Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

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EVALUACIÓN DE LA EFICACIA DE LA ADMINISTRACIÓN DE PLASMA DE CONVALECIENTE DE COVID-19 EN LA DISMINUCIÓN DE LA PROGRESIÓN A ENFERMEDAD SEVERA EN ADULTOS MAYORES CON SÍNTOMAS LEVES POR SARS-CoV2

Investigador Principal Hospital Dr. Carlos Bocalandro: Dr. Aníbal Rondan
Investigador Principal Hospital Simplemente Evita: Dra. Valeria Fernández Viña
Investigador Principal Hospital Evita Pueblo: Dra. María Clarisa Barolin
Investigador Principal Hospital San Juan de Dios: Dra. Ivonne Ritou
Investigador Principal del Programa: Dr. Fernando P. Polack (INFANT)

Co-Investigadores: Dra. Romina Libster (INFANT/CONICET), Dr. Gonzalo Pérez Marc (HMC), Dr. Diego Wappner (SMG), Dr. Jorge Lantos (Los Arcos), Dr. Ricardo Valentini (CEMIC), Dr. Federico Etchenique (Ecco), Dr. Mariano Girasolli (OSECAC), Dr. Gabriel Leberzstein (OSECAC), Dr. Miguel González (Finochietto), Dra. Andrea Gamarnik (Leloir/CONICET), Dr. Jorge Geffner (UBA/CONICET), Bioq. Silvina Coviello (INFANT), Dr. Mauricio Caballero (INFANT/CONICET), Dr. Damián Alvarez Paggi (INFANT/CONICET), Dr. Sebastián Esperante (INFANT/CONICET), Dr. Federico Dimase (HMC), Dra. Susana Pastor Argüello (HMC), Dr. Juan Sebastián Riera (Ministerio de Salud de la Provincia de Buenos Aires), Dr. Enio García (Ministerio de Salud de la Provincia de Buenos Aires), Dr. Juan Canela (Ministerio de Salud de la Provincia de Buenos Aires), Dr. Mario Rovere (Ministerio de Salud de la Provincia de Buenos Aires), Dr. Fernando Althabe (OMS), Dr. Eduardo Bergel (IECS).

Asesores: Dr. Daniel Stamboulian (FUNCEI)

1. INTRODUCCIÓN

SARS-CoV2 es un virus nuevo y particularmente agresivo para individuos de edad avanzada, quienes representan entre el 73 y 90% de los casos fatales en distintas regiones del mundo [28, 30, 40]. La mortalidad, la necesidad de cuidados intensivos, la ventilación mecánica, el requerimiento de oxígeno, y las hospitalizaciones por enfermedad respiratoria aumentan marcadamente con el avance de la edad en los pacientes [2, 3, 29, 32, 46]. De hecho, la frecuencia de muerte por enfermedad por SARS-CoV2 (COVID-19) es del 8% en los pacientes entre 70 y 80 años, y aumenta a 14,8% en los mayores de 80 [23]. Específicamente en pacientes hospitalizados mayores de 75 años, la mortalidad es de 29,4% [24], y en la terapia intensiva asciende a un alarmante 43,5% [25]. Varias comorbilidades asociadas con enfermedad vascular y/o pulmonar agravan el pronóstico de los infectados aun en pacientes menores de 70, incluyendo hipertensión arterial, diabetes, obesidad y enfermedad pulmonar obstructiva crónica (EPOC) [3,23,30,31]. A la fecha, el virus ha causado más de 290.000 muertes en el mundo, más de 300 de ellas en Argentina donde se encuentra contenido a través de una estrategia transitoria de cuarentena cuasi-universal [4]. No existe aún ningún tratamiento específico disponible. Los resultados de los ensayos de eficacia para vacunas contra SARS-CoV2 se conocerán dentro de mínimamente 10-14 meses.

