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The European clinical research response to optimise treatment of patients with COVID-19: lessons learned, future perspective, and recommendations

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Clinicians have worked feverishly to treat patients with COVID-19 while also carrying out clinical research studies. We discuss how the clinical research community responded to the pandemic in Europe, what lessons were learned, and provide recommendations for future clinical research response during pandemics. We focused on two platform trials: RECOVERY and REMAP-CAP. Both trials were able to enrol patients very rapidly during the beginning of the pandemic because of pre-established structures and procedures, and because they share simple execution and flexibility to adjust when evidence emergences. However, contracting, regulatory hurdles, and competition with (often inadequately designed or underpowered) national trials was a major challenge in several EU countries. We recommend the creation of structures and partnerships that facilitate prioritisation of clinical research, simplification of clinical trial delivery, development of digital models and procedures for data collection and sharing, development of a mechanism to rapidly leverage pandemic funding and to connect EU funding with national funding, and investment in clinical trial networks, platform trials, and master protocols. Finally, the future pandemic clinical research response of the EU should be embedded in the global response. We believe that globally connected clinical trial networks will be essential to respond more effectively to future infectious diseases outbreaks.

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Introduction

The rapid global spread of SARS-CoV-2 in the first months of 2020 confronted physicians with a new disease—COVID-19. Although the disease passed as a mild viral respiratory infection in most infected patients, many developed clinical symptoms of severe pneumonia, requiring hospitalisation and oxygen support. A substantial proportion of these patients proceeded to an even more severe disease state, characterised by rapidly developing pulmonary inflammation and intravascular thrombosis, resulting in high mortality rates. With only supportive treatment available, rapid identification of effective therapies for COVID-19 became a priority. We specifically discuss how the clinical research community responded to the pandemic in Europe, what lessons were learned, and provide recommendations for future clinical research response during pandemics.

The European clinical trial landscape

After the first reports from China, the new disease was declared a Public Health Emergency of International Concern (PHEIC) by WHO on Jan 30, 2020, and the first epidemic wave in Europe became obvious in Italy a few weeks later. From that time onwards multiple initiatives for evaluation of potential treatments were started, not only in Europe, leading to a hugely fragmented trial landscape with few international collaborations. According to data from the COVID-19 TrialsTracker project, the number of clinical studies in COVID-19 up to Nov 8, 2020, was 6416, of which 3663 were also registered with ClinicalTrials.gov.[1] Most entries were from the USA (n=892), China (n=855), India (n=711), France (n=566), Iran (n=417), and Germany (n=328). Most studies evaluated repurposed drugs with in-vitro activity against coronavirus, such as hydroxychloroquine (n=411), ritonavir–lopinavir (n=108), and azithromycin (n=91), as well as immune modulation such as steroids (n=42), interferon beta (n=33), tocilizumab (n=83), and convalescent plasma (n=223). Most studies were observational in design, exposing thousands of patients with COVID-19 to compassionate use drugs without high-quality data collection. Although it is perhaps a perfectly natural desire to use observational data to draw inferences about the effects of treatment, these data cannot be guaranteed to eliminate moderate biases arising from the failure to know with certainty why some patients receive a drug and others do not. The only way to avoid these systematic errors is to randomise.[2,3] Randomised controlled trials (RCTs) provide the highest level of evidence for treatment effects. Yet, most COVID-19 RCTs focused on a single treatment and were designed to demonstrate large, unrealistic treatment benefits, in order to justify sample sizes of several hundreds of patients per study group. A review of over 2000 registered trials of putative treatments for COVID-19 has shown that the vast majority (95%) were inadequately designed to yield actionable answers.[4]

Getting a large and robust RCT started requires an agreed protocol and analysis plan, approvals by institutional review boards and regulators, funding, finding suitable study sites, contracting and training of those study sites, and establishing data management and study drug delivery. For an international study, this process usually takes more than a year. To complicate matters, with a new disease and many studies ongoing, the standard of care can rapidly change, necessitating adaptation of interventions. Now, in December, 2021, few studies have provided results of the required evidence level to formulate international treatment guidelines for COVID-19. Several

