta	text	[Phage: "[pre_phage5_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_4_t	treatment_beta	text	[Phage: "[pre_phage5_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
tre_ph_4_c	treatment_beta	text	[Phage: "[pre_phage5_	X.X EU/kg	number_1d	0	5.1	[sc_meets_ y	
trivcl_no_ir	treatment_iv_clinical_b	descripti	<h3><span style="background-color: #e03e2					[sc_meets_inclusion] < 1	
triv_descrip	treatment_iv_clinical_b	descripti	Clinical IV Administration. This page opens when IV or oral/enteral phage therapy is selected from the Treatment page.						
trivcl_day	treatment_iv_clinical_b	radio	Select clinic	0, D0 | 1, D1 | 2, D2 | 3, D3 | 4, D4 | 5, D5 | 6, D6 | 7, D7 | 8, D8				[sc_meets_ y	
trivcl_d0_c	treatment_iv_clinical_b	checkbo	[D0] Confir	yes, Patient has received full clinical exam				[trivcl_day] y	
trivcl_1_do	treatment_iv_clinical_b	radio	Number of	1,1 | 2,2				([trivcl_day y	

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trivcl_1_do	treatment_iv_clinical_t	yesno	Dose adjusted based or Dose #1	[trivcl_day] y		
trivcl_1_do	treatment_iv_clinical_t	radio	[1] If yes, se inc, Dose increased | dec, Dose decreased	[trivcl_day] y		
trivcl_1_do	treatment_iv_clinical_t	checkbo	Confirm vit confirmed, Dose #1	([trivcl_day y		
trivcl_1_do	treatment_iv_clinical_t	checkbo	Confirm vit confirmed, Dose #1	([trivcl_day y		
trivcl_1_do	treatment_iv_clinical_t	checkbo	Confirm vit confirmed, Dose #1	([trivcl_day y		
trivcl_1_do	treatment_iv_clinical_t	yesno	Dose adjusted based or Dose #2	[trivcl_day] y		
trivcl_1_do	treatment_iv_clinical_t	radio	[2] If yes, se inc, Dose increased | dec, Dose decreased	[trivcl_day] y		
trivcl_1_do	treatment_iv_clinical_t	checkbo	Confirm vit confirmed, Dose #2	([trivcl_day y		
trivcl_1_do	treatment_iv_clinical_t	checkbo	Confirm vit confirmed, Dose #2	([trivcl_day y		
trivcl_1_do	treatment_iv_clinical_t	checkbo	Confirm vit confirmed, Dose #2	([trivcl_day y		
trivcl_2_de	treatment_iv_clinical_t	yesno	Protocol deviation?	([trivcl_day y		
trivcl_2_de	treatment_iv_clinical_t	notes	Describe the protocol deviation	[trivcl_2_de y		
trivcl_3_fev	treatment_iv_clinical_t	yesno	Did fever (temp > 37.9 Â°C) occur today (yes/no)?	([trivcl_day y		
trivcl_3_fev	treatment_iv_clinical_t	text	Specify max temp occurring prior to number_1dp	[trivcl_3_fe y		
trivcl_3_fev	treatment_iv_clinical_t	text	Specify time of max fever in hours a number_1dp	[trivcl_3_fe y		
trivcl_4_tac	treatment_iv_clinical_t	yesno	Did tachycardia occur today (yes/no)?	([trivcl_day y		
trivcl_4_tac	treatment_iv_clinical_t	text	Specify max HR occurring prior to n integer	[trivcl_4_ta y		
trivcl_4_tac	treatment_iv_clinical_t	text	Specify time of max HR in hours aft number_1dp	[trivcl_4_ta y		
trivcl_5_pai	treatment_iv_clinical_t	yesno	Did pain occur today (greater than any baseline pain) - yes/no?	([trivcl_day y		
trivcl_5_pai	treatment_iv_clinical_t	text	Specify time of pain occurrence in h number_1dp	[trivcl_5_pa y		
trivcl_5_pai	treatment_iv_clinical_t	text	Specify site of pain	[trivcl_5_pa y		@CHARLIMIT=50
trivcl_6_inf	treatment_iv_clinical_t	yesno	Any other signs or symptoms of inflammatory response (yes/no)?	([trivcl_day y		
trivcl_6_inf	treatment_iv_clinical_t	notes	If yes, specify what occurred	[trivcl_6_in y		
trivcl_6_inf	treatment_iv_clinical_t	text	Also specify time of occurrence in h number_1dp	[trivcl_6_in y		
trivcl_d15_	treatment_iv_clinical_t	yesno	Is patient still receiving phage therapy (yes/no)?	[trivcl_day] y		
trivcl_d15_	treatment_iv_clinical_t	radio	Number of 1,1 | 2,2 | 3,Has changed during this time	[trivcl_day] y		
trivcl_d15_	treatment_iv_clinical_t	yesno	Were vitals checked each day of treatment as per protocol (yes/no)?	[trivcl_day] y		
trivcl_d15_	treatment_iv_clinical_t	yesno	Will treatment continue >4 weeks (yes/no)?	[trivcl_day] y		
trivcl_d15_	treatment_iv_clinical_t	radio	How many 15,15 | 16,16 | 17,17 | 18,18 | 19,19 | 20,20 | 21,21 | 22,22 | 23	[trivcl_day] y		
trivcl_d15_	treatment_iv_clinical_t	yesno	Did fever (temp > 37.9 Â°C) occur on any (yes/no)?	[trivcl_day] y		
trivcl_d15_	treatment_iv_clinical_t	checkbo	Specify day 15,15 | 16,16 | 17,17 | 18,18 | 19,19 | 20,20 | 21,21 | 22,22 | 23	[trivcl_day] y		
trivcl_d15_	treatment_iv_clinical_t	text	Specify the max fever occurring in 2 number	[trivcl_d15_28_hi_fever_days(15)] = '1'		
trivcl_d15_	treatment_iv_clinical_t	text	Specify the max fever occurring in 2 number	[trivcl_d15_28_hi_fever_days(16)] = '1'		
trivcl_d15_	treatment_iv_clinical_t	text	Specify the max fever occurring in 2 number	[trivcl_d15_28_hi_fever_days(17)] = '1'		
trivcl_d15_	treatment_iv_clinical_t	text	Specify the max fever occurring in 2 number	[trivcl_d15_28_hi_fever_days(18)] = '1'		
trivcl_d15_	treatment_iv_clinical_t	text	Specify the max fever occurring in 2 number	[trivcl_d15_28_hi_fever_days(19)] = '1'		
trivcl_d15_	treatment_iv_clinical_t	text	Specify the max fever occurring in 2 number	[trivcl_d15_28_hi_fever_days(20)] = '1'		
trivcl_d15_	treatment_iv_clinical_t	text	Specify the max fever occurring in 2 number	[trivcl_d15_28_hi_fever_days(21)] = '1'		
trivcl_d15_	treatment_iv_clinical_t	text	Specify the max fever occurring in 2 number	[trivcl_d15_28_hi_fever_days(22)] = '1'		
trivcl_d15_	treatment_iv_clinical_t	text	Specify the max fever occurring in 2 number	[trivcl_d15_28_hi_fever_days(23)] = '1'		
trivcl_d15_	treatment_iv_clinical_t	text	Specify the max fever occurring in 2 number	[trivcl_d15_28_hi_fever_days(24)] = '1'		

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trivcl_d15_	treatment_iv_clinical_b	text	Specify the max fever occurring in 2	number	[trivcl_d15_28_hi_fever_days(25)] = '1'	
trivcl_d15_	treatment_iv_clinical_b	text	Specify the max fever occurring in 2	number	[trivcl_d15_28_hi_fever_days(26)] = '1'	
trivcl_d15_	treatment_iv_clinical_b	text	Specify the max fever occurring in 2	number	[trivcl_d15_28_hi_fever_days(27)] = '1'	
trivcl_d15_	treatment_iv_clinical_b	text	Specify the max fever occurring in 2	number	[trivcl_d15_28_hi_fever_days(28)] = '1'	
trivcl_d15_	treatment_iv_clinical_b	yesno	Did tachycardia on any day (yes/no)?		[trivcl_day] y	
trivcl_d15_	treatment_iv_clinical_b	checkbox	Specify day 15,15 | 16,16 | 17,17 | 18,18 | 19,19 | 20,20 | 21,21 | 22,22 | 23		[trivcl_day] y	
trivcl_d15_	treatment_iv_clinical_b	yesno	Did pain occur on any day (greater than any baseline pain)		[trivcl_day] y	
trivcl_d15_	treatment_iv_clinical_b	checkbox	Specify day 15,15 | 16,16 | 17,17 | 18,18 | 19,19 | 20,20 | 21,21 | 22,22 | 23		[trivcl_day] y	
trivcl_d15_	treatment_iv_clinical_b	text	Specify site of pain for day D15		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_b	text	Specify site of pain for day D16		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_b	text	Specify site of pain for day D17		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_b	text	Specify site of pain for day D18		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_b	text	Specify site of pain for day D19		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_b	text	Specify site of pain for day D20		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_b	text	Specify site of pain for day D21		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_b	text	Specify site of pain for day D22		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_b	text	Specify site of pain for day D23		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_b	text	Specify site of pain for day D24		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_b	text	Specify site of pain for day D25		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_b	text	Specify site of pain for day D26		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_b	text	Specify site of pain for day D27		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_b	text	Specify site of pain for day D28		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_b	yesno	Any other signs or symptoms of inflammatory response on any day (yes/no)?		[trivcl_day] y	
trivcl_d15_	treatment_iv_clinical_b	checkbox	Specify day 15,15 | 16,16 | 17,17 | 18,18 | 19,19 | 20,20 | 21,21 | 22,22 | 23		[trivcl_day] y	
trivcl_d15_	treatment_iv_clinical_b	text	Specify what occurred for day D15		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_b	text	Specify what occurred for day D16		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_b	text	Specify what occurred for day D17		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_b	text	Specify what occurred for day D18		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_b	text	Specify what occurred for day D19		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_b	text	Specify what occurred for day D20		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_b	text	Specify what occurred for day D21		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_b	text	Specify what occurred for day D22		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_b	text	Specify what occurred for day D23		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_b	text	Specify what occurred for day D24		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_b	text	Specify what occurred for day D25		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_b	text	Specify what occurred for day D26		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_b	text	Specify what occurred for day D27		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_b	text	Specify what occurred for day D28		[trivcl_d15_ y	@CHARLIMIT='50'
trivcl_d15_	treatment_iv_clinical_b	yesno	Dose adjusted on any day based on "kinetics" results (yes/no)?		[trivcl_day] y	
trivcl_d15_	treatment_iv_clinical_b	radio	Did the dos inc, Dose increased | dec, Dose reduced | both, Both increases an		[trivcl_day] y	
trivcl_d15_	treatment_iv_clinical_b	radio	What has b cure, 1) Cure â€“ no evidence of ongoing infection: resolution of		[trivcl_day] y	

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trivcl_d15_	treatment_iv_clinical_b	radio	Select one (	no_disability, Without persisting disability | disability, With persis	[trivcl_day]	y
trivcl_d15_	treatment_iv_clinical_b	radio	Select one (	improvement, Improvement in clinical signs and symptoms, radiol	[trivcl_day]	y
trivlab_no_	treatment_iv_labs_beta	descriptiv	<h3><span style="background-color: #e03e2		[sc_meets_inclusion]	< 1
trivlab_des	treatment_iv_labs_beta	descriptiv	Clinical IV Labs For treatments over TWO weeks, use the Monthly instrument. This page opens when IV and/or oral/			
trivlab_non	treatment_iv_labs_beta	descriptiv	This patient does not meet oral/enteral phage therapy re		([tre_ph_0_rt(iv)] = '0' and [tre_ph_0_rt(oral)] = '0') and ([tre_ph_1_rt(iv)] = '0'	
trivlab_day	treatment_iv_labs_beta	radio	Select clinic	0, D0 | 2, D2 | 4, D4 | 8, D8 | 11, D11 | 15, D15 | 29, D29 | other,	[sc_meets_	y
trivlab_oth	treatment_iv_labs_beta	text	Enter day of treatment (enter a nur	integer	[trivlab_da	y
trivlab_oth	treatment_iv_labs_beta	notes	Test performed for day [trivlab_other_day]		[trivlab_oth	y
trivlab_oth	treatment_iv_labs_beta	notes	Result for day [trivlab_other_day]		[trivlab_oth	y
trivlab_crp	treatment_ CRP results	text	[[trivlab_day]] CRP result (XXX.X mg	number_1dp	[trivlab_day]	>= 0 and [trivlab_day] and [trivlab_day] != 11
trivlab_crp_	treatment_iv_labs_beta	checkbox	[[trivlab_da	na, CRP results NOT available for [[trivlab_day]]	[trivlab_crp	y
trivlab_esr	treatment_ ESR results	text	[[trivlab_day]] ESR result (XXX mm/	integer	[trivlab_day]	>= 0 and [trivlab_day] and [trivlab_day] != 2 and [trivlab_day] != 1
trivlab_esr_	treatment_iv_labs_beta	checkbox	[[trivlab_da	na, ESR results NOT available for [[trivlab_day]]	[trivlab_esr	y
trivlab_pro	treatment_ Procalciton	text	[[trivlab_day]] Procalcitonin result (	number_2dp	[trivlab_day]	and [trivlab_day] >= 0 and [trivlab_day] != 11 and [trivlab_day] !=
trivlab_pro	treatment_iv_labs_beta	checkbox	[[trivlab_da	na, ESR results NOT available for [[trivlab_day]]	[trivlab_prc	y
trivlab_fbc_	treatment_ FBC	yesno	[[trivlab_day]] FBC all within normal range (yes/no)?		[trivlab_day]	and [trivlab_day] >= 0
trivlab_hb	treatment_ Hb results	text	[[trivlab_day]] Hb result (XXX g/L)	integer	[trivlab_fbc_isnorm]	= '0' and [trivlab_day] and [trivlab_day] >= 0
trivlab_hb_	treatment_iv_labs_beta	checkbox	[[trivlab_da	na, Hb results NOT available for [[trivlab_day]]	[trivlab_hb]	y
trivlab_plat	treatment_ Platelet cou	text	[[trivlab_day]] Platelet result (XXX x	integer	[trivlab_fbc_isnorm]	= '0' and [trivlab_day] and [trivlab_day] >= 0
trivlab_plat	treatment_iv_labs_beta	checkbox	[[trivlab_da	na, Platelet count results NOT available for [[trivlab_day]]	[trivlab_pla	y
trivlab_wcc	treatment_ WCC	text	[[trivlab_day]] WCC (XXX x10^9/L)	integer	[trivlab_fbc_isnorm]	= '0' and [trivlab_day] and [trivlab_day] >= 0
trivlab_wcc	treatment_iv_labs_beta	checkbox	[[trivlab_da	na, WCC results NOT available for [[trivlab_day]]	[trivlab_wc	y
trivlab_neu	treatment_ Neutrophil	text	[[trivlab_day]] Neutrophil count (X	number_1dp	[trivlab_fbc_isnorm]	= '0' and [trivlab_day] and [trivlab_day] >= 0
trivlab_neu	treatment_iv_labs_beta	checkbox	[[trivlab_da	na, neutrophil count results NOT available for [[trivlab_day]]	[trivlab_neu	y
trivlab_lym	treatment_ Lymphocyt	text	[[trivlab_day]] Lymphocyte count (	number_1dp	[trivlab_fbc_isnorm]	= '0' and [trivlab_day] and [trivlab_day] >= 0
trivlab_lym	treatment_iv_labs_beta	checkbox	[[trivlab_da	na, Lymphocyte count results NOT available for [[trivlab_day]]	[trivlab_lym	y
trivlab_lym	treatment_ Lymphoper	yesno	[[trivlab_day]] Lymphopenia?		[trivlab_day]	and [trivlab_day] >= 0 and [trivlab_day] != 0 and [trivlab_day] != 2
trivlab_lym	treatment_iv_labs_beta	yesno	[[trivlab_day]] Lymphocyte subsets all within normal range (yes/no)?		[trivlab_prc	y
trivlab_cd3	treatment_ CD3 count	text	[[trivlab_day]] CD3 count (XX.XX x1	number_2dp	([trivlab_lymphocyte_isnorm] = '0' or [trivlab_lymphopenia]='1') and [trivlab_c	
trivlab_cd3	treatment_iv_labs_beta	text	[[trivlab_day]] CD3 % (XX%)	integer	([trivlab_lymphocyte_isnorm] = '0' or [trivlab_lymphopenia]='1') and [trivlab_c	
trivlab_cd3	treatment_iv_labs_beta	checkbox	[[trivlab_da	na, CD3 results NOT available for [[trivlab_day]]	[trivlab_cd3	y
trivlab_cd4	treatment_ CD4 count	text	[[trivlab_day]] CD4 count (XX.XX x1	number_2dp	([trivlab_lymphocyte_isnorm] = '0' or [trivlab_lymphopenia]='1') and [trivlab_c	
trivlab_cd4	treatment_iv_labs_beta	text	[[trivlab_day]] CD4 % (XX%)	integer	([trivlab_lymphocyte_isnorm] = '0' or [trivlab_lymphopenia]='1') and [trivlab_c	
trivlab_cd4	treatment_iv_labs_beta	checkbox	[[trivlab_da	na, CD4 results NOT available for [[trivlab_day]]	[trivlab_cd4	y
trivlab_cd8	treatment_ CD8 count	text	[[trivlab_day]] CD8 count (XX.XX x1	number_2dp	([trivlab_lymphocyte_isnorm] = '0' or [trivlab_lymphopenia]='1') and [trivlab_c	
trivlab_cd8	treatment_iv_labs_beta	text	[[trivlab_day]] CD8 % (XX%)	integer	([trivlab_lymphocyte_isnorm] = '0' or [trivlab_lymphopenia]='1') and [trivlab_c	
trivlab_cd8	treatment_iv_labs_beta	checkbox	[[trivlab_da	na, CD8 results NOT available for [[trivlab_day]]	[trivlab_cd8	y
trivlab_nkc	treatment_ CD8 count	text	[[trivlab_day]] NK cell count (XX.XX	number_2dp	([trivlab_lymphocyte_isnorm] = '0' or [trivlab_lymphopenia]='1') and [trivlab_c	
trivlab_nkc	treatment_iv_labs_beta	text	[[trivlab_day]] NK cell % (XX%)	integer	([trivlab_lymphocyte_isnorm] = '0' or [trivlab_lymphopenia]='1') and [trivlab_c	
trivlab_nkc	treatment_iv_labs_beta	checkbox	[[trivlab_da	na, NK cell count results NOT available for [[trivlab_day]]	[trivlab_nkc	y
trivlab_cd1	treatment_ CD19 count	text	[[trivlab_day]] CD19 count (XX.XX x	number_2dp	([trivlab_lymphocyte_isnorm] = '0' or [trivlab_lymphopenia]='1') and [trivlab_c	

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trivlab_cd1	treatment_iv_labs_bet	text	[[trivlab_day]] CD19 % (XX%)	integer	([trivlab_lymphocyte_isnorm] = '0' or [trivlab_lymphopenia]='1') and [trivlab_c	
trivlab_cd1	treatment_iv_labs_bet	checkbo	[[trivlab_da na, CD19 results NOT available for [[trivlab_day]]		[trivlab_cd1 y	
trivlab_lft_i	treatment_iv_labs_bet	yesno	[[trivlab_day]] LFTs all within normal range (yes/no)?		[trivlab_prc y	
trivlab_albu	treatment_ Albumin	text	[[trivlab_day]] Albumin (XX g/L)	integer	[trivlab_lft_isnorm] = '0' and [trivlab_day] and [trivlab_day] >= 0 and [trivlab_d	
trivlab_albu	treatment_iv_labs_bet	checkbo	[[trivlab_da na, Albumin results are NOT available for [[trivlab_day]]		[trivlab_alb y	
trivlab_ast	treatment_ AST	text	[[trivlab_day]] AST (XXXX U/L)	integer	[trivlab_lft_isnorm] = '0' and [trivlab_day] and [trivlab_day] >= 0 and [trivlab_d	
trivlab_ast_	treatment_iv_labs_bet	checkbo	[[trivlab_da na, AST results are NOT available for [[trivlab_day]]		[trivlab_ast y	
trivlab_alt	treatment_ ALT	text	[[trivlab_day]] ALT (XXXX U/L)	integer	[trivlab_lft_isnorm] = '0' and [trivlab_day] and [trivlab_day] >= 0 and [trivlab_d	
trivlab_alt_	treatment_iv_labs_bet	checkbo	[[trivlab_da na, ALT results are NOT available for [[trivlab_day]]		[trivlab_alt] y	
trivlab_ggt	treatment_ GGT	text	[[trivlab_day]] GGT (XXXX U/L)	integer	([trivlab_lft_isnorm] = '0' or [trivlab_lymphopenia]='1') and [trivlab_day] and [t	
trivlab_ggt_	treatment_iv_labs_bet	checkbo	[[trivlab_da na, GGT results are NOT available for [[trivlab_day]]		[trivlab_ggt y	
trivlab_alp	treatment_ ALP	text	[[trivlab_day]] ALP (XXXX U/L)	integer	[trivlab_lft_isnorm] = '0' and [trivlab_day] and [trivlab_day] >= 0 and [trivlab_d	
trivlab_alp_	treatment_iv_labs_bet	checkbo	[[trivlab_da na, ALP results are NOT available for [[trivlab_day]]		[trivlab_alp y	
trivlab_uec	treatment_iv_labs_bet	yesno	[[trivlab_day]] UECs all within normal range (yes/no)?		[trivlab_prc y	
trivlab_sod	treatment_ Sodium	text	[[trivlab_day]] Sodium (XXX mmol/l	integer	[trivlab_uec_isnorm] = '0' and [trivlab_day] and [trivlab_day] >= 0 and [trivlab_	
trivlab_sod	treatment_iv_labs_bet	checkbo	[[trivlab_da na, Sodium results are NOT available for [[trivlab_day]]		[trivlab_soc y	
trivlab_ure	treatment_ Urea	text	[[trivlab_day]] Urea (XX.X mmol/L)	number_1dp	[trivlab_uec_isnorm] = '0' and [trivlab_day] and [trivlab_day] >= 0 and [trivlab_	
trivlab_ure	treatment_iv_labs_bet	checkbo	[[trivlab_da na, Urea results are NOT available for [[trivlab_day]]		[trivlab_ure y	
trivlab_cre	treatment_ Creatinine	text	[[trivlab_day]] Creatinine (XXX umo	integer	[trivlab_uec_isnorm] = '0' and [trivlab_day] and [trivlab_day] >= 0 and [trivlab_	
trivlab_cre	treatment_iv_labs_bet	checkbo	[[trivlab_da na, Creatinine results are NOT available for [[trivlab_day]]		[trivlab_cre y	
trivlab_igg	treatment_ IgG	text	[[trivlab_day]] IgG (XX.XX g/L)	number_2dp	[trivlab_day] and ([trivlab_day] = 0 or [trivlab_day] = 29)	
trivlab_igg_	treatment_iv_labs_bet	checkbo	[[trivlab_da na, IgG results are NOT available for [[trivlab_day]]		[trivlab_igg y	
trivlab_c3	treatment_ C3	text	[[trivlab_day]] C3 (X.XX g/L)	number_2dp	[trivlab_day] and ([trivlab_day] = 0 or [trivlab_day] = 15 or [trivlab_day] = 29)	
trivlab_c3_	treatment_iv_labs_bet	checkbo	[[trivlab_da na, C3 results are NOT available for [[trivlab_day]]		[trivlab_c3] y	
trivlab_c4	treatment_ C4	text	[[trivlab_day]] C4 (X.XX g/L)	number_2dp	[trivlab_day] and ([trivlab_day] = 0 or [trivlab_day] = 15 or [trivlab_day] = 29)	
trivlab_c4_	treatment_iv_labs_bet	checkbo	[[trivlab_da na, C4 results are NOT available for [[trivlab_day]]		[trivlab_c4] y	
trivlab_ch5	treatment_ CH50	text	[[trivlab_day]] CH50 (XX U/mL)	integer	[trivlab_day] and ([trivlab_day] = 0 or [trivlab_day] = 15 or [trivlab_day] = 29)	
trivlab_ch5	treatment_iv_labs_bet	checkbo	[[trivlab_da na, CH50 results are NOT available for [[trivlab_day]]		[trivlab_ch5 y	
trivlab_ph0	treatment_iv_labs_bet	descripti	Phage: "[pre_phage1_name]"		([tre_ph_0_rt(iv)] = '1' or [tre_ph_0_rt(oral)] = '1') and [pre_phage1_name] an	
trivlab_ph_	treatment_iv_labs_bet	yesno	[Phage: "[pre_phage1_name]"] Antiphage antibodies tested (yes/no)?		([tre_ph_0_ y	
trivlab_ph_	treatment_iv_labs_bet	checkbo	[Phage: "[p neutralising,Neutralising antibody assay | igmigg, IgM/IgG assay |		[trivlab_ph y	
trivlab_ph_	treatment_iv_labs_bet	text	[Phage: "[pre_phage1_name]"] Other assay type		[trivlab_ph y	@CHARLIMIT='50'
trivlab_ph_	treatment_iv_labs_bet	notes	[Phage: "[pre_phage1_name]"] Antiphage antibody result		[trivlab_ph y	
trivlab_ph1	treatment_iv_labs_bet	descripti	Phage: "[pre_phage2_name]"		([tre_ph_1_rt(iv)] = '1' or [tre_ph_1_rt(oral)] = '1') and [pre_phage2_name] an	
trivlab_ph_	treatment_iv_labs_bet	yesno	[Phage: "[pre_phage2_name]"] Antiphage antibodies tested (yes/no)?		([tre_ph_1_ y	
trivlab_ph_	treatment_iv_labs_bet	checkbo	[Phage: "[p neutralising,Neutralising antibody assay | igmigg, IgM/IgG assay |		[trivlab_ph y	
trivlab_ph_	treatment_iv_labs_bet	text	[Phage: "[pre_phage2_name]"] Other assay type		[trivlab_ph y	@CHARLIMIT='50'
trivlab_ph_	treatment_iv_labs_bet	notes	[Phage: "[pre_phage2_name]"] Antiphage antibody result		[trivlab_ph y	
trivlab_ph2	treatment_iv_labs_bet	descripti	Phage: "[pre_phage3_name]"		([tre_ph_2_rt(iv)] = '1' or [tre_ph_2_rt(oral)] = '1') and [pre_phage3_name] an	
trivlab_ph_	treatment_iv_labs_bet	yesno	[Phage: "[pre_phage3_name]"] Antiphage antibodies tested (yes/no)?		([tre_ph_2_ y	
trivlab_ph_	treatment_iv_labs_bet	checkbo	[Phage: "[p neutralising,Neutralising antibody assay | igmigg, IgM/IgG assay |		[trivlab_ph y	