El SARS-CoV2 es un virus envuelto que contiene ARN monocatenario en sentido positivo unido a una nucleoproteína (proteína N), dentro de una cápside compuesta por proteínas de la matriz (proteína M). La envoltura posee glicoproteínas en forma de espinas (proteína S) que se unen al receptor celular ACE2 en humanos y generan anticuerpos neutralizantes [13]. La primo infección por SARS-CoV2, como otras enfermedades respiratorias, genera una respuesta de anticuerpos con producción temprana de IgM seguida de IgG específica contra las proteínas virales [14]. La detección de anticuerpos neutralizantes del virus es frecuente, y alcanza niveles altos de hasta 1:21,500 $PRNT_{50}$, mayormente excediendo títulos de 1:500 después de 28 días del inicio de síntomas en pacientes leves [41]. Aproximadamente 5% de los pacientes presentan niveles de anticuerpos neutralizantes <1:40, especialmente los más jóvenes [41]. Un estudio de infección primaria vía respiratoria en macacos Rhesus, utilizando 10^6 pfu de SARS-CoV2 seguido de un segundo desafío intratraqueal usando el mismo virus y dosis 28 días más tarde, demostró ausencia de reinfección tras una extensa evaluación por RT-PCR de tejidos post-necropsia [42]. Los títulos neutralizantes antes del segundo inóculo variaban entre 1:8-1:16 $PRNT_{50}$ [42]. **Estos hallazgos - limitados por**

cierto, dada la novedad del problema- sugieren que aún bajos títulos de anticuerpos neutralizantes podrían prevenir la enfermedad severa por el virus.

Proteger a las poblaciones más vulnerables al SARS-CoV2 es imperioso, en el contexto de un germen altamente infeccioso (R_0 estimado entre 2 y 3,28) [27, 33, 34]. Su contagiosidad desborda rápidamente la capacidad sanitaria de países desarrollados en distintas regiones del mundo [5] y amenaza los recursos sanitarios de países en vías de desarrollo [6]. Regiones de Italia, España y Estados Unidos se han visto desbordadas por la pandemia, que representa una seria amenaza para Argentina, en coincidencia con el inicio de la circulación anual de otros patógenos pulmonares, como la gripe común y el virus sincicial respiratorio [26]. Evidentemente, resultaría imposible dar respuesta a una avalancha de pacientes graves [7], y toda estrategia tendiente a disminuir las infecciones y el desarrollo de enfermedad severa **se alinea directamente con el objetivo médico de salvar vidas y con las necesidades sanitarias del país para poder brindar la mejor atención posible a aquellos pacientes que lo necesiten**.

La profilaxis post-exposición a virus y el tratamiento en fases tempranas de enfermedad, a través de defensas obtenidas en plasma de convalecientes, es una práctica extendida con antecedentes exitosos en la historia de la medicina a nivel nacional y global. Ya en 1960, Brunell y col. lograron prevenir la varicela clínica en hermanos con padres enfermos, usando inmunoglobulinas anti-varicela zoster obtenidas del plasma de pacientes previamente infectados [8]. Hoy mismo, por ejemplo, la inmunoglobulina enriquecida para sarampión se utiliza en personas no vacunadas que estuvieron en contacto con un enfermo durante los 6 días previos con una eficacia cercana al 100% [9, 52]; un producto similar enriquecido para el virus de varicela zoster se administra en embarazadas, recién nacidos, e inmunosuprimidos no vacunados en contacto con infectados dentro de las 96 horas disminuyendo un 90% la incidencia de enfermedad grave [10, 53, 54]; la inmunoglobulina antitetánica suplementa la vacunación en víctimas de heridas sucias con inmunización primaria incompleta [43]; la gammaglobulina contra hepatitis B se utiliza como prevención para recién nacidos de madres infectadas con una eficacia del 75% [44, 55]; y la gammaglobulina antirrábica es ~100% efectiva en la profilaxis posterior a la agresión de un animal sospechoso [11,56]. **Las intervenciones utilizando inmunidad humana derivada del plasma de convalecientes han demostrado ser seguras, han prevenido innumerables casos de enfermedad severa, y han preservado vidas en todo el mundo.**

El objetivo principal de nuestro estudio es evaluar la eficacia del plasma de convaleciente en reducir la progresión a enfermedad severa en personas entre 65-74 años con al menos una comorbilidad y en todos los ≥ 75 años que se presenten con sintomatología leve de menos de 48 hs de evolución al momento del inicio de la pesquisa y reciban diagnóstico temprano de COVID-19. *Nuestra hipótesis central es que una dosis única de plasma de convaleciente comparada contra placebo (solución salina al 0,9%), y administrada hasta 72 horas después del inicio de los síntomas por SARS-CoV2 (o sea, hasta 24 horas después del límite de tiempo para presentarse a pesquisa y testeo), prevendrá la progresión a una enfermedad respiratoria severa en sujetos entre 65-74 años con al menos una comorbilidad y en los ≥ 75 años independientemente de presencia de comorbilidad basal.*