European platform trials, such as NOR-Solidarity, DisCoVeRy-Solidarity, RECOVERY, and REMAP-CAP, investigated different treatment interventions. NOR-Solidarity is an add-on trial to the WHO Solidarity trial, done in Norway and studying the effects of remdesivir and hydroxychloroquine.[5] DisCoVeRy is also an add-on to the Solidarity consortium of trials, done mainly in France, and studying the effects of four antiviral therapeutic strategies.[6,7] RECOVERY (Randomised Evaluation of COVID-19 Therapy) is a trial that originated in the UK and expanded more recently to other non-European countries.[8–14] REMAP-CAP (Randomised Embedded Multifactorial Adaptive Platform for Community-Acquired Pneumonia) is a trial that obtained seed funding in Europe as part of PREPARE and that expanded globally.[15–20] The latter two platform trials investigated many different treatment options and their results were published extensively in top-ranking journals. In this Personal View, we will discuss what was the key to their success and what are the lessons learned. Although these trials were done in patients admitted to hospital, the issues apply similarly to trials in other clinical settings such as primary care.

RECOVERY

The RECOVERY trial[8] is a randomised, controlled platform trial done in over 175 hospitals in the UK NHS and, more recently, in Nepal, Vietnam, and Indonesia. The protocol concept was built around the pragmatic megatrials of thrombolysis in myocardial infarction from the 1980s.[21] Simplicity was key to its rapid adoption within a national health-care infrastructure. The first patient was enrolled on March 19, 2020, just 9 days after the protocol was written and 2 days after the protocol was approved, and the first 1000 patients were enrolled in just 16 days. At its peak, RECOVERY was enrolling more than 500 patients per day. Another key to success was the existence of the National Institute for Health Research (NIHR). NIHR was established in 2006 to embed a clinical research capability within the NHS, providing staff, infrastructure, and financing for national health research priorities. Following the 2009 H1N1 influenza pandemic, NIHR established the concept of Urgent Public Health (UPH) Research. To ensure the best use of NHS resources for clinical research during the acute phase of the pandemic, NIHR established a single UK-wide process to prioritise COVID-19 research as UPH research. Only studies with UPH designation would be eligible for NIHR support. Other studies were not forbidden, but they could not call on the resources of NIHR. RECOVERY was one of the first trials to be given UPH status in the UK. A standard contract was issued to sites with a "take it or leave it" approach, allowing no room for local negotiation or adaptation. On March 16, 2020, the Chief Medical Officer for England wrote to all NHS hospital chief executives urging them to "provide your fullest support for implementation of the RECOVERY trial".[22] Extensive linkage to routine electronic clinical and vital statistics data sources was used to minimise data collection by front-line health-care staff.

RECOVERY reported its first positive result (the benefit of dexamethasone treatment) on June 16, 2020, and as of Oct 21, 2021, over 44 000 patients had been randomly assigned, 13 treatments had been included, and nine conclusions had been reached.

REMAP-CAP

The REMAP-CAP trial[15] is a randomised, embedded, multifactorial, adaptive platform trial, intentionally designed for a pandemic with a pathogen causing severe community-acquired pneumonia. It is funded through the 7th framework programme of the EU, and part of PREPARE[23] preparations started in 2014. The trial includes simultaneous randomisation to multiple treatments in several treatment domains, with the possibility of response-adaptive randomisation and allowing new interventions and domains to be flexibly added. If interventions hit predefined triggers for efficacy or futility at planned adaptive analyses, they can be discontinued. The adaptive design features, within a Bayesian statistical framework, and the option to randomly assign participants to multiple interventions in parallel, makes the trial smart and efficient. REMAP-CAP was set up to enrol patients with severe community-acquired pneumonia admitted to the intensive care unit with an overarching master protocol and modular domain-specific appendices. The first patient with community-acquired pneumonia was enrolled in the Netherlands in April, 2018. In January, 2020—just before the COVID-19 pandemic—26 clinical sites in ten EU countries had enrolled 140 patients, and a total of 395 patients had been enrolled globally. These participants were randomly assigned to different empirical antibiotic strategies, different corticosteroids strategies, different durations of macrolide treatment, and different durations of oseltamivir treatment, the latter only in those with (suspected) influenza.