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trivlab_ph_	treatment_iv_labs_beta	text	[Phage: "[pre_phage3_name]"] Other assay type	[trivlab_ph_y	@CHARLIMIT='50'
trivlab_ph_	treatment_iv_labs_beta	notes	[Phage: "[pre_phage3_name]"] Antiphage antibody result	[trivlab_ph_y	
trivlab_ph3	treatment_iv_labs_beta	descriptiv	Phage: "[pre_phage4_name]"	([tre_ph_3_rt(iv)] = '1' or [tre_ph_3_rt(oral)] = '1') and [pre_phage4_name] an	
trivlab_ph_	treatment_iv_labs_beta	yesno	[Phage: "[pre_phage4_name]"] Antiphage antibodies tested (yes/no)?	([tre_ph_3_y	
trivlab_ph_	treatment_iv_labs_beta	checkbox	[Phage: "[pr neutralising,Neutralising antibody assay | igmigg, IgM/IgG assay |	[trivlab_ph_y	
trivlab_ph_	treatment_iv_labs_beta	text	[Phage: "[pre_phage4_name]"] Other assay type	[trivlab_ph_y	@CHARLIMIT='50'
trivlab_ph_	treatment_iv_labs_beta	notes	[Phage: "[pre_phage4_name]"] Antiphage antibody result	[trivlab_ph_y	
trivlab_ph4	treatment_iv_labs_beta	descriptiv	Phage: "[pre_phage5_name]"	([tre_ph_4_rt(iv)] = '1' or [tre_ph_4_rt(oral)] = '1') and [pre_phage5_name] an	
trivlab_ph_	treatment_iv_labs_beta	yesno	[Phage: "[pre_phage5_name]"] Antiphage antibodies tested (yes/no)?	([tre_ph_4_y	
trivlab_ph_	treatment_iv_labs_beta	checkbox	[Phage: "[pr neutralising,Neutralising antibody assay | igmigg, IgM/IgG assay |	[trivlab_ph_y	
trivlab_ph_	treatment_iv_labs_beta	text	[Phage: "[pre_phage5_name]"] Other assay type	[trivlab_ph_y	@CHARLIMIT='50'
trivlab_ph_	treatment_iv_labs_beta	notes	[Phage: "[pre_phage5_name]"] Antiphage antibody result	[trivlab_ph_y	
trivlab_pth1	treatment_iv_labs_beta	descriptiv	Pathogen 1 "[pre_pth1_target]"	[pre_num_target_pathogen] > 0 and [trivlab_day] and ([trivlab_day] = 0 or [triv	
trivlab_pth_	treatment_iv_labs_beta	radio	[Pathogen 1 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ty	
trivlab_pth_	treatment_iv_labs_beta	notes	[Pathogen 1: [pre_pth1_target]] How come isolation wasn't performed?	[trivlab_pth_y	
trivlab_pth_	treatment_iv_labs_beta	radio	[Pathogen 1 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[trivlab_pth_y	
trivlab_pth_	treatment_iv_labs_beta	notes	[Pathogen 1: [pre_pth1_target]] Please specify anti-phage resistance activity	[trivlab_pth_y	
trivlab_pth_	treatment_iv_labs_beta	radio	[Pathogen 1 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ty	
trivlab_pth_	treatment_iv_labs_beta	text	[Pathogen 1: [pre_pth1_target]] Specify other site where pathogen was isolat	[trivlab_pth_y	
trivlab_pth_	treatment_iv_labs_beta	radio	[Pathogen 1 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[trivlab_pth_y	
trivlab_pth_	treatment_iv_labs_beta	notes	[Pathogen 1: [pre_pth1_target]] Please specify anti-phage resistance activity	[trivlab_pth_y	
trivlab_pth2	treatment_iv_labs_beta	descriptiv	Pathogen 2 "[pre_pth2_target]"	[pre_num_target_pathogen] > 1 and [trivlab_day] and ([trivlab_day] = 0 or [triv	
trivlab_pth_	treatment_iv_labs_beta	radio	[Pathogen 2 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ty	
trivlab_pth_	treatment_iv_labs_beta	notes	[Pathogen 2: [pre_pth2_target]] How come isolation wasn't performed?	[trivlab_pth_y	
trivlab_pth_	treatment_iv_labs_beta	radio	[Pathogen 2 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[trivlab_pth_y	
trivlab_pth_	treatment_iv_labs_beta	notes	[Pathogen 2: [pre_pth2_target]] Please specify anti-phage resistance activity	[trivlab_pth_y	
trivlab_pth_	treatment_iv_labs_beta	radio	[Pathogen 2 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ty	
trivlab_pth_	treatment_iv_labs_beta	text	[Pathogen 2: [pre_pth2_target]] Specify other site where pathogen was isolat	[trivlab_pth_y	
trivlab_pth_	treatment_iv_labs_beta	radio	[Pathogen 2 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[trivlab_pth_y	
trivlab_pth_	treatment_iv_labs_beta	notes	[Pathogen 2: [pre_pth2_target]] Please specify anti-phage resistance activity	[trivlab_pth_y	
trivlab_pth3	treatment_iv_labs_beta	descriptiv	Pathogen 3 "[pre_pth3_target]"	[pre_num_target_pathogen] > 2 and [trivlab_day] and ([trivlab_day] = 0 or [triv	
trivlab_pth_	treatment_iv_labs_beta	radio	[Pathogen 3 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ty	
trivlab_pth_	treatment_iv_labs_beta	notes	[Pathogen 3: [pre_pth3_target]] How come isolation wasn't performed?	[trivlab_pth_y	
trivlab_pth_	treatment_iv_labs_beta	radio	[Pathogen 3 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[trivlab_pth_y	
trivlab_pth_	treatment_iv_labs_beta	notes	[Pathogen 3: [pre_pth3_target]] Please specify anti-phage resistance activity	[trivlab_pth_y	
trivlab_pth_	treatment_iv_labs_beta	radio	[Pathogen 3 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ty	
trivlab_pth_	treatment_iv_labs_beta	text	[Pathogen 3: [pre_pth3_target]] Specify other site where pathogen was isolat	[trivlab_pth_y	
trivlab_pth_	treatment_iv_labs_beta	radio	[Pathogen 3 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[trivlab_pth_y	
trivlab_pth_	treatment_iv_labs_beta	notes	[Pathogen 3: [pre_pth3_target]] Please specify anti-phage resistance activity	[trivlab_pth_y	
trivlab_pth4	treatment_iv_labs_beta	descriptiv	Pathogen 4 "[pre_pth4_target]"	[pre_num_target_pathogen] > 3 and [trivlab_day] and ([trivlab_day] = 0 or [triv	
trivlab_pth_	treatment_iv_labs_beta	radio	[Pathogen 4 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ty	

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trivlab_pth	treatment_iv_labs_beta	notes	[Pathogen 4: [pre_pth4_target]] How come isolation wasn't performed?	[trivlab_pth y
trivlab_pth	treatment_iv_labs_beta	radio	[Pathogen 4 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[trivlab_pth y
trivlab_pth	treatment_iv_labs_beta	notes	[Pathogen 4: [pre_pth4_target]] Please specify anti-phage resistance activity	[trivlab_pth y
trivlab_pth	treatment_iv_labs_beta	radio	[Pathogen 4 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_t y
trivlab_pth	treatment_iv_labs_beta	text	[Pathogen 4: [pre_pth4_target]] Specify other site where pathogen was isolat	[trivlab_pth y
trivlab_pth	treatment_iv_labs_beta	radio	[Pathogen 4 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[trivlab_pth y
trivlab_pth	treatment_iv_labs_beta	notes	[Pathogen 4: [pre_pth4_target]] Please specify anti-phage resistance activity	[trivlab_pth y
trivlab_pth!	treatment_iv_labs_beta	descripti	Pathogen 5 "[pre_pth5_target]"	[pre_num_target_pathogen] > 4 and [trivlab_day] and ([trivlab_day] = 0 or [tri
trivlab_pth	treatment_iv_labs_beta	radio	[Pathogen 5 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_t y
trivlab_pth	treatment_iv_labs_beta	notes	[Pathogen 5: [pre_pth5_target]] How come isolation wasn't performed?	[trivlab_pth y
trivlab_pth	treatment_iv_labs_beta	radio	[Pathogen 5 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[trivlab_pth y
trivlab_pth	treatment_iv_labs_beta	notes	[Pathogen 5: [pre_pth5_target]] Please specify anti-phage resistance activity	[trivlab_pth y
trivlab_pth	treatment_iv_labs_beta	radio	[Pathogen 5 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_t y
trivlab_pth	treatment_iv_labs_beta	text	[Pathogen 5: [pre_pth5_target]] Specify other site where pathogen was isolat	[trivlab_pth y
trivlab_pth	treatment_iv_labs_beta	radio	[Pathogen 5 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[trivlab_pth y
trivlab_pth	treatment_iv_labs_beta	notes	[Pathogen 5: [pre_pth5_target]] Please specify anti-phage resistance activity	[trivlab_pth y
trivlab_wgs	treatment_ WGS	yesno	[[trivlab_day]] Is WGS data available for current isolate?	[trivlab_day] and ([trivlab_day] = 0 or [trivlab_day] = 4 or [trivlab_day] = 8 or [t
trivlab_wgs	treatment_iv_labs_beta	notes	[[trivlab_day]] Where is the WGS data stored?	[trivlab_wgs]='1' and [trivlab_day] and ([trivlab_day] = 0 or [trivlab_day] = 4 or
trivlab_rnat	treatment_iv_labs_beta	radio	[[trivlab_da yes, Yes/Sample obtained + stored | not_analysed,Sample proces	[trivlab_day] and [trivlab_day] >= 0
trivlab_rnat	treatment_iv_labs_beta	notes	[[trivlab_day]] Where is the RNA transcriptomics data stored?	[trivlab_rnatr]='yes' and [trivlab_day] and [trivlab_day] >= 0
trivlab_rnat	treatment_iv_labs_beta	notes	[[trivlab_day]] Where is the RNA transcriptomics sample stored?	([trivlab_rnatr]='yes' or [trivlab_rnatr]='not_analysed') and [trivlab_day] and [t
trivlab_met	treatment_ Metagenon	yesno	[[trivlab_day]] Are clinical samples available for metagenomics?	[trivlab_day] and [trivlab_day] >= 0
trivlab_met	treatment_iv_labs_beta	text	[[trivlab_day]] Specify type of sample	[trivlab_metag_samples]='1' and [trivlab_day] and [trivlab_day] >= 0
trivlab_met	treatment_iv_labs_beta	radio	[[trivlab_da 1,Yes | 0, No, samples stored	[trivlab_metag_samples]='1' and [trivlab_day] and [trivlab_day] >= 0
trivlab_met	treatment_iv_labs_beta	notes	[[trivlab_day]] Where is the metagenome data stored?	[trivlab_metag_has]='1' and [trivlab_day] and [trivlab_day] >= 0
trivlab_met	treatment_iv_labs_beta	notes	[[trivlab_day]] Where is the sample stored?	[trivlab_metag_has]='0' and [trivlab_day] and [trivlab_day] >= 0
kino_no_in	kinetics_labs_beta	descripti	<h3><span style="background-color: #e03e2	[sc_meets_inclusion] < 1
kino_descri	kinetics_labs_beta	descripti	Kinetics Labs This page opens when IV and/or oral/enteral phage therapy are selected from the Treatment page. </	
kino_nonin	kinetics_labs_beta	descripti	This patient does not meet IV or oral/enteral phage thera	([tre_ph_0_rt(iv)] = '0' and [tre_ph_0_rt(oral)] = '0') and ([tre_ph_1_rt(iv)] = '0'
kino_day	kinetics_labs_beta	radio	Select clinic 2, D2 | 4, D4 | 8, D8 | 11, D11 | 15, D15 | 29, D29	[sc_meets_ y
kino_pre_p	kinetics_lat Pre-dose /	text	[[kino_day]][Pre-Dose] Phage resul integer	[kino_day] >= 0 and [kino_day]
kino_pre_p	kinetics_labs_beta	checkbo	[[kino_day] na, Plaque assays are NOT available for [[kino_day]]	[kino_pre_ y
kino_pre_p	kinetics_labs_beta	text	[[kino_day]][Pre-Dose] Phage qPCR integer	[kino_day] >= 0 and [kino_day]
kino_pre_p	kinetics_labs_beta	checkbo	[[kino_day] na, Phage qPCR results are NOT available for [[kino_day]]	[kino_pre_ y
kino_pre_b	kinetics_labs_beta	text	[[kino_day]][Pre-Dose] Bacterial lo integer	[kino_day] >= 0 and [kino_day]
kino_pre_b	kinetics_labs_beta	checkbo	[[kino_day] na, Phage qPCR results are NOT available for [[kino_day]]	[kino_pre_ y
kino_post_	kinetics_lat 30-60 minu	text	[[kino_day]][30-60 minutes post-dc integer	[kino_day] >= 0 and [kino_day] and [kino_day] != 15 and [kino_day] != 29
kino_post_	kinetics_labs_beta	checkbo	[[kino_day] na, Phage qPCR results are NOT available for [[kino_day]]	[kino_post_ y
kino_post_	kinetics_labs_beta	text	[[kino_day]][30-60 minutes post-dc integer	[kino_day] >= 0 and [kino_day] and [kino_day] != 15 and [kino_day] != 29
kino_post_	kinetics_labs_beta	checkbo	[[kino_day] na, Phage qPCR results are NOT available for [[kino_day]]	[kino_post_ y
kino_lngpo	kinetics_lat 2-3 hours p	text	[[kino_day]][2-3 hours post-dose] P integer	[kino_day] >= 0 and [kino_day]

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kino_lngpo	kinetics_labs_beta	checkbo	[[kino_day] na, Plaque assays are NOT available for [[kino_day]]	[kino_lngpc y
kino_lngpo	kinetics_labs_beta	text	[[kino_day]][2-3 hours post-dose] P integer	[kino_day] >= 0 and [kino_day] and [kino_day] != 15 and [kino_day] != 29
kino_lngpo	kinetics_labs_beta	checkbo	[[kino_day] na, Phage qPCR results are NOT available for [[kino_day]]	[kino_lngpc y
kino_lngpo	kinetics_labs_beta	text	[[kino_day]][2-3 hours post-dose] E integer	[kino_day] >= 0 and [kino_day] and [kino_day] != 15 and [kino_day] != 29
kino_lngpo	kinetics_labs_beta	checkbo	[[kino_day] na, Phage qPCR results are NOT available for [[kino_day]]	[kino_lngpc y
trivmo_no_	treatment_iv_monthly_	descripti	<h3><span style="background-color: #e03e2	[sc_meets_inclusion] < 1
trivmo_des	treatment_iv_monthly_	descripti	Clinical IV Labs [Monthly] Use this instrument for monthly treatment monitoring. This page opens when IV and/or or	
trivmo_non	treatment_iv_monthly_	descripti	This patient does not meet IV or oral/enteral phage thera	([tre_ph_0_rt(iv)] = '0' and [tre_ph_0_rt(oral)] = '0') and ([tre_ph_1_rt(iv)] = '0'
trivmo_mth	treatment_iv_monthly_	text	Month after first dose of phage adr integer	[sc_meets_ y
trivmo_pha	treatment_iv_monthly_	yesno	[Month [trivmo_mth]] Is the patient still receiving phage therapy?	[sc_meets_ y
trivmo_pha	treatment_iv_monthly_	yesno	[Month [trivmo_mth]] Did the patient stop phage therapy within the last mon	[trivmo_ph y
trivmo_pha	treatment_iv_monthly_	radio	[Month [tri cure, No evidence of ongoing infection: resolution of clinical symp	[trivmo_ph y
trivmo_pha	treatment_iv_monthly_	radio	[Month [tri no_disability, Without persisting disability | with_disability, With	[trivmo_ph y
trivmo_pha	treatment_iv_monthly_	radio	[Month [tri improvement, Improvement in clinical signs and symptoms, radiol	[trivmo_ph y
trivmo_crp	treatment_ CRP results	text	[Month [trivmo_mth]] CRP result (number_1dp	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1")
trivmo_crp	treatment_iv_monthly_	checkbo	[Month [tri na, CRP results NOT available [Month [trivmo_mth]]	[trivmo_crp y
trivmo_fbc	treatment_ FBC	yesno	[Month [trivmo_mth]] FBC all within normal range (yes/no)?	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1")
trivmo_hb	treatment_ Hb results	text	[Month [trivmo_mth]] Hb result (X integer	[trivmo_fbc_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_st
trivmo_hb_	treatment_iv_monthly_	checkbo	[Month [tri na, Hb results NOT available [Month [trivmo_mth]]	[trivmo_hb y
trivmo_plat	treatment_ Platelet cou	text	[Month [trivmo_mth]] Platelet resu integer	[trivmo_fbc_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_st
trivmo_plat	treatment_iv_monthly_	checkbo	[Month [tri na, Platelet count results NOT available [Month [trivmo_mth]]	[trivmo_pla y
trivmo_wcc	treatment_ WCC	text	[Month [trivmo_mth]] WCC (XXX x integer	[trivmo_fbc_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_st
trivmo_wcc	treatment_iv_monthly_	checkbo	[Month [tri na, WCC results NOT available [Month [trivmo_mth]]	[trivmo_wc y
trivmo_neu	treatment_ Neutrophil	text	[Month [trivmo_mth]] Neutrophil c number_1dp	[trivmo_fbc_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_st
trivmo_neu	treatment_iv_monthly_	checkbo	[Month [tri na, neutrophil count results NOT available [Month [trivmo_mth]]	[trivmo_ne y
trivmo_lym	treatment_ Lymphocyt	text	[Month [trivmo_mth]] Lymphocyte number_1dp	[trivmo_fbc_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_st
trivmo_lym	treatment_iv_monthly_	checkbo	[Month [tri na, Lymphocyte count results NOT available [Month [trivmo_mth]	[trivmo_lyn y
trivmo_lft_	treatment_iv_monthly_	yesno	[Month [trivmo_mth]] LFTs all within normal range (yes/no)?	([trivmo_pl y
trivmo_alb	treatment_ Albumin	text	[Month [trivmo_mth]] Albumin (XX integer	[trivmo_lft_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_sto
trivmo_alb	treatment_iv_monthly_	checkbo	[Month [tri na, Albumin results are NOT available [Month [trivmo_mth]]	[trivmo_alb y
trivmo_ast	treatment_ AST	text	[Month [trivmo_mth]] AST (XXXX U integer	[trivmo_lft_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_sto
trivmo_ast_	treatment_iv_monthly_	checkbo	[Month [tri na, AST results are NOT available [Month [trivmo_mth]]	[trivmo_ast y
trivmo_alt	treatment_ ALT	text	[Month [trivmo_mth]] ALT (XXXX U integer	[trivmo_lft_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_sto
trivmo_alt_	treatment_iv_monthly_	checkbo	[Month [tri na, ALT results are NOT available [Month [trivmo_mth]]	[trivmo_alt y
trivmo_ggt	treatment_ GGT	text	[Month [trivmo_mth]] GGT (XXXX U integer	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1")
trivmo_ggt_	treatment_iv_monthly_	checkbo	[Month [tri na, GGT results are NOT available [Month [trivmo_mth]]	[trivmo_ggt y
trivmo_alp	treatment_ ALP	text	[Month [trivmo_mth]] ALP (XXXX U integer	[trivmo_lft_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_sto
trivmo_alp_	treatment_iv_monthly_	checkbo	[Month [tri na, ALP results are NOT available [Month [trivmo_mth]]	[trivmo_alp y
trivmo_uec	treatment_iv_monthly_	yesno	[Month [trivmo_mth]] UECs all within normal range (yes/no)?	([trivmo_pl y
trivmo_sod	treatment_ Sodium	text	[Month [trivmo_mth]] Sodium (XX integer	[trivmo_uec_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_s
trivmo_sod	treatment_iv_monthly_	checkbo	[Month [tri na, Sodium results are NOT available [Month [trivmo_mth]]	[trivmo_so y