2. OBJETIVOS DEL ESTUDIO

2.1. Objetivo Primario

Evaluar la eficacia del plasma de convaleciente, a partir de 12 horas de la administración, en reducir la progresión a enfermedad respiratoria severa en personas entre 65-74 años con al menos una comorbilidad y en todos los ≥ de 75 años con sintomatología leve y diagnóstico temprano de COVID-19 hasta los 15 días de administración del tratamiento (16-18 días de enfermedad considerando el periodo sintomático pre-enrolamiento),

2.2. Objetivos Secundarios

Los Objetivos Secundarios incluyen determinar si la administración de plasma de convaleciente hasta los 15 días o a partir de entonces hasta un máximo de *25 días de la administración de tratamiento si continuase internado* consigue:

- Disminuir la necesidad de soporte de oxígeno con oxigenoterapia máxima (mascara de reservorio de O2) y/o utilización de soporte respiratorio no invasivo (soporte de VNI incluyendo CPAP) y/o admisión a UTI y/o requerimiento de ventilación mecánica invasiva por SARS-CoV2 en pacientes entre 65-74 años con al menos una comorbilidad y en todos los ≥ 75 años
- Disminuir la enfermedad crítica definida como (a) presencia de falla respiratoria aguda (PaO2/FiO2 ≤ 200 mm Hg.) y/o (b) shock (definido por necesidades de soporte con drogas vasoactivas para mantener P.A.M. igual o mayor a 65 mm. Hg), y/o (c) síndrome de disfunción multiorgánica (SDMO): injuria renal aguda (definida por aumento de creatinina por dos o más veces con respecto al basal o aumento de creatinina 0.3 mg/dl), elevación de

enzimas hepáticas (transaminasas) mayor a tres veces el valor superior normal, miocardiopatía aguda (definida por elevación de troponina por encima del nivel normal y/o nuevas alteraciones electrocardiográficas o ecocardiográficas para daño miocárdico) por SARS-CoV2 en pacientes entre 65-74 años con al menos una comorbilidad y en todos los ≥ 75 años a causa de COVID-19.

- Disminuir la mortalidad por SARS-CoV2 en pacientes entre 65-74 años con al menos una comorbilidad y en todos los ≥ 75 años a causa de COVID-19.
- Disminuir la duración de soporte de oxigeno debido a COVID-19 en pacientes hipoxémicos.
- Describir la seguridad de la administración de plasma de convaleciente en pacientes entre 65-74 años con al menos una comorbilidad y en todos los ≥ 75 años con COVID-19.
- Explorar la concentración de IgG anti-S de SARS CoV2 en plasma de los participantes asociada con ausencia de enfermedad respiratoria severa obtenidas a las 24 horas de la infusión.

2.3. Objetivos Exploratorios

- Explorar si, en lugar de proteger contra la enfermedad respiratoria severa, la administración de plasma de convaleciente retarda la aparición de dicha enfermedad.
- Explorar los efectos del plasma de convaleciente sobre la respuesta inmune humoral primaria contra la infección por SARS CoV2. a los 90 días de enrolamiento
- Explorar si los efectos en enfermedad respiratoria, cardiovascular y mortalidad a largo plazo fueron afectados por la intervención a los 12 meses de enrolamiento.
- Explorar la correlación entre carga viral determinada por RT-PCR al diagnóstico y la respuesta a tratamiento con plasma.

3. CRITERIOS DE VALORACIÓN DE EFICACIA

3.1.1. Criterio Primario de Valoración de Eficacia

Enfermedad respiratoria severa por SARS-CoV2, confirmada por detección de ARN viral por RT-PCR, y definida por la presencia de cualquiera de las dos siguientes variables en forma no excluyente: (a) frecuencia respiratoria ≥30 por minuto, (b) saturación de oxígeno en aire ambiental <93% [20,21]. El endpoint primario se determinará a partir de 12 horas del inicio de la infusión hasta 15 días desde la administración del tratamiento.

3.1.2. Criterios Secundarios de Valoración de Eficacia *(hasta los 15 días o, a partir de entonces, hasta un máximo de 25 días de la administración de tratamiento si continuase internado)*

- Necesidad de soporte de oxígeno con oxigenoterapia máxima (mascara de reservorio de O2) y/o soporte respiratorio no invasivo (soporte de VNI incluyendo CPAP) y/o admisión a UTI y/o requerimiento de ventilación mecánica invasiva, por SARS-CoV2.
- Enfermedad crítica definida como (a) presencia de falla respiratoria aguda ($PaO2/FiO_2$ ≤ 200 mmHg.) y/o (b) shock, y/o (c) síndrome de disfunción multiorgánica (SDMO) según criterios detallados en sección 2.2: injuria renal aguda, elevación de enzimas hepáticas, miocardiopatía aguda, por SARS-CoV2.
- Mortalidad por COVID-19.