A pandemic stratum was added to the REMAP-CAP protocol on March 3, 2020, to allow enrolling of patients with suspected or confirmed COVID-19, both on organ support in the intensive care unit (severe state) and admitted to hospital but not receiving organ support (moderate state). The first patient with COVID-19 was enrolled on March 9, 2020, just 6 days after the stratum was added. As with RECOVERY, REMAP-CAP was given UPH status in the UK.[22] Additional funding was obtained in Europe from the EU 8th Framework Programme HORIZON2020 through the RECOVER project in September, 2020.[24] During the pandemic the number of participating study sites in Europe increased to 203, in 16 European countries, including 143 in the UK.

REMAP-CAP reported its first conclusion (the benefit of hydrocortisone treatment) on Sept 2, 2020, and as of December, 2021, more than 10 000 patients have been

randomly assigned to 50 interventions in 14 treatment domains. Ten conclusions have been reached.

Lessons learned

Both the EU and UK had established structures and procedures to facilitate a rapid, large-scale clinical research response in the event of a pandemic. REMAP-CAP was the only pre-pandemic existing international platform that had included predefined adaptations for a pandemic in the protocol, through a Pandemic Appendix to the Core Protocol. Methodologically, RECOVERY and REMAP-CAP differ in many aspects, but they share the randomised design, simple execution, and flexibility to adjust when evidence emerges. As a result, RECOVERY and REMAP-CAP were ready to include patients with COVID-19 within 40 and 33 days, respectively, after the outbreak was declared a PHEIC, and enrolled their first patient with COVID-19 within 2 and 6 days, respectively, after the protocol was approved. The real-world experience of both platform trials during the COVID-19 pandemic clearly illustrates the key factors for success during a future pandemic.

Although REMAP-CAP was designed years before the pandemic started, it faced major challenges in motivating study sites to participate in an international study in anticipation of a future pandemic. During this pre-pandemic phase, there was a low sense of urgency for pandemic preparedness and the financial reimbursement in this EU-funded project was hardly competitive to the many other study opportunities in intensive care units.

Hence, at the time of pandemic onset, REMAP-CAP was active in only 26 study sites in Europe. The UPH status and the presence of staff, infrastructure, and additional financing for national health research priorities through NIHR in NHS hospitals, was—as for RECOVERY—a major stimulus for participation for UK sites. Yet, such a mechanism was not in place in EU countries and for REMAP-CAP, each individual site needed to be contracted by the study sponsor, University Medical Center Utrecht. Contracting over 140 study sites over a period of 4 months (March–June) in the midst of a pandemic was a challenging task. Moreover, in EU countries REMAP-CAP had to compete with many national studies, some of them supported by national research funding.

Another level of complexity was added by media attention and political support for some treatment options, such as hydroxychloroquine and lopinavir–ritonavir, and obstructing randomisation options in many countries. Interest in hydroxychloroquine accelerated rapidly as early reports from observational studies of clinical efficacy in patients with COVID-19 emerged. Media attention cannot be avoided, but much stronger health warnings on these publications should have been published (eg, by scientific journals and public health bodies). National funding bodies often set priorities supporting trials studying these drugs, which resulted in a massive concentration of clinical research efforts for these drugs, which impaired enrolment of patients in trials evaluating other potential treatments. Unfortunately, most of these clinical trials did not reach their target number of inclusions and, therefore, failed to deliver solid conclusions.

Other differences in preparedness were reflected in regulatory aspects of clinical trials. In the UK, the Good Clinical Practice requirement for labelling investigational medicines was waived for repurposed drugs tested in COVID-19. Such a waiver was not granted in the EU, substantially increasing logistical complexity, costs, and timelines because of additional contracts and shipment of drugs. As a result, even within the European region of REMAP-CAP, large variability in timelines existed, the UK being substantially faster compared with mainland Europe regarding regulatory procedures. The rationale for study-specific labelling of routinely used drugs prescribed by an authorised person is questionable, particularly in a global health emergency and a disease with high mortality in patients being treated in hospital, where a risk-adapted approach is warranted.