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trivmo_ure	treatment_ Urea	text	[Month [trivmo_mth]] Urea (XX.X n	number_1dp	[trivmo_uec_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_s
trivmo_ure	treatment_iv_monthly_	checkbo	[Month [tri na, Urea results are NOT available [Month [trivmo_mth]]		[trivmo_ure y
trivmo_cre	treatment_ Creatinine	text	[Month [trivmo_mth]] Creatinine (	integer	[trivmo_uec_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_s
trivmo_cre	treatment_iv_monthly_	checkbo	[Month [tri na, Creatinine results are NOT available [Month [trivmo_mth]]		[trivmo_cre y
trivmo_igg	treatment_ IgG	text	[Month [trivmo_mth]] IgG (XX.XX g	number_2dp	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1")
trivmo_igg_	treatment_iv_monthly_	checkbo	[Month [tri na, IgG results are NOT available [Month [trivmo_mth]]		[trivmo_igg y
trivmo_c3	treatment_ C3	text	[Month [trivmo_mth]] C3 (X.XX g/L	number_2dp	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1")
trivmo_c3_	treatment_iv_monthly_	checkbo	[Month [tri na, C3 results are NOT available [Month [trivmo_mth]]		[trivmo_c3] y
trivmo_c4	treatment_ C4	text	[Month [trivmo_mth]] C4 (X.XX g/L	number_2dp	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1")
trivmo_c4_	treatment_iv_monthly_	checkbo	[Month [tri na, C4 results are NOT available [Month [trivmo_mth]]		[trivmo_c4] y
trivmo_ch5	treatment_ CH50	text	[Month [trivmo_mth]] CH50 (XX U/	integer	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1")
trivmo_ch5	treatment_iv_monthly_	checkbo	[Month [tri na, CH50 results are NOT available [Month [trivmo_mth]]		[trivmo_ch! y
trivmo_ph0	treatment_iv_monthly_	descripti	Phage: "[pre_phage1_name]"		([tre_ph_0_rt(iv)] = '1' or [tre_ph_0_rt(oral)] = '1') and [pre_phage1_name] an
trivmo_ph_	treatment_iv_monthly_	yesno	[Phage: "[pre_phage1_name]"] Antiphage antibodies tested (yes/no)?		([tre_ph_0_ y
trivmo_ph_	treatment_iv_monthly_	checkbo	[Phage: "[p neutralising,Neutralising antibody assay | igmigg, IgM/IgG assay |		[trivmo_ph y
trivmo_ph_	treatment_iv_monthly_	text	[Phage: "[pre_phage1_name]"] Other assay type		[trivmo_ph y @CHARLIMIT='50'
trivmo_ph_	treatment_iv_monthly_	notes	[Phage: "[pre_phage1_name]"] Antiphage antibody result		[trivmo_ph y
trivmo_ph1	treatment_iv_monthly_	descripti	Phage: "[pre_phage2_name]"		([tre_ph_1_rt(iv)] = '1' or [tre_ph_1_rt(oral)] = '1') and [pre_phage2_name] an
trivmo_ph_	treatment_iv_monthly_	yesno	[Phage: "[pre_phage2_name]"] Antiphage antibodies tested (yes/no)?		([tre_ph_1_ y
trivmo_ph_	treatment_iv_monthly_	checkbo	[Phage: "[p neutralising,Neutralising antibody assay | igmigg, IgM/IgG assay |		[trivmo_ph y
trivmo_ph_	treatment_iv_monthly_	text	[Phage: "[pre_phage2_name]"] Other assay type		[trivmo_ph y @CHARLIMIT='50'
trivmo_ph_	treatment_iv_monthly_	notes	[Phage: "[pre_phage2_name]"] Antiphage antibody result		[trivmo_ph y
trivmo_ph2	treatment_iv_monthly_	descripti	Phage: "[pre_phage3_name]"		([tre_ph_2_rt(iv)] = '1' or [tre_ph_2_rt(oral)] = '1') and [pre_phage3_name] an
trivmo_ph_	treatment_iv_monthly_	yesno	[Phage: "[pre_phage3_name]"] Antiphage antibodies tested (yes/no)?		([tre_ph_2_ y
trivmo_ph_	treatment_iv_monthly_	checkbo	[Phage: "[p neutralising,Neutralising antibody assay | igmigg, IgM/IgG assay |		[trivmo_ph y
trivmo_ph_	treatment_iv_monthly_	text	[Phage: "[pre_phage3_name]"] Other assay type		[trivmo_ph y @CHARLIMIT='50'
trivmo_ph_	treatment_iv_monthly_	notes	[Phage: "[pre_phage3_name]"] Antiphage antibody result		[trivmo_ph y
trivmo_ph3	treatment_iv_monthly_	descripti	Phage: "[pre_phage4_name]"		([tre_ph_3_rt(iv)] = '1' or [tre_ph_3_rt(oral)] = '1') and [pre_phage4_name] an
trivmo_ph_	treatment_iv_monthly_	yesno	[Phage: "[pre_phage4_name]"] Antiphage antibodies tested (yes/no)?		([tre_ph_3_ y
trivmo_ph_	treatment_iv_monthly_	checkbo	[Phage: "[p neutralising,Neutralising antibody assay | igmigg, IgM/IgG assay |		[trivmo_ph y
trivmo_ph_	treatment_iv_monthly_	text	[Phage: "[pre_phage4_name]"] Other assay type		[trivmo_ph y @CHARLIMIT='50'
trivmo_ph_	treatment_iv_monthly_	notes	[Phage: "[pre_phage4_name]"] Antiphage antibody result		[trivmo_ph y
trivmo_ph4	treatment_iv_monthly_	descripti	Phage: "[pre_phage5_name]"		([tre_ph_4_rt(iv)] = '1' or [tre_ph_4_rt(oral)] = '1') and [pre_phage5_name] an
trivmo_ph_	treatment_iv_monthly_	yesno	[Phage: "[pre_phage5_name]"] Antiphage antibodies tested (yes/no)?		([tre_ph_4_ y
trivmo_ph_	treatment_iv_monthly_	checkbo	[Phage: "[p neutralising,Neutralising antibody assay | igmigg, IgM/IgG assay |		[trivmo_ph y
trivmo_ph_	treatment_iv_monthly_	text	[Phage: "[pre_phage5_name]"] Other assay type		[trivmo_ph y @CHARLIMIT='50'
trivmo_ph_	treatment_iv_monthly_	notes	[Phage: "[pre_phage5_name]"] Antiphage antibody result		[trivmo_ph y
trivmo_pth	treatment_iv_monthly_	descripti	Pathogen 1 "[pre_pth1_target]"		[pre_num_target_pathogen] > 0 and ([trivmo_phage_cont] = "1" or [trivmo_pt
trivmo_pth	treatment_iv_monthly_	radio	[Pathogen 1 isolated,Isolated | not_isolated, Not isolated | na, Not performed		[pre_num_t y
trivmo_pth	treatment_iv_monthly_	notes	[Pathogen 1: [pre_pth1_target]] How come isolation wasn't performed?		[trivmo_pt y
trivmo_pth	treatment_iv_monthly_	radio	[Pathogen 1 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc		[trivmo_pt y

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trivmo_pth	treatment_iv_monthly_	notes	[Pathogen 1: [pre_pth1_target]] Please specify anti-phage resistance activity [trivmo_pth y
trivmo_pth	treatment_iv_monthly_	radio	[Pathogen 1 isolated,Isolated | not_isolated, Not isolated | na, Not performed [pre_num_ y
trivmo_pth	treatment_iv_monthly_	text	[Pathogen 1: [pre_pth1_target]] Specify other site where pathogen was isolat [trivmo_pth y
trivmo_pth	treatment_iv_monthly_	radio	[Pathogen 1 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc [trivmo_pth y
trivmo_pth	treatment_iv_monthly_	notes	[Pathogen 1: [pre_pth1_target]] Please specify anti-phage resistance activity [trivmo_pth y
trivmo_pth	treatment_iv_monthly_	descripti	Pathogen 2 "[pre_pth2_target]" [pre_num_target_pathogen] > 1 and ([trivmo_phage_cont] = "1" or [trivmo_ph
trivmo_pth	treatment_iv_monthly_	radio	[Pathogen 2 isolated,Isolated | not_isolated, Not isolated | na, Not performed [pre_num_ y
trivmo_pth	treatment_iv_monthly_	notes	[Pathogen 2: [pre_pth2_target]] How come isolation wasn't performed? [trivmo_pth y
trivmo_pth	treatment_iv_monthly_	radio	[Pathogen 2 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc [trivmo_pth y
trivmo_pth	treatment_iv_monthly_	notes	[Pathogen 2: [pre_pth2_target]] Please specify anti-phage resistance activity [trivmo_pth y
trivmo_pth	treatment_iv_monthly_	radio	[Pathogen 2 isolated,Isolated | not_isolated, Not isolated | na, Not performed [pre_num_ y
trivmo_pth	treatment_iv_monthly_	text	[Pathogen 2: [pre_pth2_target]] Specify other site where pathogen was isolat [trivmo_pth y
trivmo_pth	treatment_iv_monthly_	radio	[Pathogen 2 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc [trivmo_pth y
trivmo_pth	treatment_iv_monthly_	notes	[Pathogen 2: [pre_pth2_target]] Please specify anti-phage resistance activity [trivmo_pth y
trivmo_pth	treatment_iv_monthly_	descripti	Pathogen 3 "[pre_pth3_target]" [pre_num_target_pathogen] > 2 and ([trivmo_phage_cont] = "1" or [trivmo_ph
trivmo_pth	treatment_iv_monthly_	radio	[Pathogen 3 isolated,Isolated | not_isolated, Not isolated | na, Not performed [pre_num_ y
trivmo_pth	treatment_iv_monthly_	notes	[Pathogen 3: [pre_pth3_target]] How come isolation wasn't performed? [trivmo_pth y
trivmo_pth	treatment_iv_monthly_	radio	[Pathogen 3 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc [trivmo_pth y
trivmo_pth	treatment_iv_monthly_	notes	[Pathogen 3: [pre_pth3_target]] Please specify anti-phage resistance activity [trivmo_pth y
trivmo_pth	treatment_iv_monthly_	radio	[Pathogen 3 isolated,Isolated | not_isolated, Not isolated | na, Not performed [pre_num_ y
trivmo_pth	treatment_iv_monthly_	text	[Pathogen 3: [pre_pth3_target]] Specify other site where pathogen was isolat [trivmo_pth y
trivmo_pth	treatment_iv_monthly_	radio	[Pathogen 3 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc [trivmo_pth y
trivmo_pth	treatment_iv_monthly_	notes	[Pathogen 3: [pre_pth3_target]] Please specify anti-phage resistance activity [trivmo_pth y
trivmo_pth	treatment_iv_monthly_	descripti	Pathogen 4 "[pre_pth4_target]" [pre_num_target_pathogen] > 3 and ([trivmo_phage_cont] = "1" or [trivmo_ph
trivmo_pth	treatment_iv_monthly_	radio	[Pathogen 4 isolated,Isolated | not_isolated, Not isolated | na, Not performed [pre_num_ y
trivmo_pth	treatment_iv_monthly_	notes	[Pathogen 4: [pre_pth4_target]] How come isolation wasn't performed? [trivmo_pth y
trivmo_pth	treatment_iv_monthly_	radio	[Pathogen 4 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc [trivmo_pth y
trivmo_pth	treatment_iv_monthly_	notes	[Pathogen 4: [pre_pth4_target]] Please specify anti-phage resistance activity [trivmo_pth y
trivmo_pth	treatment_iv_monthly_	radio	[Pathogen 4 isolated,Isolated | not_isolated, Not isolated | na, Not performed [pre_num_ y
trivmo_pth	treatment_iv_monthly_	text	[Pathogen 4: [pre_pth4_target]] Specify other site where pathogen was isolat [trivmo_pth y
trivmo_pth	treatment_iv_monthly_	radio	[Pathogen 4 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc [trivmo_pth y
trivmo_pth	treatment_iv_monthly_	notes	[Pathogen 4: [pre_pth4_target]] Please specify anti-phage resistance activity [trivmo_pth y
trivmo_pth	treatment_iv_monthly_	descripti	Pathogen 5 "[pre_pth5_target]" [pre_num_target_pathogen] > 4 and ([trivmo_phage_cont] = "1" or [trivmo_ph
trivmo_pth	treatment_iv_monthly_	radio	[Pathogen 5 isolated,Isolated | not_isolated, Not isolated | na, Not performed [pre_num_ y
trivmo_pth	treatment_iv_monthly_	notes	[Pathogen 5: [pre_pth5_target]] How come isolation wasn't performed? [trivmo_pth y
trivmo_pth	treatment_iv_monthly_	radio	[Pathogen 5 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc [trivmo_pth y
trivmo_pth	treatment_iv_monthly_	notes	[Pathogen 5: [pre_pth5_target]] Please specify anti-phage resistance activity [trivmo_pth y
trivmo_pth	treatment_iv_monthly_	radio	[Pathogen 5 isolated,Isolated | not_isolated, Not isolated | na, Not performed [pre_num_ y
trivmo_pth	treatment_iv_monthly_	text	[Pathogen 5: [pre_pth5_target]] Specify other site where pathogen was isolat [trivmo_pth y
trivmo_pth	treatment_iv_monthly_	radio	[Pathogen 5 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc [trivmo_pth y
trivmo_pth	treatment_iv_monthly_	notes	[Pathogen 5: [pre_pth5_target]] Please specify anti-phage resistance activity [trivmo_pth y

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trivmo_wgs	treatment_ WGS	yesno	[Month [trivmo_mth]] Is WGS data available for current isolate?	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1")
trivmo_wgs	treatment_iv_monthly_	notes	[Month [trivmo_mth]] Where is the WGS data stored?	[trivmo_wgs]='1' and ([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo]
trivmo_rna	treatment_iv_monthly_	radio	[Month [tri yes, Yes/Sample obtained + stored | not_analysed,Sample proces	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1")
trivmo_rna	treatment_iv_monthly_	notes	[Month [trivmo_mth]] Where is the RNA transcriptomics data stored?	[trivmo_rnatr]='yes' and ([trivmo_phage_cont] = "1" or [trivmo_phage_stop_m
trivmo_rna	treatment_iv_monthly_	notes	[Month [trivmo_mth]] Where is the RNA transcriptomics sample stored?	([trivmo_rnatr]='yes' or [trivmo_rnatr]='not_analysed') and ([trivmo_phage_co
trivmo_met	treatment_ Metagenon	yesno	[Month [trivmo_mth]] Are clinical samples available for metagenomics?	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1")
trivmo_met	treatment_iv_monthly_	text	[Month [trivmo_mth]] Specify type of sample	[trivmo_metag_samples]='1' and ([trivmo_phage_cont] = "1" or [trivmo_phage
trivmo_met	treatment_iv_monthly_	radio	[Month [tri 1,Yes | 0, No, samples stored	[trivmo_metag_samples]='1' and ([trivmo_phage_cont] = "1" or [trivmo_phage
trivmo_met	treatment_iv_monthly_	notes	[Month [trivmo_mth]] Where is the metagenome data stored?	[trivmo_metag_has]='1' and ([trivmo_phage_cont] = "1" or [trivmo_phage_sto
trivmo_met	treatment_iv_monthly_	notes	[Month [trivmo_mth]] Where is the sample stored?	[trivmo_metag_has]='0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_sto
trivmo_kin	treatment_ Pre-dose /	text	[Pre-Dose] Phage result plaque ass integer	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1")
trivmo_kin	treatment_iv_monthly_	checkbo	[Pre-Dose] na, Plaque assays are NOT available	[trivmo_kin y
trivmo_kin	treatment_iv_monthly_	text	[Pre-Dose] Phage qPCR results (XX integer	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1")
trivmo_kin	treatment_iv_monthly_	checkbo	[Pre-Dose] na, Phage qPCR results are NOT available	[trivmo_kin y
trivmo_kin	treatment_iv_monthly_	text	[Pre-Dose] Bacterial load qPCR resu integer	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1")
trivmo_kin	treatment_iv_monthly_	checkbo	[Pre-Dose] na, Phage qPCR results are NOT available	[trivmo_kin y
trivmo_kin	treatment_ 30-60 minu	text	[30-60 minutes post-dose] Phage q integer	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1") and [trivmo_ph
trivmo_kin	treatment_iv_monthly_	checkbo	[30-60 min na, Phage qPCR results are NOT available	[trivmo_kin y
trivmo_kin	treatment_iv_monthly_	text	[30-60 minutes post-dose] Bacteria integer	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1") and [trivmo_ph
trivmo_kin	treatment_iv_monthly_	checkbo	[30-60 min na, Phage qPCR results are NOT available	[trivmo_kin y
trivmo_kin	treatment_ 2-3 hours p	text	[2-3 hours post-dose] Phage result integer	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1") and [trivmo_ph
trivmo_kin	treatment_iv_monthly_	checkbo	[2-3 hours na, Plaque assays are NOT available	[trivmo_kin y
trivmo_kin	treatment_iv_monthly_	text	[2-3 hours post-dose] Phage qPCR r integer	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1") and [trivmo_ph
trivmo_kin	treatment_iv_monthly_	checkbo	[2-3 hours na, Phage qPCR results are NOT available	[trivmo_kin y
trivmo_kin	treatment_iv_monthly_	text	[2-3 hours post-dose] Bacterial loa integer	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1") and [trivmo_ph
trivmo_kin	treatment_iv_monthly_	checkbo	[2-3 hours na, Phage qPCR results are NOT available	[trivmo_kin y
othcli_no_i	other_routes_clinical_b	descripti	<h3><span style="background-color: #e03e2	[sc_meets_inclusion] < 1
othcli_desc	other_routes_clinical_b	descripti	Other Routes - Clinical This page opens when non IV and/or oral/enteral phage therapy are selected from the Treatm	
othcli_noni	other_routes_clinical_b	descripti	This instrument is for patients who are NOT receiving IV	([tre_ph_0_rt(iv)] = '1' or [tre_ph_0_rt(oral)] = '1') or ([tre_ph_1_rt(iv)] = '1' or
othcli_day	other_routes_clinical_b	radio	Select clinic 0, D0 | 1, D1 | 2, D2 | 3, D3 | 4, D4 | 5, D5 | 6, D6 | 7, D7 | 8, D8	[sc_meets_ y
othcli_vital	other_routes_clinical_b	yesno	[[othcli_day]] Vitals performed 30 minutes after dose? [othcli_day]	[sc_meets_ y
othcli_devi	other_routes_clinical_b	yesno	[[othcli_day]] Protocol Deviation?	[sc_meets_ y
othcli_devi	other_routes_clinical_b	notes	[[othcli_day]] Describe the reason for deviation	[othcli_dev y
othcli_hi_fe	other_routes_clinical_b	yesno	[[othcli_day]] Did fever (temp > 37.9Â°C) occur today?	[sc_meets_ y
othcli_hi_fe	other_routes_clinical_b	text	[[othcli_day]] Specify max temp (XX number_1dp	[sc_meets_ y
othcli_hi_fe	other_routes_clinical_b	text	[[othcli_day]] Specify time of max f number_1dp	[sc_meets_ y
othcli_tach	other_routes_clinical_b	yesno	Did tachycardia occur today (yes/no)?	[sc_meets_ y
othcli_tach	other_routes_clinical_b	text	Specify max HR occurring prior to n integer	[othcli_tach y
othcli_tach	other_routes_clinical_b	text	Specify time of max HR in hours aft number_1dp	[othcli_tach y
othcli_pain	other_routes_clinical_b	yesno	Did tachycardia occur today (yes/no)?	[sc_meets_ y
othcli_pain	other_routes_clinical_b	text	Specify max HR occurring prior to n integer	[othcli_pain y

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othcli_pain	other_routes_clinical_t	text	Specify time of max HR in hours aft	number_1dp		[othcli_pair y
othcli_infla	other_routes_clinical_t	yesno	[[othcli_day]] Any other signs or symptoms of inflammatory response (yes/no			[sc_meets_ y
othcli_infla	other_routes_clinical_t	text	[[othcli_day]] Specify what occurre	number_1dp		[sc_meets_ y
othcli_infla	other_routes_clinical_t	text	[[othcli_day]] Also specify time of o	number_1dp		[sc_meets_ y
othcli_cont	other_routes_clinical_t	yesno	[[othcli_day]] Is the patient still receiving phage therapy?			[sc_meets_ y
othcli_phag	other_routes_clinical_t	radio	What has b cure, No evidence of ongoing infection: resolution of clinical symp			[othcli_con y
othcli_phag	other_routes_clinical_t	radio	Any disabili no_disability, Without persisting disability | with_disability, With p			[othcli_pha y
othcli_phag	other_routes_clinical_t	radio	Partial resp improvement, Improvement in clinical signs and symptoms, radiol			[othcli_pha y
othcli_1528	other_routes_clinical_t	yesno	[[othcli_day]] Were vitals checked each day of treatment as per protocol (yes,			[sc_meets_ y
othcli_1528	other_routes_clinical_t	yesno	[[othcli_day]] Will treatment continue >= 4 weeks (yes/no)?			[sc_meets_ y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] How many days of ph	integer	14 28	[sc_meets_ y
othcli_1528	other_routes_clinical_t	checkbox	[[othcli_day]] 15, D15 | 16, D16 | 17, D17 | 18, D18 | 19, D19 | 20, D20 | 21, D2			[sc_meets_ y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] Specify max temp (XX	number_1dp		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] Specify max temp (XX	number_1dp		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] Specify max temp (XX	number_1dp		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] Specify max temp (XX	number_1dp		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] Specify max temp (XX	number_1dp		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] Specify max temp (XX	number_1dp		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] Specify max temp (XX	number_1dp		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] Specify max temp (XX	number_1dp		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] Specify max temp (XX	number_1dp		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] Specify max temp (XX	number_1dp		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] Specify max temp (XX	number_1dp		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] Specify max temp (XX	number_1dp		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] Specify max temp (XX	number_1dp		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] Specify max temp (XX	number_1dp		[othcli_152 y
othcli_1528	other_routes_clinical_t	checkbox	[[othcli_day]] 15, D15 | 16, D16 | 17, D17 | 18, D18 | 19, D19 | 20, D20 | 21, D2			[sc_meets_ y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify max HR occur	integer		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify max HR occur	integer		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify max HR occur	integer		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify max HR occur	integer		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify max HR occur	integer		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify max HR occur	integer		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify max HR occur	integer		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify max HR occur	integer		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify max HR occur	integer		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify max HR occur	integer		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify max HR occur	integer		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify max HR occur	integer		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify max HR occur	integer		[othcli_152 y
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify max HR occur	integer		[othcli_152 y

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othcli_1528	other_routes_clinical_t	checkbox	[[othcli_day 15, D15 | 16, D16 | 17, D17 | 18, D18 | 19, D19 | 20, D20 | 21, D2	[sc_meets_ y	
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify site of pain for D15	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify site of pain for D16	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify site of pain for D17	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify site of pain for D18	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify site of pain for D19	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify site of pain for D20	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify site of pain for D21	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify site of pain for D22	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify site of pain for D23	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify site of pain for D24	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify site of pain for D25	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify site of pain for D26	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify site of pain for D27	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify site of pain for D28	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_t	checkbox	[[othcli_day 15, D15 | 16, D16 | 17, D17 | 18, D18 | 19, D19 | 20, D20 | 21, D2	[sc_meets_ y	
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify what occurred for D15	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify what occurred for D16	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify what occurred for D17	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify what occurred for D18	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify what occurred for D19	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify what occurred for D20	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify what occurred for D21	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify what occurred for D22	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify what occurred for D23	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify what occurred for D24	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify what occurred for D25	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify what occurred for D26	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify what occurred for D27	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_t	text	[[othcli_day]] specify what occurred for D28	[othcli_152 y	@CHARLIMIT='50'
othcli_1528	other_routes_clinical_t	radio	[[othcli_day na, Not adjusted | increased, Dose increased | reduced, Dose red	[othcli_152 y	
othro_no_i	other_routes_lab_beta	descriptiv	<h3><span style="background-color: #e03e2	[sc_meets_inclusion] < 1	
othro_desc	other_routes_lab_beta	descriptiv	Other Routes - Lab This page opens when non IV and/or oral/enteral phage therapy are selected from the Treatment		
othro_noni	other_routes_lab_beta	descriptiv	This instrument is for patients who are NOT receiving IV (	([tre_ph_0_rt(iv)] = '1' or [tre_ph_0_rt(oral)] = '1') or ([tre_ph_1_rt(iv)] = '1' or	
othro_iv	other_routes_lab_beta	yesno	Is IV phage also being administered (yes/no)?	[sc_meets_ y	
othro_day	other_routes_lab_beta	radio	Select clinic 0, D0 | 2, D2 | 4, D4 | 8, D8 | 15, D15 | 29, D29 | other,Other Day	[sc_meets_ y	
othro_othe	other_routes_lab_beta	text	Enter day of treatment (enter a nur integer	[othro_day y	
othro_othe	other_routes_lab_beta	notes	Test performed for day [othro_other_day]	[othro_oth y	
othro_othe	other_routes_lab_beta	notes	Result for day [othro_other_day]	[othro_oth y	
othro_crp	other_rout	CRP results	text [[othro_day]] CRP result (XXX.X mg number_1dp	[othro_day] >= 0 and [othro_day] and [othro_day] != 11	
othro_crp_	other_routes_lab_beta	checkbox	[[othro_day na, CRP results NOT available for [[othro_day]]	[othro_crp] y	

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othro_fbc_i	other_routi	FBC	yesno	[[othro_day]] FBC all within normal range (yes/no)?		[othro_day] and [othro_day] >= 0
othro_hb	other_routi	Hb results	text	[[othro_day]] Hb result (XXX g/L)	integer	[othro_fbc_isnorm] = '0' and [othro_day] and [othro_day] >= 0
othro_hb_r	other_routes_lab_beta	checkbo	[[othro_da	na, Hb results NOT available for [[othro_day]]		[othro_hb] y
othro_plate	other_routi	Platelet cou	text	[[othro_day]] Platelet result (XXX x	integer	[othro_fbc_isnorm] = '0' and [othro_day] and [othro_day] >= 0
othro_plate	other_routes_lab_beta	checkbo	[[othro_da	na, Platelet count results NOT available for [[othro_day]]		[othro_plat y
othro_wcc	other_routi	WCC	text	[[othro_day]] WCC (XXX x10^9/L)	integer	[othro_fbc_isnorm] = '0' and [othro_day] and [othro_day] >= 0
othro_wcc_	other_routes_lab_beta	checkbo	[[othro_da	na, WCC results NOT available for [[othro_day]]		[othro_wcc y
othro_neut	other_routi	Neutrophil	text	[[othro_day]] Neutrophil count (XX	number_1dp	[othro_fbc_isnorm] = '0' and [othro_day] and [othro_day] >= 0
othro_neut	other_routes_lab_beta	checkbo	[[othro_da	na, neutrophil count results NOT available for [[othro_day]]		[othro_neu y
othro_lymp	other_routi	Lymphocyt	text	[[othro_day]] Lymphocyte count (X	number_1dp	[othro_fbc_isnorm] = '0' and [othro_day] and [othro_day] >= 0
othro_lymp	other_routes_lab_beta	checkbo	[[othro_da	na, Lymphocyte count results NOT available for [[othro_day]]		[othro_lym y
othro_lft_is	other_routes_lab_beta	yesno	[[othro_day]] LFTs all within normal range (yes/no)?			[othro_day y
othro_albu	other_routi	Albumin	text	[[othro_day]] Albumin (XX g/L)	integer	[othro_lft_isnorm] = '0' and [othro_day] and [othro_day] >= 0 and [othro_day]
othro_albu	other_routes_lab_beta	checkbo	[[othro_da	na, Albumin results are NOT available for [[othro_day]]		[othro_albu y
othro_ast	other_routi	AST	text	[[othro_day]] AST (XXXX U/L)	integer	[othro_lft_isnorm] = '0' and [othro_day] and [othro_day] >= 0 and [othro_day]
othro_ast_	other_routes_lab_beta	checkbo	[[othro_da	na, AST results are NOT available for [[othro_day]]		[othro_ast] y
othro_alt	other_routi	ALT	text	[[othro_day]] ALT (XXXX U/L)	integer	[othro_lft_isnorm] = '0' and [othro_day] and [othro_day] >= 0 and [othro_day]
othro_alt_r	other_routes_lab_beta	checkbo	[[othro_da	na, ALT results are NOT available for [[othro_day]]		[othro_alt] y
othro_ggt	other_routi	GGT	text	[[othro_day]] GGT (XXXX U/L)	integer	([othro_lft_isnorm] = '0') and [othro_day] and [othro_day] >= 0 and [othro_da
othro_ggt_	other_routes_lab_beta	checkbo	[[othro_da	na, GGT results are NOT available for [[othro_day]]		[othro_ggt] y
othro_alp	other_routi	ALP	text	[[othro_day]] ALP (XXXX U/L)	integer	[othro_lft_isnorm] = '0' and [othro_day] and [othro_day] >= 0 and [othro_day]
othro_alp_	other_routes_lab_beta	checkbo	[[othro_da	na, ALP results are NOT available for [[othro_day]]		[othro_alp] y
othro_uec_	other_routes_lab_beta	yesno	[[othro_day]] UECs all within normal range (yes/no)?			[othro_day y
othro_sodi	other_routi	Sodium	text	[[othro_day]] Sodium (XXX mmol/L	integer	[othro_uec_isnorm] = '0' and [othro_day] and [othro_day] >= 0 and [othro_da
othro_sodi	other_routes_lab_beta	checkbo	[[othro_da	na, Sodium results are NOT available for [[othro_day]]		[othro_sodi y
othro_urea	other_routi	Urea	text	[[othro_day]] Urea (XX.X mmol/L)	number_1dp	[othro_uec_isnorm] = '0' and [othro_day] and [othro_day] >= 0 and [othro_da
othro_urea	other_routes_lab_beta	checkbo	[[othro_da	na, Urea results are NOT available for [[othro_day]]		[othro_urea y
othro_crea	other_routi	Creatinine	text	[[othro_day]] Creatinine (XXX umol	integer	[othro_uec_isnorm] = '0' and [othro_day] and [othro_day] >= 0 and [othro_da
othro_crea	other_routes_lab_beta	checkbo	[[othro_da	na, Creatinine results are NOT available for [[othro_day]]		[othro_crea y
othro_ph0	other_routes_lab_beta	descripti	Phage: "[pre_phage1_name]"			([tre_ph_0_rt(iv)] = '1' or [tre_ph_0_rt(oral)] = '1') and [pre_phage1_name] an
othro_ph_(	other_routes_lab_beta	yesno	[Phage: "[pre_phage1_name]"] Antiphage antibodies tested (yes/no)?			([tre_ph_0_ y
othro_ph_(	other_routes_lab_beta	checkbo	[Phage: "[p	neutralising,Neutralising antibody assay | igmigg, IgM/IgG assay |		[othro_ph_ y
othro_ph_(	other_routes_lab_beta	text	[Phage: "[pre_phage1_name]"] Other assay type			[othro_ph_ y @CHARLIMIT='50'
othro_ph_(	other_routes_lab_beta	notes	[Phage: "[pre_phage1_name]"] Antiphage antibody result			[othro_ph_ y
othro_ph1	other_routes_lab_beta	descripti	Phage: "[pre_phage2_name]"			([tre_ph_1_rt(iv)] = '1' or [tre_ph_1_rt(oral)] = '1') and [pre_phage2_name] an
othro_ph_1	other_routes_lab_beta	yesno	[Phage: "[pre_phage2_name]"] Antiphage antibodies tested (yes/no)?			([tre_ph_1_ y
othro_ph_1	other_routes_lab_beta	checkbo	[Phage: "[p	neutralising,Neutralising antibody assay | igmigg, IgM/IgG assay |		[othro_ph_ y
othro_ph_1	other_routes_lab_beta	text	[Phage: "[pre_phage2_name]"] Other assay type			[othro_ph_ y @CHARLIMIT='50'
othro_ph_1	other_routes_lab_beta	notes	[Phage: "[pre_phage2_name]"] Antiphage antibody result			[othro_ph_ y
othro_ph2	other_routes_lab_beta	descripti	Phage: "[pre_phage3_name]"			([tre_ph_2_rt(iv)] = '1' or [tre_ph_2_rt(oral)] = '1') and [pre_phage3_name] an
othro_ph_2	other_routes_lab_beta	yesno	[Phage: "[pre_phage3_name]"] Antiphage antibodies tested (yes/no)?			([tre_ph_2_ y

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othro_ph_2	other_routes_lab_beta checkbo	[Phage: "[p neutralising,Neutralising antibody assay | igmigg, IgM/IgG assay |	[othro_ph_ y	
othro_ph_2	other_routes_lab_beta text	[Phage: "[pre_phage3_name]"] Other assay type	[othro_ph_ y	@CHARLIMIT='50'
othro_ph_2	other_routes_lab_beta notes	[Phage: "[pre_phage3_name]"] Antiphage antibody result	[othro_ph_ y	
othro_ph3	other_routes_lab_beta descripti	Phage: "[pre_phage4_name]"	([tre_ph_3_rt(iv)] = '1' or [tre_ph_3_rt(oral)] = '1') and [pre_phage4_name] an	
othro_ph_3	other_routes_lab_beta yesno	[Phage: "[pre_phage4_name]"] Antiphage antibodies tested (yes/no)?	([tre_ph_3_ y	
othro_ph_3	other_routes_lab_beta checkbo	[Phage: "[p neutralising,Neutralising antibody assay | igmigg, IgM/IgG assay |	[othro_ph_ y	
othro_ph_3	other_routes_lab_beta text	[Phage: "[pre_phage4_name]"] Other assay type	[othro_ph_ y	@CHARLIMIT='50'
othro_ph_3	other_routes_lab_beta notes	[Phage: "[pre_phage4_name]"] Antiphage antibody result	[othro_ph_ y	
othro_ph4	other_routes_lab_beta descripti	Phage: "[pre_phage5_name]"	([tre_ph_4_rt(iv)] = '1' or [tre_ph_4_rt(oral)] = '1') and [pre_phage5_name] an	
othro_ph_4	other_routes_lab_beta yesno	[Phage: "[pre_phage5_name]"] Antiphage antibodies tested (yes/no)?	([tre_ph_4_ y	
othro_ph_4	other_routes_lab_beta checkbo	[Phage: "[p neutralising,Neutralising antibody assay | igmigg, IgM/IgG assay |	[othro_ph_ y	
othro_ph_4	other_routes_lab_beta text	[Phage: "[pre_phage5_name]"] Other assay type	[othro_ph_ y	@CHARLIMIT='50'
othro_ph_4	other_routes_lab_beta notes	[Phage: "[pre_phage5_name]"] Antiphage antibody result	[othro_ph_ y	
othro_pth1	other_routes_lab_beta descripti	Pathogen 1 "[pre_pth1_target]"	[pre_num_target_pathogen] > 0 and [othro_day] and ([othro_day] = 0 or [othr	
othro_pth_	other_routes_lab_beta radio	[Pathogen 1 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ y	
othro_pth_	other_routes_lab_beta notes	[Pathogen 1: [pre_pth1_target]] How come isolation wasn't performed?	[othro_pth_ y	
othro_pth_	other_routes_lab_beta radio	[Pathogen 1 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[othro_pth_ y	
othro_pth_	other_routes_lab_beta notes	[Pathogen 1: [pre_pth1_target]] Please specify anti-phage resistance activity	[othro_pth_ y	
othro_pth_	other_routes_lab_beta radio	[Pathogen 1 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ y	
othro_pth_	other_routes_lab_beta text	[Pathogen 1: [pre_pth1_target]] Specify other site where pathogen was isolat	[othro_pth_ y	
othro_pth_	other_routes_lab_beta radio	[Pathogen 1 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[othro_pth_ y	
othro_pth_	other_routes_lab_beta notes	[Pathogen 1: [pre_pth1_target]] Please specify anti-phage resistance activity	[othro_pth_ y	
othro_pth2	other_routes_lab_beta descripti	Pathogen 2 "[pre_pth2_target]"	[pre_num_target_pathogen] > 1 and [othro_day] and ([othro_day] = 0 or [othr	
othro_pth_	other_routes_lab_beta radio	[Pathogen 2 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ y	
othro_pth_	other_routes_lab_beta notes	[Pathogen 2: [pre_pth2_target]] How come isolation wasn't performed?	[othro_pth_ y	
othro_pth_	other_routes_lab_beta radio	[Pathogen 2 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[othro_pth_ y	
othro_pth_	other_routes_lab_beta notes	[Pathogen 2: [pre_pth2_target]] Please specify anti-phage resistance activity	[othro_pth_ y	
othro_pth_	other_routes_lab_beta radio	[Pathogen 2 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ y	
othro_pth_	other_routes_lab_beta text	[Pathogen 2: [pre_pth2_target]] Specify other site where pathogen was isolat	[othro_pth_ y	
othro_pth_	other_routes_lab_beta radio	[Pathogen 2 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[othro_pth_ y	
othro_pth_	other_routes_lab_beta notes	[Pathogen 2: [pre_pth2_target]] Please specify anti-phage resistance activity	[othro_pth_ y	
othro_pth3	other_routes_lab_beta descripti	Pathogen 3 "[pre_pth3_target]"	[pre_num_target_pathogen] > 2 and [othro_day] and ([othro_day] = 0 or [othr	
othro_pth_	other_routes_lab_beta radio	[Pathogen 3 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ y	
othro_pth_	other_routes_lab_beta notes	[Pathogen 3: [pre_pth3_target]] How come isolation wasn't performed?	[othro_pth_ y	
othro_pth_	other_routes_lab_beta radio	[Pathogen 3 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[othro_pth_ y	
othro_pth_	other_routes_lab_beta notes	[Pathogen 3: [pre_pth3_target]] Please specify anti-phage resistance activity	[othro_pth_ y	
othro_pth_	other_routes_lab_beta radio	[Pathogen 3 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ y	
othro_pth_	other_routes_lab_beta text	[Pathogen 3: [pre_pth3_target]] Specify other site where pathogen was isolat	[othro_pth_ y	
othro_pth_	other_routes_lab_beta radio	[Pathogen 3 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[othro_pth_ y	
othro_pth_	other_routes_lab_beta notes	[Pathogen 3: [pre_pth3_target]] Please specify anti-phage resistance activity	[othro_pth_ y	
othro_pth4	other_routes_lab_beta descripti	Pathogen 4 "[pre_pth4_target]"	[pre_num_target_pathogen] > 3 and [othro_day] and ([othro_day] = 0 or [othr	

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othro_pth_	other_routes_lab_beta	radio	[Pathogen 4 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ty	
othro_pth_	other_routes_lab_beta	notes	[Pathogen 4: [pre_pth4_target]] How come isolation wasn't performed?	[othro_pth_ y	
othro_pth_	other_routes_lab_beta	radio	[Pathogen 4 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[othro_pth_ y	
othro_pth_	other_routes_lab_beta	notes	[Pathogen 4: [pre_pth4_target]] Please specify anti-phage resistance activity	[othro_pth_ y	
othro_pth_	other_routes_lab_beta	radio	[Pathogen 4 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ty	
othro_pth_	other_routes_lab_beta	text	[Pathogen 4: [pre_pth4_target]] Specify other site where pathogen was isolat	[othro_pth_ y	
othro_pth_	other_routes_lab_beta	radio	[Pathogen 4 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[othro_pth_ y	
othro_pth_	other_routes_lab_beta	notes	[Pathogen 4: [pre_pth4_target]] Please specify anti-phage resistance activity	[othro_pth_ y	
othro_pth5	other_routes_lab_beta	descriptio	Pathogen 5 "[pre_pth5_target]"	[pre_num_target_pathogen] > 4 and [othro_day] and ([othro_day] = 0 or [othr	
othro_pth_	other_routes_lab_beta	radio	[Pathogen 5 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ty	
othro_pth_	other_routes_lab_beta	notes	[Pathogen 5: [pre_pth5_target]] How come isolation wasn't performed?	[othro_pth_ y	
othro_pth_	other_routes_lab_beta	radio	[Pathogen 5 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[othro_pth_ y	
othro_pth_	other_routes_lab_beta	notes	[Pathogen 5: [pre_pth5_target]] Please specify anti-phage resistance activity	[othro_pth_ y	
othro_pth_	other_routes_lab_beta	radio	[Pathogen 5 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ty	
othro_pth_	other_routes_lab_beta	text	[Pathogen 5: [pre_pth5_target]] Specify other site where pathogen was isolat	[othro_pth_ y	
othro_pth_	other_routes_lab_beta	radio	[Pathogen 5 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc	[othro_pth_ y	
othro_pth_	other_routes_lab_beta	notes	[Pathogen 5: [pre_pth5_target]] Please specify anti-phage resistance activity	[othro_pth_ y	
othro_wgs	other_route	WGS	yesno	[[othro_day]] Is WGS data available for current isolate?	[othro_day] and ([othro_day] = 0 or [othro_day] = 4 or [othro_day] = 8 or [oth
othro_wgs_	other_routes_lab_beta	notes		[[othro_day]] Where is the WGS data stored?	[othro_wgs]='1' and [othro_day] and ([othro_day] = 0 or [othro_day] = 4 or [ot
othmo_no_	other_routes_monthly_	descriptio	<h3><span style="background-color: #e03e2	[sc_meets_inclusion] < 1	
othmo_des	other_routes_monthly_	descriptio	Other Routes [Monthly Monitoring] Use this instrument for monthly treatment monitoring. This page opens when n		
othmo_nor	other_routes_monthly_	descriptio	This patient does not meet IV or oral/enteral phage thera	([tre_ph_0_rt(iv)] = '1' or [tre_ph_0_rt(oral)] = '1') or ([tre_ph_1_rt(iv)] = '1' or	
othmo_mth	other_routes_monthly_	text		Month after first dose of phage adr integer	[sc_meets_ y
othmo_pha	other_routes_monthly_	yesno		[Month [othmo_mth]] Is the patient still receiving phage therapy?	[sc_meets_ y
othmo_pha	other_routes_monthly_	yesno		[Month [othmo_mth]] Did the patient stop phage therapy within the last mon	[othmo_ph y
othmo_pha	other_routes_monthly_	radio		[Month [oth cure, No evidence of ongoing infection: resolution of clinical symp	[othmo_ph y
othmo_pha	other_routes_monthly_	radio		[Month [oth no_disability, Without persisting disability | with_disability, With p	[othmo_ph y
othmo_pha	other_routes_monthly_	radio		[Month [oth improvement, Improvement in clinical signs and symptoms, radiol	[othmo_ph y
othmo_fbc_	other_route	FBC	yesno	[Month [othmo_mth]] FBC all within normal range (yes/no)?	([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1")
othmo_hb	other_route	Hb results	text	[Month [othmo_mth]] Hb result (X) integer	[othmo_fbc_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_st
othmo_hb_	other_routes_monthly_	checkbox		[Month [oth na, Hb results NOT available [Month [othmo_mth]]	[othmo_hb y
othmo_plat	other_route	Platelet cou	text	[Month [othmo_mth]] Platelet resu integer	[othmo_fbc_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_st
othmo_plat	other_routes_monthly_	checkbox		[Month [oth na, Platelet count results NOT available [Month [othmo_mth]]	[othmo_pla y
othmo_wcc	other_route	WCC	text	[Month [othmo_mth]] WCC (XXX x integer	[othmo_fbc_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_st
othmo_wcc	other_routes_monthly_	checkbox		[Month [oth na, WCC results NOT available [Month [othmo_mth]]	[othmo_wc y
othmo_neu	other_route	Neutrophil	text	[Month [othmo_mth]] Neutrophil c number_1dp	[othmo_fbc_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_st
othmo_neu	other_routes_monthly_	checkbox		[Month [oth na, neutrophil count results NOT available [Month [othmo_mth]]	[othmo_ne y
othmo_lym	other_route	Lymphocyte	text	[Month [othmo_mth]] Lymphocyte number_1dp	[othmo_fbc_isnorm] = '0' and ([trivmo_phage_cont] = "1" or [trivmo_phage_st
othmo_lym	other_routes_monthly_	checkbox		[Month [oth na, Lymphocyte count results NOT available [Month [othmo_mth]	[othmo_lyn y
othmo_pth	other_routes_monthly_	descriptio	Pathogen 1 "[pre_pth1_target]"	[pre_num_target_pathogen] > 0 and ([trivmo_phage_cont] = "1" or [trivmo_ph	
othmo_pth	other_routes_monthly_	radio		[Pathogen 1 isolated,Isolated | not_isolated, Not isolated | na, Not performed	[pre_num_ty

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othmo_pth	other_routes_monthly	notes	[Pathogen 1: [pre_pth1_target]] How come isolation wasn't performed?
othmo_pth	other_routes_monthly	radio	[Pathogen 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc
othmo_pth	other_routes_monthly	notes	[Pathogen 1: [pre_pth1_target]] Please specify anti-phage resistance activity
othmo_pth	other_routes_monthly	radio	[Pathogen isolated,Isolated | not_isolated, Not isolated | na, Not performed
othmo_pth	other_routes_monthly	text	[Pathogen 1: [pre_pth1_target]] Specify other site where pathogen was isolat
othmo_pth	other_routes_monthly	radio	[Pathogen 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc
othmo_pth	other_routes_monthly	notes	[Pathogen 1: [pre_pth1_target]] Please specify anti-phage resistance activity
othmo_pth	other_routes_monthly	descripti	Pathogen 2 "[pre_pth2_target]"
othmo_pth	other_routes_monthly	radio	[Pathogen isolated,Isolated | not_isolated, Not isolated | na, Not performed
othmo_pth	other_routes_monthly	notes	[Pathogen 2: [pre_pth2_target]] How come isolation wasn't performed?
othmo_pth	other_routes_monthly	radio	[Pathogen 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc
othmo_pth	other_routes_monthly	notes	[Pathogen 2: [pre_pth2_target]] Please specify anti-phage resistance activity
othmo_pth	other_routes_monthly	radio	[Pathogen isolated,Isolated | not_isolated, Not isolated | na, Not performed
othmo_pth	other_routes_monthly	text	[Pathogen 2: [pre_pth2_target]] Specify other site where pathogen was isolat
othmo_pth	other_routes_monthly	radio	[Pathogen 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc
othmo_pth	other_routes_monthly	notes	[Pathogen 2: [pre_pth2_target]] Please specify anti-phage resistance activity
othmo_pth	other_routes_monthly	descripti	Pathogen 3 "[pre_pth3_target]"
othmo_pth	other_routes_monthly	radio	[Pathogen isolated,Isolated | not_isolated, Not isolated | na, Not performed
othmo_pth	other_routes_monthly	notes	[Pathogen 3: [pre_pth3_target]] How come isolation wasn't performed?
othmo_pth	other_routes_monthly	radio	[Pathogen 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc
othmo_pth	other_routes_monthly	notes	[Pathogen 3: [pre_pth3_target]] Please specify anti-phage resistance activity
othmo_pth	other_routes_monthly	radio	[Pathogen isolated,Isolated | not_isolated, Not isolated | na, Not performed
othmo_pth	other_routes_monthly	text	[Pathogen 3: [pre_pth3_target]] Specify other site where pathogen was isolat
othmo_pth	other_routes_monthly	radio	[Pathogen 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc
othmo_pth	other_routes_monthly	notes	[Pathogen 3: [pre_pth3_target]] Please specify anti-phage resistance activity
othmo_pth	other_routes_monthly	descripti	Pathogen 4 "[pre_pth4_target]"
othmo_pth	other_routes_monthly	radio	[Pathogen isolated,Isolated | not_isolated, Not isolated | na, Not performed
othmo_pth	other_routes_monthly	notes	[Pathogen 4: [pre_pth4_target]] How come isolation wasn't performed?
othmo_pth	other_routes_monthly	radio	[Pathogen 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc
othmo_pth	other_routes_monthly	notes	[Pathogen 4: [pre_pth4_target]] Please specify anti-phage resistance activity
othmo_pth	other_routes_monthly	radio	[Pathogen isolated,Isolated | not_isolated, Not isolated | na, Not performed
othmo_pth	other_routes_monthly	text	[Pathogen 4: [pre_pth4_target]] Specify other site where pathogen was isolat
othmo_pth	other_routes_monthly	radio	[Pathogen 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc
othmo_pth	other_routes_monthly	notes	[Pathogen 4: [pre_pth4_target]] Please specify anti-phage resistance activity
othmo_pth	other_routes_monthly	descripti	Pathogen 5 "[pre_pth5_target]"
othmo_pth	other_routes_monthly	radio	[Pathogen isolated,Isolated | not_isolated, Not isolated | na, Not performed
othmo_pth	other_routes_monthly	notes	[Pathogen 5: [pre_pth5_target]] How come isolation wasn't performed?
othmo_pth	other_routes_monthly	radio	[Pathogen 1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc
othmo_pth	other_routes_monthly	notes	[Pathogen 5: [pre_pth5_target]] Please specify anti-phage resistance activity
othmo_pth	other_routes_monthly	radio	[Pathogen isolated,Isolated | not_isolated, Not isolated | na, Not performed
othmo_pth	other_routes_monthly	text	[Pathogen 5: [pre_pth5_target]] Specify other site where pathogen was isolat