Although almost all EU countries realised fast-track approval of study protocols in the initial phase of the pandemic, large differences in approval times of institutional review boards between countries remained during the pandemic. In the UK, the average time for approval of study protocols and amendments was around 1 week, both for RECOVERY and REMAP-CAP. This was a mean of about 3 months for REMAP-CAP in the EU sites (ranging from 7 days to over 12 months)

Future perspective and recommendations

Create structures and partnerships that facilitate prioritisation of clinical research

Although a centralised pandemic clinical research response is challenging in the EU with divergent payer, health-care delivery, and clinical research systems, a European pandemic clinical research authority should be created to oversee pandemic preparation, clinical research response, and to prioritise clinical studies. This authority should be advised by a pan-European board of clinical researchers with experience in running trials under difficult conditions, such as a pandemic. A partnership should be developed between the EU Member States and the European Commission to agree on aligned goals of clinical research in response to pandemics. This partnership requires a comprehensive strategy, dedicated leadership, and political commitment of ministers of health and research. The pharmaceutical and biotechnology industry should be connected to this partnership. Ethics and data protection requirements are interpreted with varying degrees of restriction by local and national control bodies, and harmonisation by law could substantially facilitate the conduct of clinical trials.

However, the legally binding acts of the Union adopted under the provisions of the Treaty on the Functioning of

the EU on public health cannot involve any harmonisation of the laws or regulations of the Member States. Since the EU Member States have decided to maintain primary sovereignty on public health, a unified and centralised EU response for COVID-19 was legally not feasible. Therefore, health should be of high importance in the political agenda, and robust health reforms at all levels are needed.

Simplify clinical trial delivery

The core design principle of both RECOVERY and REMAP-CAP trials is to facilitate integration of clinical research with front-line clinical care, with a "front end" that minimises administrative burden and facilitates patient inclusion. This overarching design principle was, we believe, crucial to the success of these platform trials compared with traditional, highly burdensome, clinical trial approaches. The implementation of clinical trials has grown increasingly complex and costly, and some of the quality standards for studies evaluating experimental drugs under normal conditions cannot be maintained when evaluating repurposed drugs during a pandemic. For instance, movement restrictions reduce the possibility of on-site initiation visits and data audits, and the required speed of data analysis precludes extensive source verification of all endpoints. These aspects conflict with current standards used by national regulatory bodies. We urgently need defined standards for trial execution during pandemics.

Develop digital models and procedures for data collection and sharing

The European pandemic clinical research authority should develop models and procedures to mandate data centralisation and sharing. Trials are facilitated during a pandemic response if digital and information technology infrastructure is available. Transfer and sharing of data are hampered if trial-specific agreements and contracts have not been set up. Cross-institutional solutions should be developed to standardise data collection, and agreements should be in place to share these data. Pooling data from different trials can provide more robust answers to meaningful clinical questions. Despite these challenges, collaborative efforts did succeed during the pandemic. Examples are the multiplatform randomised clinical trials done by the REMAP-CAP, ATTACC, and ACTIV-4 consortia,[19,20] and the prospective meta-analysis on corticosteroids[25] and interleukin-6 inhibitors[26] published early during the pandemic, where REMAP-CAP data were included before the trial itself was published, in the interest of timely public release of information.

Develop a mechanism to rapidly leverage pandemic funding and to connect EU funding with national funding

In response to COVID-19, substantial research funding was quickly made available through competitive calls in the ongoing EU research framework programme Horizon2020 to support clinical research. As a result, hundreds of clinical researchers spent several weeks writing grant proposals in early 2020, rather than focusing on developing a rapid clinical research response to the pandemic. Moreover, these EU research programmes were disconnected from clinical research funding of Member States. Therefore, a mechanism should be in place to rapidly leverage EU funding and to connect this funding with national public funding programmes. These funds provided by the EU Members States should incentivise academic and non-academic hospitals to participate in EU-funded clinical trials. The USA has several government agencies that can provide rapidly structural funding when it comes to clinical research preparedness and response, such as the National Institutes of Health and Biomedical Advanced Research and Development Authority. Such agencies are lacking in the EU. The European Commission has recognised this and is now developing a new Directorate-General, the Health Emergency Preparedness and Response Authority (HERA), to leverage funding during future pandemics and to build partnerships with Member States. This action should prevent a fragmented clinical research response in the EU during the next pandemic. In order to prepare for HERA, the European Commission launched on Feb 17, 2021, the HERA Incubator, and building clinical trial networks and data infrastructures are key action areas of the HERA Incubator.