[othmo_pt	y
[othmo_pt	y
[othmo_pt	y
[pre_num_	y
[othmo_pt	y
[othmo_pt	y
[othmo_pt	y
[pre_num_target_pathogen] > 1 and ([trivmo_phage_cont] = "1" or [trivmo_p	
[pre_num_	y
[othmo_pt	y
[othmo_pt	y
[othmo_pt	y
[pre_num_	y
[othmo_pt	y
[othmo_pt	y
[othmo_pt	y
[pre_num_target_pathogen] > 2 and ([trivmo_phage_cont] = "1" or [trivmo_p	
[pre_num_	y
[othmo_pt	y
[othmo_pt	y
[othmo_pt	y
[pre_num_	y
[othmo_pt	y
[othmo_pt	y
[othmo_pt	y
[pre_num_target_pathogen] > 3 and ([trivmo_phage_cont] = "1" or [trivmo_p	
[pre_num_	y
[othmo_pt	y
[othmo_pt	y
[othmo_pt	y
[pre_num_	y
[othmo_pt	y
[othmo_pt	y
[othmo_pt	y
[pre_num_target_pathogen] > 4 and ([trivmo_phage_cont] = "1" or [trivmo_p	
[pre_num_	y
[othmo_pt	y
[othmo_pt	y
[othmo_pt	y
[pre_num_	y
[othmo_pt	y

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othmo_pth	other_routes_monthly_	radio	[Pathogen 5	1,Yes | 0,Not tested | resistance,Evidence of anti-phage resistanc			[othmo_pth	y
othmo_pth	other_routes_monthly_	notes	[Pathogen 5: [pre_pth5_target]] Please specify anti-phage resistance activity				[othmo_pth	y
othmo_wgs	other_route	WGS	yesno	[Month [othmo_mth]] Is WGS data available for current isolate?			([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo] = "1")	
othmo_wgs	other_routes_monthly_	notes	[Month [othmo_mth]] Where is the WGS data stored?				[othmo_wgs]='1' and ([trivmo_phage_cont] = "1" or [trivmo_phage_stop_mo]	
ae_no_inclu	adverse_events_beta	descriptiv	<h3><span style="background-color: #e03e2				[sc_meets_inclusion] < 1	
ae_date_of	adverse_events_beta	text	Date of Event â€" this is a change!	date_dmy				y
ae_day_of_	adverse_events_beta	text	If still receiving phage therapy, spec	integer	1			
ae_last_dos	adverse_events_beta	radio	Did the pati	1, Yes, within 72 hours (<= 72h) | 2, No				y
ae_hours_s	adverse_events_beta	text	If last dose	If last dose of phage ad	number_1d	0	72	[ae_last_do y
ae_days_sir	adverse_events_beta	text	If last dose	of phage administered a	number_1d	0	180	[ae_last_do y
ae_phages_	adverse_events_beta	checkbox	Which phag	phage1,phage1 | phage2,phage2 | phage3,phage3 | phage4,phage4 | phage5				y
ae_meddra	adverse_events_beta	text	Event term	BIOPORTAL:MEDDRA				
ae_details	adverse_events_beta	notes	Details of Event					y
ae_severity	adverse_events_beta	radio	Severity (m	1, Mild | 2, Moderate | 3, Severe				y
ae_is_serio	adverse_events_beta	yesno	Is this a Serious Adverse Event?					y
ae_serious_	adverse_events_beta	checkbox	How does e	1, Resulted in death | 2, Was immediately life threatening | 3, Rec			[ae_is_seric	y
ae_has_rep	adverse_events_beta	checkbox	Confirm SA	1, Yes, I have reported to the trial sponsor			[ae_is_seric	y
ae_related_	adverse_events_beta	radio	Is adverse e	1, Unrelated | 2, Unlikely | 3, Possible | 4, Probably | 5, Definite				y
ae_related_	adverse_events_beta	checkbox	What phag	0, Other trial-related procedure (e.g. blood draw) | phage1,phage			[ae_related	y
ae_has_cor	adverse_events_beta	checkbox	Confirm Se	1, Yes, I have confirmed with the site PI			[ae_is_seric	y
ae_is_susar	adverse_events_beta	yesno	Does event qualify as a SUSAR?				[ae_is_seric	y
ae_has_rep	adverse_events_beta	checkbox	<div class=""	1, Yes, SUSAR reported to Sponsor, Chair of the DSMB, and the CP			[ae_is_seric	y
ae_req_tre	adverse_events_beta	notes	Any required treatment or evaluation?					
ae_final_ou	adverse_events_beta	radio	Final outco	1, Resolution | 2, Stabilisation | 3, No longer clinically significant | 4, Participa				y
ae_date_fir	adverse_events_beta	text	Date of final outcome	date_dmy				
wd_no_incl	withdrawal_beta	descriptiv	<h3><span style="background-color: #e03e2				[sc_meets_inclusion] < 1	
wd_reason	withdrawal_beta	radio	Withdrawal	1, Participant completed trial including at least 6 month follow-up			[sc_meets_	y
wd_withdra	withdrawal_beta	text	Date of Withdrawal	date_dmy			[sc_meets_	y
fp_no_inclu	followup_beta	descriptiv	<h3><span style="background-color: #e03e2				[sc_meets_inclusion] < 1	
fp_has_6m	followup_beta	yesno	Was follow-up performed at least 6 months after completion of phage therap				[sc_meets_	y
fp_no_follo	followup_beta	notes	Why wasn't followup performed?				[sc_meets_	y
fp_months_	followup_beta	radio	How long a	1, 1 month after completion | 2, 2 months | 3, 3 months | 4, 4 mo			[sc_meets_	y
fp_months_	followup_beta	radio	How long a	1, 6 months after completion | 2, 6-12 months | 3, > 12 months			[sc_meets_	y
fp_last_visi	followup_beta	text	Date of final follow-up visit	date_dmy			[sc_meets_	y
fp_clinical_	followup_beta	radio	What clinic	1, Cure - no evidence of ongoing infection: resolution of clinical sy			[sc_meets_	y
fp_resp_cu	followup_beta	radio	If Cure:	0, Without persisting disability | 1, With persisting disability			[sc_meets_	y
fp_resp_pa	followup_beta	radio	If Partial re	1, Improvement in clinical signs and symptoms, radiological or lab			[sc_meets_	y
fp_has_ae_	followup_beta	radio	Have all AE	1, Yes | 0, No | 2, Not sure			[sc_meets_	y
fp_has_ae_	followup_beta	radio	Have all SA	1, Yes | 0, Did not receive | 2, Received but did not complete			[sc_meets_	y
fp_has_qol	followup_beta	radio	Has the par	1, Yes | 0, Did not receive | 2, Received but did not complete			[sc_meets_	y
fp_msg_ask	followup_beta	notes	Please ask participant if they are happy to complete the QoL survey now				[sc_meets_inclusion] = "1" and [fp_has_qol_survey] != "1"	

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fp_3mo_pt	followup_beta	radio	For particip	1, Yes | 0, Did not receive | 2, Received but did not complete | 3,	[sc_meets_inclusion] = "1"	
abx_no_inc	antibiotics_beta	descriptiv	<h3><span style="background-color: #e03e2		[sc_meets_inclusion] < 1	
abx_name	antibiotics_beta	dropdow	Antibiotic n	1, amikacin | 2, amoxyc	autocomplete	[sc_meets_ y
abx_other	antibiotics_beta	text	Other antibiotic		[sc_meets_ y	@CHARLIMIT=50
abx_usage	antibiotics_beta	checkbox	Specify anti	used_prev, Used previously | used_curr, Used currently | use_cor	[sc_meets_ y	
abx_admin	antibiotics_beta	checkbox	How is [abx	aero, Aerosolised / Nebulised | instl, Instillation | iv, Intravenous (	[sc_meets_ y	
abx_admin	antibiotics_beta	text	Specify administration method		[sc_meets_ y	@CHARLIMIT='50'
abx_pth1_c	antibiotics_beta	descriptiv	Pathogen 1		[sc_meets_inclusion] = "1" and [pre_num_target_pathogen] > 0	
abx_pth1_p	antibiotics_beta	yesno	[Pathogen 1] Is phage-antibiotic synergy testing data available for [abx_name]		[abx_name y	
abx_pth1_p	antibiotics_beta	yesno	[Pathogen 1] Is phage-antibiotic synergy testing data available for [abx_name]		[abx_name y	
abx_pth1_p	antibiotics_beta	descriptiv	[Pathogen 1] :: Phage: "[pre_phage1_name]"		[pre_phage1_name] and [pre_num_phage]>0 and ([abx_pth1_pxb_data_spc] c	
abx_pth1_p	antibiotics_beta	yesno	[Pathogen 1] Data available against phage: "[pre_phage1_name]"?		[pre_phage y	
abx_pth1_p	antibiotics_beta	radio	[Pathogen 1	synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth1_ y	
abx_pth1_p	antibiotics_beta	notes	[Pathogen 1] Additional phage-antibiotic-pathogen synergy notes against pha		([abx_pth1_ y	
abx_pth1_p	antibiotics_beta	descriptiv	[Pathogen 1] :: Phage: "[pre_phage2_name]"		[pre_phage2_name] and [pre_num_phage]>1 and ([abx_pth1_pxb_data_spc] c	
abx_pth1_p	antibiotics_beta	yesno	[Pathogen 1] Data available against phage: "[pre_phage2_name]"?		[pre_phage y	
abx_pth1_p	antibiotics_beta	radio	[Pathogen 1	synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth1_ y	
abx_pth1_p	antibiotics_beta	notes	[Pathogen 1] Additional phage-antibiotic-pathogen synergy notes against pha		([abx_pth1_ y	
abx_pth1_p	antibiotics_beta	descriptiv	[Pathogen 1] :: Phage: "[pre_phage3_name]"		[pre_phage3_name] and [pre_num_phage]>2 and ([abx_pth1_pxb_data_spc] c	
abx_pth1_p	antibiotics_beta	yesno	[Pathogen 1] Data available against phage: "[pre_phage3_name]"?		[pre_phage y	
abx_pth1_p	antibiotics_beta	radio	[Pathogen 1	synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth1_ y	
abx_pth1_p	antibiotics_beta	notes	[Pathogen 1] Additional phage-antibiotic-pathogen synergy notes against pha		([abx_pth1_ y	
abx_pth1_p	antibiotics_beta	descriptiv	[Pathogen 1] :: Phage: "[pre_phage4_name]"		[pre_phage4_name] and [pre_num_phage]>3 and ([abx_pth1_pxb_data_spc] c	
abx_pth1_p	antibiotics_beta	yesno	[Pathogen 1] Data available against phage: "[pre_phage4_name]"?		[pre_phage y	
abx_pth1_p	antibiotics_beta	radio	[Pathogen 1	synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth1_ y	
abx_pth1_p	antibiotics_beta	notes	[Pathogen 1] Additional phage-antibiotic-pathogen synergy notes against pha		([abx_pth1_ y	
abx_pth1_p	antibiotics_beta	descriptiv	[Pathogen 1] :: Phage: "[pre_phage5_name]"		[pre_phage5_name] and [pre_num_phage]>4 and ([abx_pth1_pxb_data_spc] c	
abx_pth1_p	antibiotics_beta	yesno	[Pathogen 1] Data available against phage: "[pre_phage5_name]"?		[pre_phage y	
abx_pth1_p	antibiotics_beta	radio	[Pathogen 1	synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth1_ y	
abx_pth1_p	antibiotics_beta	notes	[Pathogen 1] Additional phage-antibiotic-pathogen synergy notes against pha		([abx_pth1_ y	
abx_pth2_c	antibiotics_beta	descriptiv	Pathogen 2		[sc_meets_inclusion] = "1" and [pre_num_target_pathogen] > 1	
abx_pth2_p	antibiotics_beta	yesno	[Pathogen 2] Is phage-antibiotic synergy testing data available for [abx_name]		[abx_name y	
abx_pth2_p	antibiotics_beta	yesno	[Pathogen 2] Is phage-antibiotic synergy testing data available for [abx_name]		[abx_name y	
abx_pth2_p	antibiotics_beta	descriptiv	[Pathogen 2] :: Phage: "[pre_phage1_name]"		[pre_phage1_name] and [pre_num_phage]>0 and ([abx_pth2_pxb_data_spc] c	
abx_pth2_p	antibiotics_beta	yesno	[Pathogen 2] Data available against phage: "[pre_phage1_name]"?		[pre_phage y	
abx_pth2_p	antibiotics_beta	radio	[Pathogen 2	synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth2_ y	
abx_pth2_p	antibiotics_beta	notes	[Pathogen 2] Additional phage-antibiotic-pathogen synergy notes against pha		([abx_pth2_ y	
abx_pth2_p	antibiotics_beta	descriptiv	[Pathogen 2] :: Phage: "[pre_phage2_name]"		[pre_phage2_name] and [pre_num_phage]>1 and ([abx_pth2_pxb_data_spc] c	
abx_pth2_p	antibiotics_beta	yesno	[Pathogen 2] Data available against phage: "[pre_phage2_name]"?		[pre_phage y	
abx_pth2_p	antibiotics_beta	radio	[Pathogen 2	synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth2_ y	
abx_pth2_p	antibiotics_beta	notes	[Pathogen 2] Additional phage-antibiotic-pathogen synergy notes against pha		([abx_pth2_ y	

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abx_pth2_p	antibiotics_beta	descriptio	[Pathogen 2] :: Phage: "[pre_phage3_name]"	[pre_phage3_name] and [pre_num_phage]>2 and ([abx_pth2_pxb_data_spc] c
abx_pth2_p	antibiotics_beta	yesno	[Pathogen 2] Data available against phage: "[pre_phage3_name]"?	[pre_phage y
abx_pth2_p	antibiotics_beta	radio	[Pathogen 2 synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth2_ y
abx_pth2_p	antibiotics_beta	notes	[Pathogen 2] Additional phage-antibiotic-pathogen synergy notes against pha	([abx_pth2_ y
abx_pth2_p	antibiotics_beta	descriptio	[Pathogen 2] :: Phage: "[pre_phage4_name]"	[pre_phage4_name] and [pre_num_phage]>3 and ([abx_pth2_pxb_data_spc] c
abx_pth2_p	antibiotics_beta	yesno	[Pathogen 2] Data available against phage: "[pre_phage4_name]"?	[pre_phage y
abx_pth2_p	antibiotics_beta	radio	[Pathogen 2 synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth2_ y
abx_pth2_p	antibiotics_beta	notes	[Pathogen 2] Additional phage-antibiotic-pathogen synergy notes against pha	([abx_pth2_ y
abx_pth2_p	antibiotics_beta	descriptio	[Pathogen 2] :: Phage: "[pre_phage5_name]"	[pre_phage5_name] and [pre_num_phage]>4 and ([abx_pth2_pxb_data_spc] c
abx_pth2_p	antibiotics_beta	yesno	[Pathogen 2] Data available against phage: "[pre_phage5_name]"?	[pre_phage y
abx_pth2_p	antibiotics_beta	radio	[Pathogen 2 synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth2_ y
abx_pth2_p	antibiotics_beta	notes	[Pathogen 2] Additional phage-antibiotic-pathogen synergy notes against pha	([abx_pth2_ y
abx_pth3_c	antibiotics_beta	descriptio	Pathogen 3	[sc_meets_inclusion] = "1" and [pre_num_target_pathogen] > 2
abx_pth3_p	antibiotics_beta	yesno	[Pathogen 3] Is phage-antibiotic synergy testing data available for [abx_name]	[abx_name y
abx_pth3_p	antibiotics_beta	yesno	[Pathogen 3] Is phage-antibiotic synergy testing data available for [abx_name]	[abx_name y
abx_pth3_p	antibiotics_beta	descriptio	[Pathogen 3] :: Phage: "[pre_phage1_name]"	[pre_phage1_name] and [pre_num_phage]>0 and ([abx_pth3_pxb_data_spc] c
abx_pth3_p	antibiotics_beta	yesno	[Pathogen 3] Data available against phage: "[pre_phage1_name]"?	[pre_phage y
abx_pth3_p	antibiotics_beta	radio	[Pathogen 3 synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth3_ y
abx_pth3_p	antibiotics_beta	notes	[Pathogen 3] Additional phage-antibiotic-pathogen synergy notes against pha	([abx_pth3_ y
abx_pth3_p	antibiotics_beta	descriptio	[Pathogen 3] :: Phage: "[pre_phage2_name]"	[pre_phage2_name] and [pre_num_phage]>1 and ([abx_pth3_pxb_data_spc] c
abx_pth3_p	antibiotics_beta	yesno	[Pathogen 3] Data available against phage: "[pre_phage2_name]"?	[pre_phage y
abx_pth3_p	antibiotics_beta	radio	[Pathogen 3 synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth3_ y
abx_pth3_p	antibiotics_beta	notes	[Pathogen 3] Additional phage-antibiotic-pathogen synergy notes against pha	([abx_pth3_ y
abx_pth3_p	antibiotics_beta	descriptio	[Pathogen 3] :: Phage: "[pre_phage3_name]"	[pre_phage3_name] and [pre_num_phage]>2 and ([abx_pth3_pxb_data_spc] c
abx_pth3_p	antibiotics_beta	yesno	[Pathogen 3] Data available against phage: "[pre_phage3_name]"?	[pre_phage y
abx_pth3_p	antibiotics_beta	radio	[Pathogen 3 synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth3_ y
abx_pth3_p	antibiotics_beta	notes	[Pathogen 3] Additional phage-antibiotic-pathogen synergy notes against pha	([abx_pth3_ y
abx_pth3_p	antibiotics_beta	descriptio	[Pathogen 3] :: Phage: "[pre_phage4_name]"	[pre_phage4_name] and [pre_num_phage]>3 and ([abx_pth3_pxb_data_spc] c
abx_pth3_p	antibiotics_beta	yesno	[Pathogen 3] Data available against phage: "[pre_phage4_name]"?	[pre_phage y
abx_pth3_p	antibiotics_beta	radio	[Pathogen 3 synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth3_ y
abx_pth3_p	antibiotics_beta	notes	[Pathogen 3] Additional phage-antibiotic-pathogen synergy notes against pha	([abx_pth3_ y
abx_pth3_p	antibiotics_beta	descriptio	[Pathogen 3] :: Phage: "[pre_phage5_name]"	[pre_phage5_name] and [pre_num_phage]>4 and ([abx_pth3_pxb_data_spc] c
abx_pth3_p	antibiotics_beta	yesno	[Pathogen 3] Data available against phage: "[pre_phage5_name]"?	[pre_phage y
abx_pth3_p	antibiotics_beta	radio	[Pathogen 3 synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth3_ y
abx_pth3_p	antibiotics_beta	notes	[Pathogen 3] Additional phage-antibiotic-pathogen synergy notes against pha	([abx_pth3_ y
abx_pth4_c	antibiotics_beta	descriptio	Pathogen 4	[sc_meets_inclusion] = "1" and [pre_num_target_pathogen] > 3
abx_pth4_p	antibiotics_beta	yesno	[Pathogen 4] Is phage-antibiotic synergy testing data available for [abx_name]	[abx_name y
abx_pth4_p	antibiotics_beta	yesno	[Pathogen 4] Is phage-antibiotic synergy testing data available for [abx_name]	[abx_name y
abx_pth4_p	antibiotics_beta	descriptio	[Pathogen 4] :: Phage: "[pre_phage1_name]"	[pre_phage1_name] and [pre_num_phage]>0 and ([abx_pth4_pxb_data_spc] c
abx_pth4_p	antibiotics_beta	yesno	[Pathogen 4] Data available against phage: "[pre_phage1_name]"?	[pre_phage y
abx_pth4_p	antibiotics_beta	radio	[Pathogen 4 synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth4_ y

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abx_pth4_p	antibiotics_beta	notes	[Pathogen 4] Additional phage-antibiotic-pathogen synergy notes against pha	([abx_pth4_ y
abx_pth4_p	antibiotics_beta	descripti	[Pathogen 4] :: Phage: "[pre_phage2_name]"	[pre_phage2_name] and [pre_num_phage]>1 and ([abx_pth4_pxb_data_spc] c
abx_pth4_p	antibiotics_beta	yesno	[Pathogen 4] Data available against phage: "[pre_phage2_name]"?	[pre_phage y
abx_pth4_p	antibiotics_beta	radio	[Pathogen 4 synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth4_ y
abx_pth4_p	antibiotics_beta	notes	[Pathogen 4] Additional phage-antibiotic-pathogen synergy notes against pha	([abx_pth4_ y
abx_pth4_p	antibiotics_beta	descripti	[Pathogen 4] :: Phage: "[pre_phage3_name]"	[pre_phage3_name] and [pre_num_phage]>2 and ([abx_pth4_pxb_data_spc] c
abx_pth4_p	antibiotics_beta	yesno	[Pathogen 4] Data available against phage: "[pre_phage3_name]"?	[pre_phage y
abx_pth4_p	antibiotics_beta	radio	[Pathogen 4 synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth4_ y
abx_pth4_p	antibiotics_beta	notes	[Pathogen 4] Additional phage-antibiotic-pathogen synergy notes against pha	([abx_pth4_ y
abx_pth4_p	antibiotics_beta	descripti	[Pathogen 4] :: Phage: "[pre_phage4_name]"	[pre_phage4_name] and [pre_num_phage]>3 and ([abx_pth4_pxb_data_spc] c
abx_pth4_p	antibiotics_beta	yesno	[Pathogen 4] Data available against phage: "[pre_phage4_name]"?	[pre_phage y
abx_pth4_p	antibiotics_beta	radio	[Pathogen 4 synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth4_ y
abx_pth4_p	antibiotics_beta	notes	[Pathogen 4] Additional phage-antibiotic-pathogen synergy notes against pha	([abx_pth4_ y
abx_pth4_p	antibiotics_beta	descripti	[Pathogen 4] :: Phage: "[pre_phage5_name]"	[pre_phage5_name] and [pre_num_phage]>4 and ([abx_pth4_pxb_data_spc] c
abx_pth4_p	antibiotics_beta	yesno	[Pathogen 4] Data available against phage: "[pre_phage5_name]"?	[pre_phage y
abx_pth4_p	antibiotics_beta	radio	[Pathogen 4 synergy, Synergy | none, No interaction | antagonism, Antagonisr	([abx_pth4_ y
abx_pth4_p	antibiotics_beta	notes	[Pathogen 4] Additional phage-antibiotic-pathogen synergy notes against pha	([abx_pth4_ y
abx_pth5_c	antibiotics_beta	descripti	Pathogen 5	[sc_meets_inclusion] = "1" and [pre_num_target_pathogen] > 4
abx_pth5_p	antibiotics_beta	yesno	[Pathogen 5] Is phage-antibiotic synergy testing data available for [abx_name]	[abx_name y
abx_pth5_p	antibiotics_beta	yesno	[Pathogen 5] Is phage-antibiotic synergy testing data available for [abx_name]	[abx_name y
abx_pth5_p	antibiotics_beta	descripti	[Pathogen 5] :: Phage: "[pre_phage1_name]"	[pre_phage1_name] and [pre_num_phage]>0 and ([abx_pth5_pxb_data_spc] c
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PROTOCOL

Standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy

Short title: Standardised Treatment and Monitoring of Phage therapy (STAMP)

Version: 1.1

Date: 15/07/2022

For peer review only

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This document is confidential and the property of the Phage Australia Network. No part of it may be transmitted, reproduced, published, or used without prior written authorisation from the institution.

Statement of Compliance

This document is a protocol for a research project. This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

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ADMINISTRATIVE INFORMATION

1. TITLE

Standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy

Short title: Standardised Treatment and Monitoring of Phage therapy (STAMP)

2. TRIAL REGISTRATION

2A REGISTRY

anzctr.org:

2B DATA SET

Data Category	**Information**
Primary registry and study identifying number	anzctr.org ACTRN12621001526864
Date of registration in primary registry	10 November 2021
Secondary identifying numbers	WHO UTN: U1111-1269-6000
Source(s) of monetary or material support	Medical Research Futures Fund (Australia) Frontiers Stage 1 (RFRHPI000017; Iredell) National Health and Medical Research Council (Australia) Investigator Grant (APP1197534; Iredell)
Primary Sponsor	Western Sydney Local Health District
Contact for public queries	Ameneh Khatami (ameneh.khatami@health.nsw.gov.au)
Contact for scientific queries	Ameneh Khatami (ameneh.khatami@health.nsw.gov.au)

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Data Category	Information
Public title	Standardised Treatment and Monitoring of Phage therapy (STAMP)
Scientific title	Standardised treatment and monitoring protocol for adult and paediatric patients receiving bacteriophage therapy
Countries of recruitment	Australia
Health condition(s) or problem(s) studied	Any infectious syndrome requiring bacteriophage therapy
Intervention(s)	A standardised treatment and monitoring protocol for bacteriophage therapy
Key inclusion and exclusion criteria	**Inclusion criteria (all must be present):** 1) Patient with confirmed bacterial infection, for whom at least **two** appropriately qualified clinical specialists, including at least one specialist in infection management and one with experience of phage therapy, have agreed that available anti-infective therapy and source control has been optimised and that adjunctive phage therapy should be offered. 2) A suitable phage(s) product is available that complies with all relevant regulatory requirements for therapeutic administration, including at least Therapeutic Goods Administration (TGA) Special Access Scheme (SAS) notification **Exclusion criteria:** 1) Participant or person responsible has not provided informed consent 2) Participant unable or unlikely to adhere to schedule of monitoring and follow-up
Study type	Open-label, single arm trial of a standardised treatment and monitoring protocol
Date of first enrolment	April 2022
Target sample size	50-100 participants over 5 years

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Data Category	Information
Primary outcome	Safety and tolerability of phage therapy (defined as absence serious adverse events attributable to phage therapy) assessed 15 days after completion of therapy
Key secondary outcomes	1) Long-term safety and tolerability of phage therapy (defined as absence of serious adverse events, or any adverse events attributable to phage therapy) assessed 6 months after completion of phage therapy. 2) Feasibility of a standardised protocol as assessed by the proportion of participants with >80% of Minimum Data Requirements available for analysis. **Exploratory outcomes (assessed across the total cohort and subgroups of participants):** 1) Clinical response to phage therapy assessed 15 days after completion of therapy 2) Patient satisfaction of outcome assessed at multiple time-points during and after completion of therapy 3) Microbiological clearance of target pathogen(s), as defined by bacterial cultures of relevant sites a. Proportion with documented clearance and time to clearance b. Emergence of anti-phage resistance on treatment 4) Laboratory markers of phage and host responses, including: a. Phage pharmacokinetics b. Antibody development c. Host immune responses 5) Changes in microbiome assessed by metagenomics during and after completion of therapy

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3. Protocol Version

Issue Date:	Version 1, 20 December 2021
Protocol amendment number:	N/A
Author(s):	Ameneh Khatami Jonathan Iredell Steven Tong Morgyn Warner Anton Peleg Thomas Snelling Julia Warning (NSW Ministry of Health) Elizabeth Barnes (independent statistician) Phage Australia Clinical Stream Committee members

Revision Chronology:

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Date of change	Summary of changes
Version 1.1 29 May 2022	Section 2B (Registry Data Set): first participant enrolled April 2022, not Jan 2022. Date of registration and registry identifier added. Section 3: Version 1 issue date 20/12/21, not 30/09/21; and addition of Dr Julia Warning to the author list (previously missed in error) Section 5D: Clarification that additional recruitment sites and laboratories may be added during the trial, with new PIs added to the Investigator Group Section 11.4: Administered doses corrected from AT LEAST 10^9 PFU/mL (IV) or 10^{10}PFU/mL non-IV, to APPROXIMATELY 10^9 PFU/mL (IV) or 10^{10}PFU/mL non-IV Section 12 (microbiological endpoints): clarification that "Time to clearance" will be measured for each site of infection. Figure 1: Clarification in footnotes that patients receiving longer courses of phage therapy will have an additional quality-of-life survey at 12 months after completion of therapy, as outlined elsewhere in the protocol Section 26: Clarification that repeated courses of treatment in the trial will only be described but not included in the primary analyses (as outlined elsewhere in the protocol). Throughout: All referenced to 2 weeks changed to either 14 days (treatment) or 15 days (follow-up) as appropriate, and one month replaced with 29 days to remove ambiguity about durations, in line with information outlined in table 2/3 and figure 1.

4. Funding

Initial set-up costs for the trial, including database design and development and project management, are funded by a Medical Research Futures Fund (MRFF) Frontiers Stage 1 grant (RFRHPI000017; PHAGE AUSTRALIA: Integrating Australian Phage Biobanking and Therapeutic Networks and Delivering Solutions for Antimicrobial Resistance, CIA Iredell).

Local phage product development including Good Manufacturing Practice (GMP)-grade therapeutic products, and development of companion diagnostics are supported by the MRFF Frontiers Stage 1 grant, and a National Health and Medical Research Council Investigator Grant (GNT1197534: Positive Solutions for Critical Infection, CIA Iredell).

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Phage and companion diagnostics support may come from research and professional partners, provided they are fit for purpose and satisfy all national, state and local institutional requirements as determined by authorities responsible for clinical and research governance and for regulating the provision and quality control of diagnostic and therapeutic goods.

Patients included in this trial may receive therapeutic phage products sourced from industry partners/commercial suppliers provided on "compassionate grounds".

All investigators provide their time and expertise as in-kind contributions without payment. Local Health Districts (LHDs) and Health Networks cover the costs of inpatient and outpatient care of patients according to usual standards.

5. Roles and Responsibilities

5a Contributorship

AK and JI conceived the study. AK, JI, ST and MW initiated the study design and protocol development. JI is a grant holder. TS and EZ provided statistical expertise. All authors contributed to refinement of the study protocol.

5b Sponsor Contact Information

Study Sponsor	Western Sydney Local Health District
Contact name	Sharon Lee
Address	WSLHD Research and Education Network, Clinical Trials Support Unit, Westmead Hospital, Hawkesbury Road, Westmead NSW 2145
Telephone	02 8890 9942,
Email	WSLHD-ClinicalTrialsSupportUnit@health.nsw.gov.au

5c Sponsor and Funder

The study Sponsor delegates responsibility for study design; collection, management, analysis, and interpretation of data; writing of the report and the decision to submit the report for publication to the CPI and the Trial Steering Committee (TSC). Any funding body involved in the trial will not have any role in these responsibilities.

5d Committees

1. Investigator Group
    a. Co-ordinating Principal Investigator: Jonathan Iredell
    b. Principal Investigators (PIs) for clinical recruitment sites
        i. Westmead Hospital: Jonathan Iredell
        ii. Sydney Children's Hospitals Network: Ameneh Khatami
        iii. The Alfred Hospital: Anton Peleg
        iv. Royal Melbourne Hospital: Steven Tong
        v. Central Adelaide Local Health Network: Morgyn Warner
        vi. Royal Brisbane and Women's Hospital: David Paterson
        vii. Queensland Children's Hospital: Adam Irwin

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viii. Fiona Stanley Hospital, Murdoch: Christopher Heath
ix. Perth Children's Hospital: Stephen Stick
x. Additional sites may be added during the course of the trial with new PIs added to the Investigator Group

c. Principal Investigators (PIs) for research institutes and laboratories where participant samples may be processed
i. Westmead Institute for Medical Research: Jonathan Iredell
ii. Monash Centre to Impact Antimicrobial Resistance: Anton Peleg
iii. Telethon Kid's Institute: Stephen Stick
iv. The Doherty Institute: Deborah Williamson

v. Additional sites may be added during the course of the trial with new PIs added to the Investigator Group

2. The TSC will be the Clinical Stream Steering Committee of Phage Australia, a multidisciplinary group that, collectively, have experience/expertise in the management of patients with condition(s) relevant to the study, pathways for use of phage therapy, anticipated adverse events, and in the conduct and monitoring of randomised clinical trials. Co-conveners are Steven Tong (Victoria), Ameneh Khatami (New South Wales [NSW], paediatrics), Morgyn Warner (South Australia). The committee also includes members with statistical expertise and stakeholder representatives including consumer representatives and NSW Ministry of Health representatives. Details of membership and specified roles and responsibilities are outlined in the Terms of Reference for this Committee.

3. A Data Safety Monitoring Board will include a chair with management experience in clinical trials and 5 additional members, of whom at least 1 will be paediatrician, at least 1 will be an adult physician and at least 1 will have established clinical expertise in the delivery of phage therapy. Additional details of membership and specified roles and responsibilities are outlined in the Terms of Reference for the DSMB. The DSMB will have access to all safety data available at the time of each meeting. They will be asked to review the data and make a recommendation to the CPI and site PIs within 4 weeks of the meeting. Review of the safety data may result in a recommendation for:
   - Cessation of the trial for all participants or for a subgroup (e.g. only paediatric participants, participants treated for a specific indication, or participants from a given site)
   - Interim suspension while reviewing the data in more detail
   - Modification of the trial
   - Continuation of the trial

INTRODUCTION

6. BACKGROUND AND RATIONALE

Antibiotics are now failing due to growing antimicrobial resistance (AMR) which at least doubles mortality and health care costs of infection. Without novel solutions, AMR infections are predicted to be the leading cause of death by 2050, cost US$30 billion annually in lost productivity of the global

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economy, and threaten many advances in medicine(*1*). A key unmet need is for new strategies to manage difficult-to-treat infections, including chronic infections in cystic fibrosis (CF), other infections that respond poorly to antibiotics (e.g. prosthetic device infections) and highly drug resistant infections.

Bacteriophages (phages) are viruses that naturally infect and kill bacteria. Phages prey equally well on antibiotic-sensitive and -resistant bacteria and offer a novel (non-antibiotic) approach to treat infections. Unlike antibiotics that kill both disease-causing and beneficial bacteria leaving the patient vulnerable to other pathogens(*2*), the highly selective bacterial killing by phages reduces their impact on our healthy microbiome(*3*), as well as the risk of further increasing drug resistance. Phages do not attack human cells and phage therapy has a proven safety record, offering hope for people with highly drug resistant infections(*4-10*). Other critical advantages over antibiotics include the ability of phages to kill bacteria in biofilms (bacteria that hide away in a layer of slime, often on artificial surfaces) when antibiotics typically cannot(*11*), since phages are unaffected by the mechanisms that shield bacteria in biofilms from antibiotics(*12*). Biofilms are present in a wide variety of human infections and are usual in CF and on infected prosthetic devices and artificial heart valves(*13*).

Phages can be used in combination with antibiotics or substitute for them when antibiotics fail and can even be used to restore the potency of failing antibiotics(*14-16*). **Currently, phage therapy is not in wide use because there is no experience outside of a few centres in the world; standardised therapeutic protocols are lacking; there is a paucity of rigorous clinical trial data assessing efficacy and phages are generally not readily available in sufficiently purified form for use.** We and others(*5*) have built on a century of international experience to prove the value of phage therapy after antibiotic failure in severe sepsis(*6, 8*), bladder(*9*) and bone infection(*10*), and in CF [manuscript in preparation]. Our group were the first in the world to use intravenous (IV) phages in a systematic trial in severe infection in adults and thus gained new insights into dosing, disposition in the body (kinetics of distribution and clearance) and effects on the immune system(*8*). In parallel, we have established a program for compassionate access to phage therapy for children at Sydney Children's Hospitals Network (SCHN) and this protocol represents a national expansion of this programme for adults and children, providing a standardised treatment and monitoring protocol, and linked to a national database to facilitate standardised data collection. This will allow rapid and efficient data generation without wastage of a currently "scarce" resource, and will strengthen the evidence base, including for dosing and monitoring, required to establish phage therapy in the national formulary.

A standardised treatment and monitoring protocol for Australian adult and paediatric patients receiving bacteriophage therapy is proposed, with no comparator arm. Patients included are those who have exhausted other therapeutic options for control of their infection and are being treated with phage products according to the special access scheme (SAS) as determined by the Australian Therapeutic Goods Administration (TGA) – so-called "compassionate access". Patients who are assessed to be suitable for phage therapy will receive this as outlined in this protocol, as an adjunct to routine clinical care. **The purpose of the study is to standardise therapeutic management and data collection, including safety and tolerability, in this setting and to assess the feasibility of such a standardised protocol.**

7. Study Objectives

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a. **Primary Objective**: To determine the short-term safety and tolerability of phage therapy in adults and children with bacterial infections

b. **Secondary Objectives**:

   i. To determine the long-term safety and tolerability of phage therapy in adults and children with bacterial infections

   ii. To assess the feasibility of a standardised protocol used for the administration and monitoring of phage therapy in adults and children

c. **Exploratory Objectives:**

   i. To describe proportions of patients with good clinical response to phage therapy, assessed 15 days after completion of therapy, across the cohort of participants and according to clinical indication

   ii. To describe patient-reported quality-of-life indicators during and after phage therapy across the cohort of participants and according to clinical indication using a validated Patient Reported Outcome Measures (PROMs) tool (EQ-5D-5L/EQ-5D-Y)

   iii. To describe proportions of patients with microbiological clearance, and time to clearance, across the cohort of participants and according to clinical indication

   iv. To describe the rate of phage resistance emergence while on therapy

   v. To explore pharmacokinetics (distribution and clearance kinetics) of phages administered via different routes and according to different dosing schedules

   vi. To explore innate and adaptive immune responses to phage therapy (include age-related differences) administered via different routes and for different clinical indications

   vii. To explore optimal dosing schedules and durations for phage products used according to different routes of administration (IV, oral, nebulised/aerosolised, topical) for different clinical indications

   viii. To explore key biomarkers that can be used as diagnostic surrogates of clinical efficacy

   ix. To explore significant differences between different phage products used for the same clinical indication with respect to phage pharmacokinetics, innate and adaptive immune responses, safety and tolerability and clinical efficacy

   x. To explore microbiome changes as assessed by non-human metagenomics of available clinical samples during and after completion of phage therapy.

8. Study Design

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Open-label, single-arm trial investigating a standardised treatment and monitoring protocol for phage therapy, with multiple subgroups stratified according to clinical indication and route of administration of phages (see section 11A – Interventions).

METHODS: PARTICIPANTS, INTERVENTIONS, OUTCOMES

9. STUDY SETTING

Participants can be recruited from any hospital (public or private) in Australia, where ethics and site-specific approval has been gained. Participants can be treated as inpatients or outpatients.

9.1 Study sites

Study sites will be selected based on:

1) Access to appropriate facilities and staff to undertake the full treatment and monitoring protocol according to all regulatory approvals (e.g. physical containment [PC] level 2 facilities for use of a GMO phage, if applicable)
2) An identified site PI with experience in phage therapy or infection management.
3) A site feasibility survey is completed and approved by the Trial Steering Committee

10. ELIGIBILITY CRITERIA

10.1 **Inclusion Criteria for Participants** (all must be present):

1. Patient with confirmed bacterial infection, for whom at least **two** appropriately qualified clinical specialists, including at least one specialist in infection management and one with experience of phage therapy, have agreed that available anti-infective therapy and source control has been optimised and that adjunctive phage therapy should be offered (see section 11.2 below). The assessment of the need for/suitability for phage therapy will be based on clinical criteria and will not constitute a research activity.
2. Suitable phage(s) product (with lytic activity against the target pathogen/s) is available that complies with all relevant regulatory requirements for therapeutic administration. These requirements may include:
   i. Local hospital/network drug committee and/or Executive board approval (or equivalent), as applicable
   ii. Therapeutic Goods Administration (TGA) special access scheme (SAS) notification **(required)**
   iii. Bicon Permit from the Department of Agriculture for importation of phage products from international suppliers, if applicable
   iv. Material Transfer Agreement (MTA) that may be required from third-party suppliers of phage products, if applicable
   v. Licence to handle and administer genetically modified organisms (GMOs) from the Office of the Gene Technology Regulator, if applicable
   vi. Any other local requirements as determined by the primary medical professional caring for the patient (Primary Clinician) or hospital/network Executive board

Selection and sourcing of the phage product to be administered will be based on clinical criteria and will not constitute a research activity.

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10.2 **Exclusion criteria for Participants:**

1. Participant, parent or guardian or person responsible has not provided informed consent.
2. Participant unable or unlikely to adhere to schedule of monitoring and follow-up

11. INTERVENTIONS

11A INTERVENTIONS

11.1 Summary of research activities

This protocol will be embedded within standard clinical care. The following table provides a summary of research activities and standard clinical activities that will be occurring simultaneously.

Table 1: Summary research and clinical activities that occur during phage therapy

Clinical activities	**Research activities**
Decision to access phage therapy	Confirming eligibility of patients to participate, including ensuring suitable phage(s) product (with lytic activity against the target pathogen/s) is available.
Choice of appropriate phage to be administered Route and duration of phage therapy*	Route and duration of phage therapy* Dosing schedule and dose adjustments
Regulatory oversight including TGA SAS notification, hospital drug committee/executive approval (see section 10.1)	Human research ethics committee (HREC) and site-specific approvals
All other healthcare decisions including adjunctive antibiotics, other medications, investigations for underlying health conditions, allied health interventions and standard of care for monitoring investigations for infections.	Schedule of monitoring **relevant to phage therapy**
Frequency of follow-up visits and ongoing monitoring.	Collection of data regarding adverse events during phage therapy and follow-up
	Systematic collection of data to create a registry of phage use in Australia

* Route and duration of phage therapy will be a joint decision between the site PI (research activity) and the Primary Clinician (standard clinical activity)

11.2 Participant identification and referral pathway

Patients for whom phage therapy may be suitable can be identified by any medical professional caring for the patient (Primary Clinician). Each case must be discussed with and approved by at least one infectious diseases specialist who is relevantly clinically privileged at that recruitment site, and who must ensure optimised anti-infective therapy and infection source control. This "approval" can be by

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consultation with an infectious diseases specialist or **can** be undertaken by the Primary Clinician if they are so qualified. A second specialist (site PI) must approve and take responsibility for the phage therapy administered according to this protocol. If the available site PI is operating outside their usual professional scope of practice (for example, non-infectious disease specialist) and cannot reasonably take that clinical responsibility, the case should be referred to a suitably experienced PI operating within their normal scope of practice, including by telemedicine consultation, according to the normal rules that govern such consultations. If the site PI is the Primary Clinician, the case must be discussed with one other infectious disease specialist at the site, or at a referral centre. If all inclusion criteria can be met for the patient to be included, the following data should be obtained and entered on the study REDCap database (electronic case report form; eCRF). *****Minimum Data Requirements.

11.2.1 Screening logs

Site PIs should maintain a record of all patients referred for inclusion in the trial including the outcome of assessment for eligibility. Screening for eligibility will occur prior to obtaining consent to participate (see also section 10 above). For patients who are not included in the trial, the reason for this should be clearly documented in a screening log:

i) Antibiotic therapy sub-optimal to date/viable alternative antibiotic therapy available
ii) Source control sub-optimal
iii) Polymicrobial infection (>2 key pathogens)
iv) Pathogen driving infectious syndrome not appropriately confirmed
v) Phage product identified unsuitable
    1. Phage activity against target pathogen(s) limited/undocumented
    2. Formulation not safe for clinical use
    3. Regulatory approvals not completed
vi) Patient/parent or guardian/responsible person unable or unlikely to adhere to schedule of treatment and monitoring
vii) Other (specify)

11.3 Pre-treatment work-up/data

11.3.1 Clinical

i) Primary infectious diagnosis (site of infection, confirmed or potential pathogens, presence of prosthetic material etc.)*****

ii) Current/planned/ongoing adjunctive antibiotics*****

iii) Other interventions performed to control the infection (source control)

iv) Additional medical or surgical conditions that directly impact management of the infection (e.g. CF in a patient with lung infection)*

v) Immune suppressive conditions or therapies*

vi) Indication for phage therapy as assessed by clinical team*
    (1) Intolerance of standard therapy due to side effects, and/or
    (2) Failure of standard therapy, and/or

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(3) Extensive drug resistance profile of target pathogen(s), and/or
(4) Other (to be specified)

11.3.2 Microbiology

i) Culture confirmation from site of infection. If the site of infection is not directly accessible, alternative sites may be sampled if it is reasonable to assume these represent pathogen(s) at the site of infection (e.g. blood culture)*

ii) Phage-bacteria matching (degree of lytic activity between selected phage(s) and target pathogen(s)*. This can be performed at the study site if this service is available within an appropriately accredited laboratory, or within Phage Australia partner sites (e.g. at the Westmead Institute for Medical Research, NSW, the Doherty Institute, Victoria, or the Department of Infectious Diseases laboratory at the Alfred Hospital, Victoria), or by third party phage suppliers (including commercial suppliers, either in Australia or internationally). This may be facilitated by external partners such as Phage Directory (https://phage.directory) and will be confirmed by an appropriately accredited Australian laboratory.

iii) Whole genome sequencing (WGS) of main pathogen(s) according to laboratory standard operating procedures (SOP), and identification of prophages.

iv) WGS of phage(s) to be used

v) Phage-bacteria-antibiotic synergy testing according to laboratory SOP. Lytic activity of suitable phage(s) to be tested against the pathogen of interest in the presence of adjunctive antibiotics as determined through consultation between the Primary Clinician and infectious disease specialists with whom the case has been discussed (see section 11.1 and 11.2 above). This can be performed at the study site if this service is available within an appropriately accredited laboratory, or within Phage Australia partner sites (e.g. at the Westmead Institute for Medical Research, NSW, the Doherty Institute, Victoria, or the Department of Infectious Diseases laboratory at the Alfred Hospital, Victoria).

11.4 Treatment and Monitoring Protocols

The specific phage product to be administered will be determined jointly by the Primary Clinician and Infectious Disease(s) specialist involved in the care of the patient, including consultation with the site PI responsible for oversight of phage therapy according to this protocol (see sections 10.1 and 11.2).

The optimal duration and route of administration of phage will be determined individually for each patient by the PI involved (see section 11.2 above) and will depend on the site of infection, confirmed or suspected pathogens, patient factors (e.g. immune compromise, IV access) and availability of phage products (e.g. formulation, purification).

For intravenously administered phage, the dose will be determined by the endotoxin level of the phage product, keeping below the accepted human pyrogenic threshold of 5 EU/kg per dose set by the United States Food and Drug Administration (FDA). Within this limit, the aim is to administer approximately 10^9 plaque forming units (pfu) of the phage at each dose. 10^9 pfu/dose is aimed to

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achieve a multiplicity of infection (MOI; number of phage virions per bacterial target) of 10-100 per bacterium in the bloodstream for common bacteraemias.

If multiple routes of administration are used, the total dose administered at the same time must not exceed the endotoxin limit outlined above. For enteral, aerosolised/nebulised or topical administration of phage a dose limit has not been determined but is likely to be considerably higher. If a non-intravenous route is selected as the primary route of administration (not just as an adjunct to IV administration), the aim is to administer approximately 10^{10} pfu/dose.