Invest in clinical trial networks, platform trials, and master protocols

A pandemic requires trials that rapidly answer a research question with protocols that can be executed even when a health-care system is overwhelmed. During this pandemic the best evidence was provided by platform trials such as REMAP-CAP and RECOVERY. Success was explained by existing structures that could coalesce around a common goal, and an accepted mechanism for decision making. In the case of RECOVERY, this was a national health system with an embedded research infrastructure, an existing concept of urgent public health research, sustainable funding, and centralised powers to prioritise research. In the case of REMAP-CAP, this was an established international multicentre clinical trial with an explicit pandemic response function ready to fire up quickly when a pandemic struck, and an established global governance structure. These platform trials have been especially useful in enabling simultaneous, sequential evaluation of multiple treatment regimes, resulting in highly efficient trials with fewer patients and shorter time to interpretable results. The COVID-19 HERA Incubator programme recently funded a consortium to conduct an adaptive platform trial for COVID-19 treatment in primary care (ECRAID-PRIME) that started on Dec 1, 2021.

It is obvious that such trials should be prepared during interpandemic periods, because success depends

on existing infrastructures and governance. Building on past successes in EU projects such as COMBACTE,[27] PREPARE,[23] and VALUE-Dx,[28] we are building a European Clinical Research Alliance on Infectious Diseases (Ecraid) with clinical trial networks in hospital care (CLIN-Net), primary care, and long-term care. We are also building a laboratory network in COMBACTE (LAB-Net) in more than 40 European countries to support clinical trials. CLIN-Net and LAB-Net are used to support the vaccine trials in VACCELERATE.[29] Ecraid's vision is to efficiently generate rigorous evidence to improve the diagnosis, prevention, and treatment of infections and to better respond to infectious disease threats. A business plan was published in June, 2021, as part of the EU-funded ECRAID-Plan[30] project and a legal entity (not-for-profit Ecraid Foundation) will be established in January, 2022, under Dutch law.

Embed the EU pandemic clinical research response in the global response

The European clinical research response should be harmonised with the global response. European clinical trial networks should be embedded globally. An international body should prioritise clinical research questions and therapeutic agents to be evaluated to avoid research redundancy and fragmentation. This body should provide incentives for global collaboration and foster collaboration across clinical trial networks. The clinical research itself should be led by established research active networks. A structure should be in place for real-time mapping of all clinical research efforts, to inform therapeutic decision making in clinical trials. Several clinical trial networks were built globally before the COVID-19 pandemic, and new networks were funded during the pandemic. Although these networks might have their own governance, methods, and operational procedures, efforts should be made to align research questions of critical and international importance, to streamline clinical trial conduct, to share clinical trials' data, and to support the conduct of trials in countries with the majority of the pandemic burden. International financing for multicountry clinical trials should be aligned and potentially resources should be pooled across funders. In 2013, the Global Research Collaboration for Infectious Disease Preparedness (GloPID-R) was established to fund research in pandemics.[31] The health research funders of GloPID-R and WHO met in January, 2020, to discuss calls for proposals. Unfortunately, research priorities, processes to publish calls and select proposals, and procedural requirements were not sufficiently aligned. If GloPID-R were to coordinate future clinical research funding during pandemics, mechanisms should be established to rapidly release funds from pre-established pools available at the agencies to jumpstart clinical research. This research should not only include clinical trials with therapeutics, but also basic and translational research on the natural history of the new disease, clinical course, transmission, risk factors, and more, facilitated by the clinical trial infrastructure. WHO can play an important normative role, bringing together relevant expertise to make authoritative recommendations on research priorities, data standards, and best practices.

Conclusion

Clinicians have worked feverishly to treat patients with COVID-19 while also carrying out clinical research studies in overstretched and overwhelmed health-care systems. However, most clinical trials were too small and did not provide meaningful results. The search for a successful drug needs the power of scale. After this pandemic, the global health community should rapidly respond to make sure mechanisms are in place for scaling and collaboration, so that we can move more quickly to larger, definitive trials for treatment, prevention, and diagnostics during the next pandemic. Coordination and collaboration should be more effectively facilitated by investing in globally connected clinical trial networks, structured through platform trials, and established under a master protocol framework. We believe that this model of clinical research will be essential to respond effectively to future infectious diseases outbreaks. Let us stop saying we will do better next time—we have had enough warnings. It matters now.

Contributors

HG conceptualised the paper, supervised writing, collected comments from all authors, and prepared the final manuscript. LD, PH, and MB contributed to conceptualisation, writing, review, and editing. All authors approved this manuscript.

Declaration of interests

We declare no competing interests.

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