All other care, including adjunctive antibiotics or other medications to be administered, investigations (radiology, laboratory or other), allied health interventions, etc., will be according to routine clinical care and will be determined by the Primary Clinician and the Infectious Disease specialist(s) directly involved in the care of the patient.

11.4.1 Clinical monitoring:

- Full physical examination within 24 hours prior to starting phage therapy (any route of administration)
- Measurement of "vitals" (heart rate [HR], respiratory rate [RR], blood pressure [BP], oxygen saturation, temperature) within 15 minutes prior to, and then 15 and 30 minutes after each dose of phage administered. For patients receiving only topical or nebulised/aerosolised phage products where minimal systemic absorption is expected, only one set of vital signs are required 30 minutes after administration of the phage product.
- Additional clinical monitoring will be according to routine clinical care.

11.4.2 Timing of phage doses:

Frequency of phage doses to be administered for patients receiving 14 days of phage therapy is outlined in Table 2 below. Morning doses should be administered at the same time each day, preferably between 6-10am. On days where twice daily dosing is used, these should be administered 12 hours (+/- 2 hours) apart. Multiple routes of administration may be appropriate for individual patients e.g. IV and nebulised phage therapy for lung infections. For critically unwell patients where urgent control of infection is needed, initial twice daily dosing may be used (i.e. from day 1) after discussion with the site PI. Day of treatment refers to a working day, starting at 6am. Day 0 is any time within 24 hours prior to first dose of phage.

Invasive routes of administration (e.g. intra-articular or endobronchial), should be considered additional to the primary route of administration (e.g. IV) with timing and frequency of such administration determined by the Primary Clinician and the infectious disease specialists/PI involved in the care of the patient.

For patients planned to receive phage therapy for longer than 14 days, dosing frequency will be determined taking into consideration practical limitations. For example, long-term hospital in the home administration of phage therapy may only be possible once daily.

For patients receiving only non-systemically administered phage products where minimal systemic distribution (i.e. viremic dissemination) is expected phage(s) should be administered once daily throughout the course to facilitate outpatient setting administration. The timing of non-systemic

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administration will be determined by the Primary Clinician and the infectious disease specialists/PI involved in the care of the patient.

11.4.3 Laboratory monitoring:

Table 2 outlines laboratory monitoring required for the first 4 weeks in patients receiving 14 days of intravenous phage therapy (majority of participants). Patients receiving oral/enteral therapy should also follow this protocol. Each of the tests listed are included in the Minimum Data Requirements for phage therapy. If it is not practical to obtain samples according to this protocol (e.g. difficult to access site of infection, difficult venous access in young children) this should be discussed with the site PI and reasons documented in the eCRF.

If abnormalities are detected (including worsening of prior abnormalities) on any blood sample that were not present at baseline, these should be followed-up beyond the intervention period (day 0-29) until resolution with frequency of monitoring determined by the Primary Clinician and the infectious disease specialists involved in the care of the patient.

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Table 2: Treatment and laboratory monitoring protocol for standard 14-day intravenous/oral phage therapy

Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	29
Phage doses		OD	OD	BD	BD	BD	BD	BD	BD	BD	BD	BD	BD	BD	BD		
CRP	X		X		X				X							X	X
ESR	X				X				X							X	X
Procalcitonin (if available)	X		X		X				X							X	
FBC	X		X		X				X			X				X	X
Lymphocyte subsets	X		X		If lymphopenic[£]				If lymphopenic			If lymphopenic				If lymphopenic	If lymphopenic
LFTs	X		X		X				X							X	X
UECs	X		X		X				X							X	X
Phage antibodies*	X											X				X	X
Total IgG	X															X	X
C3, C4, CH50	X															X	X
Cultures**	X				X				X							X	X
Phage susceptibility***	X				X				X							X	X
Kinetics****			X		X				X			X				X	X
Transcriptomics and metagenomics	X		X		X				X			X				X	X

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Day 0 – up to 24 hours prior to first dose of phage; OD – once daily; BD – twice daily; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; FBC – full blood count; LFTs – liver function tests; EUCs – electrolytes, urea, creatinine; IgG – total immunoglobulin G; C3, C4, CH50 – complement levels.

Tests in bold are those available in routine clinical laboratories and considered standard of care for monitoring treatment of infections. Although the timing for these tests has been specified according to this protocol to enable standardisation of data collection and analysis, the tests can and should be performed in an appropriately accredited clinical laboratory linked to the recruitment site, as per usual care.

* Phage antibodies - antibodies against relevant therapeutic phages, measured in order to define risk of antibody-mediated neutralisation and/or immune responses. This can be performed at the study site if this service is available within an appropriately accredited laboratory according to SOP, or within Phage Australia partner sites (e.g. at the Westmead Institute for Medical Research, NSW, the Doherty Institute, Victoria, or the Department of Infectious Diseases laboratory at the Alfred Hospital, Victoria), or by third party phage suppliers (including commercial suppliers, either in Australia or internationally).

** For invasive samples baseline (day 0) and post-treatment (day 15) samples are sufficient for monitoring. For patients known or suspected to be bacteraemic at the start of phage therapy, blood cultures should be obtained daily until bacteraemia resolves.

*** All positive cultures of the target pathogen(s) that are isolated after day 1 should be reassessed for ongoing phage-susceptibility, and should have whole genome sequencing performed according to lab SOP.

**** Kinetics - see details in Table 4 and section 11.4.6

[£] Lymphopenia will be defined as <1.0 x 10^9/L in individuals aged >12 years, <1.5 x10^9/L in children aged 1-12 years, <4.0 x10^9/L for infants aged 1-12 months, and <3.0 x10^9/L for neonates <1 month.

11.4.4 Ongoing monitoring for long-term systemic phage therapy

For patients planned to receive long-term phage therapy (longer than 14 days), ongoing monitoring will be performed on a monthly basis until 1 month after the end of phage therapy. The following samples and tests will be required for ongoing monthly monitoring for patients receiving >14 days of phage therapy.

- **C-reactive protein**
- **Full blood count**
- **Liver function tests**
- **Urea, creatinine and electrolytes**
- **Total IgG**
- **Complement levels: C3, C4, CH50**
- **Relevant microbiological cultures**
- Phage susceptibility of ongoing positive cultures - All positive cultures of the target pathogen(s) that are isolated after day 1 should be reassessed for ongoing phage-susceptibility, and should have whole genome sequencing performed according to lab SOP.

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- Kinetics - see details in Table 4 and section 11.4.6
- Transcriptomics and metagenomics
- Anti-phage antibodies – measured according to lab SOP.

Tests in bold are those available in routine clinical laboratories and considered standard of care for monitoring treatment of infections. These tests can and should be performed in an appropriately accredited clinical laboratory linked to the recruitment site, as per usual care.

11.4.5 Laboratory monitoring for non-systemic therapy

For patients receiving only non-systemically administered phage products where minimal systemic distribution is expected (e.g. topical administration to a wound, or nebulised/aerosolised therapy), Table 3 outlines the laboratory monitoring required for the first 4 weeks. Each of the tests listed are included in the Minimum Data Requirements for phage therapy. If it is not practical to obtain samples according to this protocol (e.g. difficult to access site of infection, difficult venous access in young children) this should be discussed with the site PI and reasons documented in the eCRF.

Table 3: Treatment and laboratory monitoring protocol for standard 14-day non-systemic phage therapy

Day	0	1	2	3	4	5-7	8	9-14	15	29
Phage doses		OD	OD	OD	OD	OD	OD	OD		
CRP	X		X		X		X		X	
FBC	X		X		X		X		X	X
LFTs	X						X		X	
UECs	X						X		X	
Phage antibodies	X								X	X
Cultures*	X						X		X	X
Phage susceptibility**	X						X		X	X

OD – once daily; CRP – C-reactive protein; FBC – full blood count; LFTs – liver function tests; EUCs – electrolytes, urea, creatinine.

* For invasive samples baseline (day 0) and post-treatment (day 15) samples are sufficient for monitoring.

** All positive cultures of the target pathogen(s) that are isolated after day 1 should be reassessed for ongoing phage-susceptibility, and should have whole genome sequencing performed according to lab SOP.

Tests in bold are those available in routine clinical laboratories and considered standard of care for monitoring treatment of infections. These tests can and should be performed in an appropriately accredited clinical laboratory linked to the recruitment site, as per usual care.

For patients planned to receive long-term phage therapy (>14 days), ongoing monitoring will be performed on a monthly basis until 1 month after the end of phage therapy. The following samples

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and tests will be required for ongoing monthly monitoring for patients receiving >14 days of non-systemic phage therapy:

- Full blood count - should be performed in an appropriately accredited clinical laboratory linked to the recruitment site, as per usual care.
- Relevant microbiological cultures and phage susceptibility of ongoing positive cultures - All positive cultures of the target pathogen(s) that are isolated after day 1 should be reassessed for ongoing phage-susceptibility, and should have whole genome sequencing performed according to lab SOP.

11.4.6 Timing of blood samples:

All blood samples should be collected in the morning, prior to the first dose of phage, unless otherwise specified (e.g. post-dose samples for kinetics).

"Kinetics bloods" refers to quantification of phage and bacterial loads in patient blood/serum for patients receiving systemic therapy. These should be determined according to SOP by plaque assay (phage) and quantitative polymerase chain reaction (qPCR; phage and bacteria). The timing of kinetics bloods is outlined in Table 4.

Table 4: Timing of blood samples for quantification of phage and bacterial loads ("kinetics bloods") during phage therapy

	Immediately prior to phage dose	30-60 minutes after phage dose	2-3 hours after phage dose
Phage (plaque assay)	X		X
Phage (qPCR)	X	X	X
Bacteria (qPCR)	X	X	X

All 3 time-points (prior to dose, 30 minutes and 2 hours post-dose) should be drawn for "kinetics" on days 2, 4, 8 and 11. On days 15 and 29, only a single blood draw in the morning is required as no further phage doses will be administered.

11.4.7 Microbiological surveillance

Bacterial cultures should be obtained from the site of infection (or representative site) as outlined above. This may include cultures from blood, urine, sputum, swabs or other clinical specimens. For invasive samples other than blood or routine endotracheal aspirates (e.g. bronchoalveolar lavage or surgical biopsies) baseline (day 0) and post-treatment (day 15) samples are sufficient for monitoring. For patients known or suspected to be bacteraemic at the start of phage therapy, blood cultures should be obtained daily until bacteraemia resolves.

Metagenomics will be performed on clinical samples including blood (as well as sputum, urine, faeces or other samples that may have been collected) to investigate changes in the microbiome during treatment. The analysis pipeline will be restricted to non-human genetic material and will only be used to determine the microbiome of various clinical specimens during and after phage therapy, including endogenous phages.

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11.4.8 Quality-of life questionnaire

A quality-of-life questionnaire will be sent to participants via a survey link in REDCap on days 0 (baseline) and 29, 15 days after completion of the 14-day course of phage therapy, and again at 3 and 6 months (from start of phage therapy). For patients receiving longer than 3 months of phage therapy, the survey link will also be sent out at 12 months.

A validated PROMs tool (EQ-5D-5L/EQ-5D-Y) will be used as the basis of the questionnaire (see section 30 in Appendices) and will ask participants to grade various indicators for quality of life before receiving phage therapy, during and after completion of the course of treatment. Responses to the quality-of life- questionnaires will be reviewed by the site PI within 15 days of completion for each participant.

11.4.9 RNA samples

Whole blood should be obtained for analysis of human transcriptome according to SOP, using a panel that includes both innate and adaptive immune response markers. Analysis will be restricted to immune response genes only.

11.4.10 Long-term follow-up

All participants will be followed-up by the Primary Clinician for a minimum of 6 months after completion of phage therapy. Frequency of follow-up visits will be determined by the Primary Clinician based on the underlying clinical condition (according to routine clinical care). As a minimum, patients should be reviewed clinically, with additional investigations (laboratory or radiology) also determined by the Primary Clinician based on the underlying clinical condition (according to routine clinical care).

11B MODIFICATIONS

11.5 Criteria for modifying phage dose:

Evidence of severe immune-related phenomena after infusion may be criteria for cessation of therapy, as for any severe adverse reaction (see section 20 – Adverse Events Monitoring). Decisions regarding cessation of phage therapy will be made by the Primary Clinician in consultation with the PI based on clinical judgement. The reason for cessation of therapy will be documented in the eCRF. Early cessation of phage therapy will not constitute a withdrawal criterion from the trial for a participant (see 11.6 below) and every effort should be made by the PI to continue all other monitoring of the patient as per the protocol to ensure data integrity and safety monitoring.

Phage levels in the blood prior to re-dosing may be used to determine dosage adjustments(*10*). Doses may be adjusted on the basis of qPCR results for bacteria and phage, or plaque assay for phage, in consultation with the PI. Dose adjustment should be considered in the following scenarios, but should also take into consideration clinical response to treatment at the time.

Table 5: Criteria for consideration of changes to phage doses administered daily

Current dosing schedule	Pre-dose serum phage level by plaque assay	Adjustment
Once daily	$<10^2$ pfu/mL	Increase to twice daily dosing

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Once daily	$\geq 10^2$ pfu/mL	Continue once daily dosing
Twice daily	$<10^2$ pfu/mL	Continue twice daily dosing
Twice daily	$\geq 10^2$ pfu/mL	Reduce to once daily dosing

For patients receiving a cocktail of more than one phage, dose adjustments of the whole cocktail should be based on results obtained for the phage with the lowest detectable level of circulating viable phage.

11.6 Criteria for withdrawal of participants:

- Withdrawal of consent – a participant or their parent/guardian/person responsible may withdraw consent to participate in the trial at any point. Any data obtained prior to withdrawal of consent will be retained and the reason for withdrawal recorded in the eCRF. Routine clinical care of the patient will continue, and may include ongoing use of phage for clinical purposes. They will be given the options of:
    - Withdrawing from all subsequent monitoring samples and subsequent collection of clinical data
    - Withdrawing from all subsequent monitoring samples but allowing continued collection of clinical data
- Loss to follow-up – if a non-admitted patient is unable to be contacted (e.g. during the period of follow-up) after multiple attempts to contact them, including at least 3 phone calls and a letter mailed to their last known address, they will be assumed to be lost to follow-up. Any data collected up to that time will remain part of the study data.
- Cessation or dose-modification of phage therapy for medical reasons will not be a criterion for withdrawal from the trial and ongoing monitoring of the participant should continue as per the protocol (see section 11.5 above).

11c Ensuring Adherence to the Interventions

The first 14 days of intravenous phage therapy will be administered in hospital by clinical staff (nursing, pharmacy, medical) and monitored as per SOP and good clinical practice (as outlined in section 11a – Interventions). If phage therapy is planned for longer than 14 days, further treatment can be administered via "Hospital in the Home"-like services. Purely topical, aerosolised or oral/enteral administration of phage can occur in the outpatient setting but must be administered by qualified clinical staff (nursing, pharmacy, medical).

All doses of phage therapy administered will be prescribed by a suitably qualified doctor, dispensed from the hospital pharmacy and recorded in standard medical records (electronic or paper). Additionally, this information will be recorded on the eCRF, including modifications to the dosing schedule or early cessation of therapy.

11d Concomitant Care

Normal optimal anti-infective therapy, including optimised antibiotic and surgical therapy (e.g. source control), vouched for and managed by the responsible/consulting ID physician, is a condition of enrolment and should be recorded on the eCRF. Antibiotic synergy and antagonism (with phage/s) will be tested *in vitro* as soon as feasible. *In vitro* findings of antagonistic phage-antibiotic combinations

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will be notified to the responsible clinical team and will necessitate review of phage and/or antibiotic therapy.

All other care, including other medications to be administered, investigations (radiology, laboratory or other), allied health interventions, etc., will be according to routine clinical care and will be determined by the Primary Clinician and the infectious disease specialists directly involved in the care of the patient.

12. Outcomes and Endpoints

Primary outcome: Short-term Safety

We have previously reported the safe use of bacteriophages in severe sepsis and septic shock(*8*) but phage therapy is still classified as experimental. Although there is 100 years of safety data, there are very few definitive randomised clinical trials (RCTs) and previously undetected adverse events may be uncovered by a more rigorous measurement regime, such as we define herein.

Safety and tolerability will be assessed through adverse events (AEs), vital signs, and clinical laboratory assessments. All AEs will be assessed for severity, causality, and seriousness and will be elicited and assessed from the first dosing until 6 months after the last dose of phage. The PI and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or serious AE (SAE) and remain responsible for following up SAEs that are considered related to the phage therapy or study procedures. The PI is responsible for reporting all SAEs that are observed or reported during the trial, regardless of their clinical significance or relatedness to the administered phage.

Safety will be defined by the absence of serious adverse events (SAEs) attributable to study material (phage). As phages do not attack or integrate into mammalian cells, AEs related to phage therapy are predominantly expected during active administration or shortly thereafter. As such the **primary endpoint** for safety assessments will be any SAE attributable to phage therapy occurring from day 1 (first dose of phage administered) until 15 days after completion of therapy (day 29 for patients receiving 14 days of therapy).

Further details regarding assessing and reporting AEs is provided in section 20 – Adverse Events Monitoring.

Secondary outcomes

1) *Additional safety outcomes*

During the follow-up period (15 days-6 months after the last dose of phage) only non-serious AEs considered by the investigator to be related to phage therapy, or any SAEs will be reported. These will be ascertained through discussion with the Primary Clinician undertaking the 6-month follow-up and/or review of medical records 6 months following the last dose of phage administered.

Secondary safety endpoints will thus be any SAE OR any AE attributable to phage therapy occurring from day 1 (first dose of phage administered) until 6 months after completion of phage therapy.

2) *Feasibility*

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Feasibility of using a standardised treatment and monitoring protocol will be assessed as the proportion of participants with >80% of Minimum Data Requirements available for analysis. Minimum Data Requirements are outlined in section 11 above and will vary according to course of phage therapy administered. The **feasibility endpoint** will be assessed at least 15 days after completion of phage therapy.

Exploratory outcomes

We have previously demonstrated eradication of pathogens in settings in which it was unexpected and this can be used as a surrogate for clinical efficacy. The heterogeneity of the casemix and the lack of a control arm (in this non-comparative study design) makes clinical efficacy difficult to assess. The data we develop here will allow the best quality design of formal RCTs and help to inform regulatory reviews.

1) Clinical response to phage therapy

Defined as:

1) Cure – no evidence of ongoing infection: resolution of all clinical symptoms and signs of infection, radiological and laboratory parameters of infection, and microbiological clearance of target pathogen from site of infection (excludes any symptoms, signs, or abnormal radiological and laboratory parameters associated with underlying disease)
    a. Without persisting disability
    b. With persisting disability
2) Partial response
    a. Improvement in clinical signs and symptoms, radiological or laboratory parameters of disease, but with evidence that infection is not completely resolved
    b. Stabilisation of previously documented decline in function, but without obvious improvements, and evidence that infection is not completely resolved
3) No response – evidence of ongoing infection with worsening clinical signs and symptoms, radiological or laboratory parameters of disease

Clinical endpoint: Good clinical response will be defined as all participants assessed as "cured" or with "partial response" at least 15 days after completion of phage therapy.

2) Quality-of-life indicators

Participants will be asked to complete a brief quality-of-life questionnaire using a validated PROMs tool (EQ-5D-5L/EQ-5D-Y) (see section 30 in Appendices). This will ask participants to grade various indicators for quality of life before receiving phage therapy, during and after completion of the course of treatment (see section 11.4.8).

Quality-of-life-endpoints: Changes in EQ-5D-5L/EQ-5D-Y results from baseline to each subsequent assessment (day 29, 3, 6 or 12 months after starting phage therapy).

3) Microbiological clearance of target pathogen(s)

As defined by bacterial cultures of relevant sites (see section 11.4.3-11.4.5 above and Tables 2 and 3). Emergence of anti-phage resistance on treatment will be assessed with all positive cultures of the

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target pathogen(s) that are isolated after day 1 of treatment reassessed for ongoing phage-susceptibility.

Microbiological endpoints include:

- Time to clearance (for each infected site) - day of first negative culture, measured from first day of phage therapy, among participants with sustained clearance (at least 2 consecutive negative cultures with no further positive cultures during the intervention and follow-up period)
- Proportion of participants with sustained microbiological clearance by the end of the intervention period (including up to day 29) – defined as at least 2 consecutive negative cultures by day 29.

4) Phage kinetics over time, antibody development, host immune responses

Dosing strategies at first assume simple clearance – that is, the initial volume of distribution is a simple function of phage delivery/penetration and the clearance is a simple function of usual mechanisms (innate effector cells, renal clearance, non-specific inactivation of viral particles in different body fluids and compartments). However, both (i) phage amplification in target bacterial populations that change over time (predator-prey dynamic that waxes and wanes in a manner that is unique to every single infection), and (ii) development of acquired immune clearance (e.g. neutralising antibodies, likely to vary with individuals) may influence phage kinetics and dose adjustments may be made in response to diagnostic data(*8, 10*). Finally, the host immune response may vary as a function of all these or be independent of them – and significant beneficial immunomodulation may occur in severe sepsis(*8*) and in chronic sepsis(*10*).

These data are observational in nature but are essential for both safety monitoring and for design of future studies. Phage kinetics and human host immune responses as assessed by transcriptomics will be assessed for patients receiving intravenous/oral phage. Anti-phage neutralising/total antibodies will be measured for all patients receiving phage in any formulation (see sections 11.4.3-11.4.5 above and Tables 2 and 3).

5) Microbiome changes

Metagenomics will be performed on any available clinical samples (blood, sputum, urine, faeces or other samples that may have been collected) to investigate changes in the microbiome during treatment. The analysis pipeline will be restricted to non-human genetic material and will only be used to determine the microbiome of various clinical specimens during and after phage therapy, including endogenous phages.

13. Participant Timeline

Figure 1: Schedule of enrolment, interventions, and assessments for each participant

	STUDY PERIOD			
	Enrolment	**Intervention**		**Follow-up**
TIMEPOINT	***-4w* to Day 0***	***Day 1-14*****	***Day 15-29***	***Day 30-210******

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ENROLMENT:				
Eligibility screen	X			
Informed consent	X			
Pre-treatment work-up*	X			
Determination of duration and route of phage administration	X			
PHAGE THERAPY**		X		
MONITORING:***				
Blood and clinical sampling	X	X	X	
Quality-of-life questionnaire		X	X	X
Adverse Event Reporting		X	X	X

* Pre-treatment work-up (as outlined in section 11.3) should be performed within 4 weeks of starting phage therapy. If there is a delay (e.g. time required to source phage, or meet legal or regulatory requirements) pre-treatment work up should be repeated within 4 weeks of starting phage therapy. Any invasive sampling or other assessments that are impractical or unsafe to repeat may be referred to the most recently available investigation.

** For some patients, the duration of phage therapy may be longer than 14 days as determined by the PI/infectious disease specialist. Details of phage therapy administration and monitoring are outlined in section 11.4 above.

*** For patients receiving longer than 14 days of phage therapy, long term follow-up will be for 6 months after completion of phage therapy for safety data. An additional quality-of-life survey at 12 months after completion of phage therapy will also occur for patients receiving longer than 3 months of phage therapy. Details of phage therapy administration and monitoring are outlined in section 11.4 above.

14. Sample Size

This is an open-label, single-arm clinical trial. All eligible participants that are identified will be recruited until the trial end-date (31 December 2026). No sample-size calculation has been determined. It is estimated that in the first 2 years of the study, 1-4 participants may be recruited at each study site. In subsequent years, greater numbers of participants may be identified and additional study sites will be open for recruitment. The aim is to have 50-100 participants recruited over the 5 years of the study. A study of at least 50 participants receiving phage therapy will enable the proportion who experience an SAE attributable to phage therapy (SARs) to be estimated with a 95% confidence interval (CI) of maximum width ±15%. If the proportion is low the CI will be narrower, and if no participants in 50 experience any such SAE we can be confident that the rate is not higher than 7% (95% CI of 0-7%).

We expect the rate of SARs to be <5%. If 20% or more participants suffer an SAE attributable to the therapy (SARs) then the treatment may not be considered acceptably safe in its current form. An analysis of the first 30 participants who are followed at least 29 days after commencing treatment has 80% statistical power at 5% one-sided alpha to rule out a rate of 20% or higher if the true rate is 5%

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or lower, using an exact one-sample binomial test. If 3 or more of these 30 participants have experienced an SAE attributable to therapy (SAR) then consideration will be given to stopping or modifying the study due to safety concerns. Otherwise, recruitment will continue to the target of 50-100 participants to collect data on other outcomes.

15. Recruitment

Participants will be recruited from any hospital (private or public) which is an eligible study site and where human research ethics committee (HREC), governance and all other regulatory approvals are in place (see section 10 – Eligibility Criteria). Outpatient and inpatient healthcare settings (including hospital-in-the-home-like services) will be supported as appropriate, as defined in section 11.4 above. Regional, remote and rural settings will be supported to participate through usual referral pathways to access secondary and tertiary-level care and specialist services. Site PIs have been selected for their ability to identify potentially eligible patients, as well as their clinical expertise in overseeing phage therapy. The majority of PIs are infectious diseases specialists working in tertiary referral centres where patients with difficult-to-treat infections are referred to. This will ensure optimal recruitment of participants into the trial.

Additional activities of the Phage Australia Network outside of this trial, in areas of continuing medical education, community education and workforce development will also ensure that as many suitable patients are screened for eligibility and recruited into the trial as possible.

Consumer co-design and involvement of Cystic Fibrosis Australia representatives in the TSC will also enable recruitment of participants from this patient group which is usually very successful.

Methods: Data Collection, Management, Analysis

16. Data Collection Methods

16a Data Collection Methods

Study data will be hosted on the REDCap platform on the University of Sydney server, secured, managed, and backed-up centrally. Data management practices will follow the principles of the Australian Code for the Responsible Conduct of Research. All data will be handled in accordance with the University of Sydney data handling guidelines. An external data officer/data architect will be contracted for REDCap database construction. Data entry on the REDCap database will be the responsibility of site PIs or a qualified designee. Overall responsibility for data management and data quality control will be with the Investigator team (site PIs).

16b Retention

Cessation or dose-modification of phage therapy for medical reasons will not be a criterion for withdrawal from the trial and every effort should be made to continue all other monitoring of the patient as per the protocol to ensure data integrity and safety monitoring.

If a participant or their parent/guardian/person responsible withdraws consent to participate in the trial, any data obtained prior to withdrawal of consent will be retained. The Primary Clinician is responsible to ensure at least 6 months of clinical monitoring and follow-up after the last dose of administered phage takes place. All attempts will be made to record 6-month follow-up data (for safety monitoring) if the participant provides ongoing consent for this (see section 11.6 above).

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17. Data Management, Protection and Confidentiality

REDCap is a secure platform endorsed by the University of Sydney and many Australian hospitals for research data collection. The REDCap system is hosted on a server behind the University of Sydney controlled firewall, and access is restricted with multi-factor authentication and encrypted connections. Only Principal Investigators or delegates and treating clinicians will be given access to this project through REDCap. They will be able to log on to the project with their access credentials.

Clinical data will be coded but re-identifiable by treating clinicians when collected on REDCap. The 'Data access group' function on REDCap will be used to ensure that clinicians only have access to re-identifiable data for their own patients, not for patients who they are not treating. PIs will have access to re-identifiable data for all patients at their respective recruitment sites.

The 'User rights' function on REDCap will be used to ensure that all data is de-identified when exported for analysis. No user will be able to create data exports from REDCap that contain identifiable information. Scientists involved in biological investigations and data analysis will not require REDCap access; they will only access de-identified exported datasets as needed. All patient data will be de-identified for analysis and dissemination in papers, reports, or presentations.

As part of the responsibilities assumed by participating in the trial, the PI and their delegated proxies (including site sub-investigators) agree to maintain adequate eCRFs and source documents for participants treated as part of the research under this protocol. Source documents may include laboratory and radiology reports, study site notes from medical records, etc. Data quality will be optimised through use of range checks for data values, and error messages for missing data points. Interim analyses as outlined in section 19b below will also be used to highlight errors in data collection/entry.

Most biological samples collected as part of the trial will be processed in clinical diagnostic laboratories and will be stored, processed and discarded as per routine laboratory procedures for clinical samples. Exceptions include samples obtained for measurement of human transcriptomes, metagenomic analysis, anti-phage antibody measurements and phage and bacterial kinetics (see section 11.4 above). For these non-routine assessments, if biological samples are to be shipped for processing at a laboratory external to the recruitment site or their standard diagnostic referral pathways (e.g. at a state-based referral lab for whole genome sequencing of bacterial isolates), including at non-clinical Medical Research Institutes, they will be coded (using the participant's study code + sample details such as date and time of collection, sample type) prior to shipment, storage and analysis. They will be re-identifiable to the PIs and treating clinicians only.

17a Storage

Any left-over biological samples, that have been coded and de-identified may be retained up to 15 years after the study is completed, or until the youngest participant reaches the age of 25, after which they will be destroyed according to laboratory SOP for handling and disposal of clinical waste.

Clinical data and data pertaining to biological samples will be stored on REDCap for 15 years after the trial is completed and data has been exported for analysis, or until the youngest participant reaches the age of 25. Data exported for analysis will be stored on health servers at recruiting sites and accessed via secure-access computers with password protection.

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Any paper records (e.g. consent forms) will be stored in locked offices at recruiting sites and only accessible by study investigators and will be destroyed by shredding, in keeping with healthcare privacy policies. At this point, all electronic data will be completely de-identified.

18. Statistical Methods

18a Outcomes

The primary outcome of the proportion of participants who experience one or more SAEs attributable to study therapy will be presented with a 95% confidence interval. An interim analysis of safety data will be undertaken after 30 participants have been followed for at least one month after commencing treatment. A final analysis will be undertaken when the last enrolled participant has been followed up for at least 6 months after the last dose of phage.

All trial outcomes will be summarised and presented using standard descriptive statistics: frequencies and percentages for categorical data and mean, standard deviation and range or median, quartiles and range for continuous data and the Kaplan-Meier method for time-to-event variables. Results will be presented overall and by sub-groups. Participants may be sub-grouped according to clinical indication (infectious syndrome), route of administration or phage formulation used, or by patient demographics (e.g. age). Exploratory comparisons for all outcomes between subgroups (e.g. adult vs. paediatric patients; those receiving treatment targeting different groups of organisms [Gram-positive vs. Gram-negative organisms]; or different infectious phenotypes [acute bacteraemia vs. chronic osteoarticular infections]) will use standard statistical methods: t-test, chi-square test, log-rank test and corresponding regression models if applicable.

18b Analysis Population and Missing Data

Safety data will be reported for all participants who received any dose of phage therapy. Clinical response to therapy and microbiological clearance outcomes will be reported for participants who received at least 5 days of phage therapy (cumulative). All other outcomes will be reported for all enrolled participants based on available data with no adjustment for missing data.

Methods: Monitoring

19. Data Monitoring

19a Formal Committee

The primary outcome of interest (safety), as well as data completeness, rates of recruitment and clinical outcome assessments, will be monitored by a formal DSMB as outlined in the DSMB Terms of Reference and section 5d.

19b Interim Analyses

A review of included and excluded participants and reasons for inclusion/exclusion will be undertaken annually by the CPI and at least one of the TSC co-conveners to ensure appropriateness of patient selection. Results of this review will be available for the investigator group and the DSMB and may be used for amending the trial protocol.

An interim safety analysis for the primary outcome will be conducted after 30 participants have been followed for at least one month after commencing treatment. If 3 or more of these participants have

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experienced an SAE attributable to therapy (SAR) then consideration will be given to stopping or modifying the study. Study progress including data on all safety, secondary and exploratory outcomes will be regularly reviewed by the trial steering committee. Reports will be provided 6 monthly and will be available for the investigator group and the DSMB and may be used for amending the trial protocol, external reporting and publication, or early termination of the trial. Final decision to terminate the trial rests with the CPI.

Thereafter, trial results will be analysed at the end of 5 years (end of study).

20. Adverse Event Monitoring

20.1 Definitions

An AE is defined as any untoward medical occurrence in a participant enrolled into this trial regardless of its causal relationship to the administered phage product.

An SAE is defined as any event that

- results in death
- is immediately life threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalisation may be considered SAEs when, based upon appropriate medical judgment, they may jeopardise the participant or may require medical or surgical intervention to prevent one of the outcomes listed in the definition of an SAE.

A suspected, unexpected, serious adverse reaction (SUSAR) is defined as an AE that is serious in nature (i.e. meets SAE criteria), is at least probably (probably or definitely) related to phage therapy (SAR; see section 20.2.2 below) and is an unexpected reaction based on what is known and has been reported in the literature regarding phage therapy. SUSARs will be adjudicated by site PIs.

20.2 Eliciting, Documenting and Reporting Adverse Events

In accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines, all PIs are responsible for recording and reporting adverse events (AE) observed during and after the study. AEs will be assessed from the first dose of phage until the end of the follow-up period, which is 6 months after the last dose of phage.

All AEs that occur during the intervention period (phage administration) and up to 15 days after the last dose of phage will be will be actively collected and reported irrespective of their seriousness or relatedness to administered phage. While patients are admitted to hospital AEs will be solicited through daily clinical reviews. If the patient is discharged home for any duration between day 15 and day 28, AEs occurring over this time will be sought on day 29. For patients receiving outpatient or hospital-in-the-home style therapy, AEs will be solicited at each outpatient appointment/home visit.

During the follow-up period (15 days-6 months after the last dose of phage) only non-serious AEs considered by the investigator to be related to phage therapy, or any SAEs will be reported. These will

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be ascertained through discussion with the Primary Clinician undertaking the 6-month follow-up and/or review of medical records 6 months following the last dose of phage administered.

All AEs and SAEs will be documented on the AE page in the eCRF.

20.2.1 Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the participant's daily activities. The intensity of the AE will be rated as mild, moderate, or severe using the following criteria:

- Mild: These events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate: These events result in a low level of inconvenience or concern. Moderate events may cause some interference with normal functioning.
- Severe: These events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

20.2.2 Assessment of Causality

The relationship of the administered phage in causing or contributing to an AE will be characterised using the following classification and criteria:

- Unrelated: There is no association between the administered phage and the reported event.
- Unlikely: There is a temporal relationship between the administered phage and the reported event; however, it is more likely that the event could have been produced by the participant's clinical state or other treatment(s) administered.
- Possible: The administered phage caused or contributed to the AE, but it could also have been produced by other factors.
- Probable: A reasonable temporal sequence of the event with phage administration exists and, based on previously reported adverse reactions to therapeutic phage, or judgment based on the investigator's clinical experience, the association of the event with the phage seems likely.
- Definite: A definite causal relationship exists between phage administration and the AE, and other conditions (concurrent illness, progression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the phage is readministered.

20.3 Reporting Adverse Events

All AEs reported or observed during the trial will be recorded on the AE page in the eCRF. Information to be collected includes the following:

- Phage product
- Phage dose and date/time of last administration
- Event term (MedDRA preferred term)
- Date/time of onset, including day of phage therapy
- Investigator-specified assessment of severity (section 20.2.1) and relationship to the study drug (section 20.2.2)
- Date/time of resolution of the event, including day of phage therapy
- Seriousness (yes/no)

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- Any required treatment or evaluations
- Outcome

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. Any medical condition that is present at the time that the participant is recruited that deteriorates at any time during the trial, should be recorded as an AE.

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs. All AEs will be followed to adequate resolution, or until the investigator deems the event to be chronic/stable or not clinically significant, or the participant is lost to follow-up.

Any abnormal laboratory test results or other safety assessments (e.g., vital signs measurements), including those that worsen from baseline, felt to be clinically significant in the medical judgment of the investigator are to be recorded as AEs or SAEs.

20.3.1 Reporting Serious Adverse Events

Any AE that meets SAE criteria (Section 20.1) must be reported by site investigators to the Sponsor within 48 hours after site personnel first learn of the event. The SAE should be reported by completing an SAE report form (template provided in section 29 of Appendices) and emailed to the Sponsor at:

WSLHD-ResearchOffice@health.nsw.gov.au

All SUSARs should also be reported using the SAE report form and notified to the study Sponsor, the chair of the DSMB and trial CPI within 48 hours after site personnel first learn of the event:

WSLHD-ResearchOffice@health.nsw.gov.au AND

ian.seppelt@sydney.edu.au AND

jonathan.iredell@sydney.edu au

An acknowledgement of receipt of email all notifications will be made within 48 hours, with the report forwarded to the responsible HREC (see section 21 – Research Ethics Approval). If events occur over a weekend/public holiday, up to 96 hours is allowed for submitting reports and for acknowledgements. The sponsor will follow NHMRC guidance on investigating and reporting SUSARS, including reporting to the responsible HREC.

In addition, annual safety reports will be provided to the responsible HREC by the trial CPI or qualified delegate which will include a line listing of all SAEs, SARs and SUSARs.

Ethics and Dissemination

21. Research Ethics Approval

The trial protocol and all trial documents will be submitted for review by the Sydney Children's Hospitals Network (SCHN) HREC under the National Mutual Agreement (NMA). Additional HREC review may be required for sites that are not covered by the NMA (e.g. private hospitals).

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22. Protocol Amendments

All major protocol amendments will be submitted for review by SCHN HREC and will only be implemented after approval is gained from HREC (for all participating sites) and local governance committees for each participating recruitment site. Protocol amendments will also be notified to the relevant trial registries, and the journal to which the protocol will be submitted for peer-review and publication.

23. Consent

In accordance with ICH GCP guidelines, written informed consent will be obtained by the PI or a qualified designee from all potential trial participants or from their person responsible for adults with diminished capacity to provide consent, or from a parent or legal guardian for patients aged younger than 18 years. Templates of the Master Participant Information Sheet and Consent Form (PICF) for adult patients (self-consenting, or by person responsible) and for patients younger than 18 (consent from parent/guardian and young person information sheet) are provided in section 28 of the Appendices. The young person participant information sheet will be provided for all young people aged over 10 years. Only HREC-approved PICF will be used to obtain written informed consent. At least 24 hours will be allowed between providing PICFs and obtaining consent for potential participants to consider the information.

24. Declaration of Interests

All financial and other competing interests for PIs and the Trial Steering Committee will be documented according to the Terms of Reference for the Clinical Stream Committee of Phage Australia.

25. Access to Data

The final trial dataset will be made available to the Investigator group. The investigator team will have ongoing custody of data or research outputs, including any intellectual property ownership, with the CPI having overall responsibility.

26. Ancillary and Post-Trial Care

Ancillary and post-trial care will be according to routine practice and will be the responsibility of the Primary Clinician. If further episodes of infection occur, including relapses or refractory illness that require further courses of phage treatment, these will be treated as separate events and will be assessed for eligibility in the trial as for the initial course of treatment (i.e. one patient can be enrolled in the trial more than once if repeated courses of phage therapy are administered that meet all inclusion and exclusion criteria). Courses of phage therapy should be separated by at least 15 days to allow assessment of primary outcome to occur for each course. The first episode per patient will be used for primary analayses, with additional courses described.

26a Unexpected and Secondary Findings

Unexpected secondary findings are extremely unlikely. Whole blood obtained for analysis of human transcriptomes will only be used to investigate immunological responses to the phage therapy using a panel that includes both innate and adaptive immune response markers. No other human genetic analyses are planned and will not be undertaken unless express HREC approval is obtained via an amendment. Metagenomic analyses will be restricted to non-human genetic material used only to analyse changes in the microbiome (including endogenous phages) during treatment. In the unlikely

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event that abnormal immune responses are detected (e.g. limited or reduced gene expression profiles) that may suggest immune deficiency or dysregulation, the results will be fed back to the Primary Clinician and Infectious Disease specialist involved in the care of the patient so that additional clinical or diagnostic assessments can be undertaken as indicated.

27. Dissemination Policy

27a Trial Results

Following interim and final analyses, trial results will be shared with the Investigator group and may be prepared for scientific publication or presentation. Final results will be submitted for publication in a peer-reviewed scientific journal. Authorship on publications arising from the trial will be determined by the Trial Steering Committee as per the Terms of Reference for the Clinical Stream Committee of Phage Australia. A lay summary of the final trial results will be made available for participants and the public on the Phage Australia website (https://criticalinfection.com/phage-australia/). A link to the website will be provided to all study participants upon recruitment. There are no restrictions on publication rights for any data generated from the study.

As the protocol is embedded in usual clinical practice, participants may expect to be informed of test results, response to treatment etc. from their Primary Clinicians. All routinely available clinical assays will be available for clinicians to discuss with participants. For some of the more specialised tests, the results may or may not be available while the patient is being treated. For example, phage/bacterial kinetics will be available and will be used to make dosing adjustments. As the study is not blinded and non-comparative, research staff or Primary Clinicians may inform participants about these results and explain why dose adjustments are being made. Other results such as transcriptomics and metagenomics will be processed at a later stage. The results of these tests will not be reported individually to participants as they will not be clinically meaningful for individuals; however, all patients have a right to access their health and medical records through their usual clinical teams (Primary Clinician).

27b Reproducible Research

The trial protocol will be submitted for publication in an open-access peer-reviewed journal such as BMJ Open or Trials. Specific consent will be obtained for use of data and left-over samples for other related research and where this is granted, this will be used for research which has been approved by an appropriate HREC and upon reasonable written request to the CPI. The de-identified participant-level dataset will be provided on written request to the CPI when the final trial results are submitted for publication.

Appendices

28. Informed consent Materials

Adult Participant Information Sheet and Consent Form (see separate document)

Person Responsible Participant Information Sheet and Consent Form (see separate document)

Parent/Guardian Participant Information Sheet and Consent Form (see separate document)

Youth Participant Information Sheet (see separate document)

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29. Adverse Event/Serious Adverse Event (SAE) Report Form Template

Adverse Event Reporting Form Template (data to be entered directly onto REDCap)

Date of event:

If still receiving phage therapy, specify day of therapy (day 1 = day of first dose administration):

If last dose of phage administered <72 hours prior, specify time of onset of event in hours since last dose of phage:

If last dose of phage administered at least 72 hours prior, specify time of onset of event in days since last dose of phage:

Which phages has participant received at least 1 dose of prior to onset of the event?

Event term (according MedDRA):

Details of event:

Severity: Mild / Moderate / Severe

Serious: Yes / No

If yes, select seriousness criteria (multiple can be selected):

1) resulted in death

2) was immediately life threatening

3) required inpatient hospitalisation or prolongation of existing hospitalisation

4) resulted in persistent or significant disability/incapacity

5) congenital anomaly/birth defect

6) Other, may jeopardise the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Related: Unrelated / Unlikely / Possible / Probable / Definite

If Probable or Definite relatedness, select from related to (multiple can be selected):

1) phage(s), specify which if multiple used

2) other trial related procedure (e.g. blood draw)

If the event is Serious, confirm SAE has been reported to the Sponsor (WSLHD-ResearchOffice@health.nsw.gov.au) ☐

If the event is Serious with either Probable or Definite relatedness, confirm SAR has been discussed with site PI ☐

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In the opinion of the PI, if the event is Serious with either Probable or Definite relatedness, does it qualify as a SUSAR (Suspected, Unexpected Serious Adverse Reaction)? Yes / No

If yes, confirm SUSAR has been reported to the Sponsor (WSLHD-ResearchOffice@health.nsw.gov.au) AND the chair of the DSMB (ian.seppelt@sydney.edu.au) AND the CPI (jonathan.iredell@sydney.edu.au) ☐

Any required treatments or evaluations:

Final outcome: Resolution / Stabilisation / No longer clinically significant / Participant lost to follow-up

Date of final outcome:

If AE requires reporting to the Sponsor, the chair of the DSMB or the CPI/TSC, please print out a report from REDCap and email as an attachment to the appropriate person.

30. Quality-of-Life Questionnaires

EQ-5D-5L (see separate document)

EQ-5D-Y (see separate document)

References

1. J. O'Neill, "Tackling Drug-Resistant Infections Globally: Final Report and Recommendations," (Wellcome Trust, London, 2016).
2. M. J. Blaser, Antibiotic use and its consequences for the normal microbiome. *Science* **352**, 544-545 (2016).
3. A. Petrovic Fabijan *et al.*, Phage therapy for severe bacterial infections: a narrative review. *Med J Aust*, (2019).
4. R. M. Dedrick *et al.*, Engineered bacteriophages for treatment of a patient with a disseminated drug-resistant Mycobacterium abscessus. *Nat Med* **25**, 730-733 (2019).
5. R. T. Schooley *et al.*, Development and Use of Personalized Bacteriophage-Based Therapeutic Cocktails To Treat a Patient with a Disseminated Resistant Acinetobacter baumannii Infection. *Antimicrobial agents and chemotherapy* **61**, (2017).
6. S. Maddocks *et al.*, Bacteriophage Therapy of Ventilator-associated Pneumonia and Empyema caused by Pseudomonas aeruginosa. *American journal of respiratory and critical care medicine*, (2019).
7. T. Gilbey, J. Ho, L. A. Cooley, A. Petrovic Fabijan, J. R. Iredell, Adjunctive bacteriophage therapy for prosthetic valve endocarditis due to Staphylococcus aureus. *Med J Aust* **211**, 142-143 e141 (2019).
8. A. Petrovic Fabijan *et al.*, Safety of bacteriophage therapy in severe Staphylococcus aureus infection. *Nat Microbiol* **5**, 465-472 (2020).
9. A. Khawaldeh *et al.*, Bacteriophage therapy for refractory Pseudomonas aeruginosa urinary tract infection. *J Med Microbiol* **60**, 1697-1700 (2011).
10. A. Khatami *et al.*, Bacterial lysis, autophagy and innate immune responses during adjunctive phage therapy in a child. *EMBO Mol Med*, e13936 (2021).
11. D. Sharma, L. Misba, A. U. Khan, Antibiotics versus biofilm: an emerging battleground in microbial communities. *Antimicrob Resist Infect Control* **8**, 76 (2019).

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12. R. Y. K. Chang *et al.*, Bacteriophage PEV20 and Ciprofloxacin Combination Treatment Enhances Removal of Pseudomonas aeruginosa Biofilm Isolated from Cystic Fibrosis and Wound Patients. *AAPS J* **21**, 49 (2019).
13. C. Roder, V. Gunjaca, O. Otome, S. M. Gwini, E. Athan, Cost and Outcomes of Implantable Cardiac Electronic Device Infections in Victoria, Australia. *Heart Lung Circ* **29**, e140-e146 (2020).
14. T. Morrisette, R. Kebriaei, K. L. Lev, S. Morales, M. J. Rybak, Bacteriophage Therapeutics: A Primer for Clinicians on Phage-Antibiotic Combinations. *Pharmacotherapy* **40**, 153-168 (2020).
15. A. M. Segall, D. R. Roach, S. A. Strathdee, Stronger together? Perspectives on phage-antibiotic synergy in clinical applications of phage therapy. *Curr Opin Microbiol* **51**, 46-50 (2019).
16. B. K. Chan *et al.*, Phage selection restores antibiotic sensitivity in MDR Pseudomonas aeruginosa. *Sci Rep* **6**, 26717 (2016).

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered,	2

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		name of intended registry	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2, 3, 4
Protocol version	#3	Date and version identifier	15
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 16, 17
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	16
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16, 17
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16

Introduction

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Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	n/a
Objectives	#7	Specific objectives or hypotheses	7, 8
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg,	8

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		surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-13
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	12, 13
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8, 12
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13, 14
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9

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Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a

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Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values).	13

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		Reference to where details of data management procedures can be found, if not in the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13, 14, 15
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial	12, 13

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		conduct	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	15
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	13
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of	#28	Financial and other competing interests for principal	17

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interests		investigators for the overall trial and each study site	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	8, 12
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	18
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	14

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