4. HIPÓTESIS Y JUSTIFICACIÓN

4.1. Hipótesis

Nuestra hipótesis central es que una dosis de plasma de convaleciente comparada contra placebo, y administrada hasta 72 horas desde el inicio de los síntomas leves, prevendrá la progresión a enfermedad respiratoria severa por COVID-19 en pacientes entre 65-74 años con al menos una comorbilidad y en todos los ≥ 75 años que se presenten con menos de 48 horas de evolución al proceso de pesquisa y con sintomatología leve.

4.2. Justificación

La eficacia de una preparación terapéutica contra el SARS-CoV2 económicamente accesible analizada mediante un estudio aleatorizado, doble ciego, en pacientes vulnerables permitiría escalar de inmediato su aplicabilidad a nivel nacional e internacional mediante campañas masivas de donación de plasma de convalecientes a la espera de soluciones definitivas tales como medicamentos exitosos, anticuerpos monoclonales, o vacunas [17]. Inclusive, de existir protección parcial concentrada en el tracto respiratorio inferior [18], *esta misma estrategia podría hipotéticamente permitir la inmunización de los sujetos mediante la replicación controlada del germen en el tracto respiratorio alto* (como en el caso de la administración pasiva de anticuerpos contra el virus sincicial respiratorio en lactantes [19]).

5. DISEÑO DEL ESTUDIO

Un estudio aleatorizado, doble-ciego, controlado con placebo para testear la eficacia del plasma de convaleciente, administrado hasta 72 horas después del inicio de síntomas, con el fin de evitar la progresión hacia una enfermedad respiratoria severa. El estudio se llevará a cabo en sujetos entre 65-74 años con al menos una comorbilidad y en todos los ≥ 75 años que se presenten con sintomatología leve de menos de 48 horas de evolución al momento de la pesquisa (definida en sección 5.1) y diagnóstico precoz de COVID-19. El estudio se realizará durante un período de observación mínimo de 15 días en el que los participantes permanecerán bajo control médico diario por protocolo para determinar el criterio de valoración primario. El período de monitoreo se extenderá a partir de entonces, hasta un máximo de 25 días de la administración de tratamiento, si continuase internado, para analizar los criterios de valoración de eficacia secundarios.

Se proyecta que el estudio incorpore un máximo estimado de 210 pacientes (ver 9.0 Tamaño muestral). Los participantes serán aleatorizados en una proporción de 1:1.

Tabla 1. Asignaciones de Tratamiento

Grupo de Tratamiento	Rango de sujetos asignados por rama	Artículo de Prueba	Volumen de Dosificación intravenoso	Día de Administración de la intervención
A	105	Placebo (solución salina al 0,9%)	250 cc	Día 0
B	105	Plasma de convaleciente		

Todos los participantes recibirán una dosis única endovenosa (EV) - acorde a las NORMAS ADMINISTRATIVAS Y TÉCNICAS RM 797/13 – 139/14 – 1507/15 Dirección de Sangre y Hemoderivados Ministerio de Salud de la Nación (por http://www.msal.gob.ar/disahe/images/stories/pdf/normas-hemoterapia.pdf) el Día 0 con el artículo de prueba asignado, plasma de convaleciente o placebo (ver Tabla 1). Para cada sujeto, la participación en el estudio se extenderá un mínimo de 15 días o hasta la resolución de síntomas desde la administración del artículo de prueba con un máximo de 25 días. Los sujetos participantes serán monitoreados durante y después de la administración del artículo de prueba para evaluar eventos de seguridad esperables y no esperables luego de la administración de plasma. Un Comité de Monitoreo de Datos y Seguridad supervisará el enrolamiento, la eficacia y la seguridad de los participantes a lo largo del estudio.

El estudio se llevará a cabo en el Hospital San Juan de Dios, el Hospital Simplemente Evita, el Hospital Dr. Carlos Bocalandro, el Hospital Evita Pueblo, en estrecha coordinación con los efectores sanitarios del Ministerio de Salud provincial y en el Hospital Militar Central, el Sanatorio de Los Arcos, CEMIC, el Centro de Investigación OSECAC, garantizando que no se interferirá con los cuidados y las normas de atención de pacientes dispuestas para la notificación y manejo de esta enfermedad.

5.1. Criterios de elegibilidad

5.1.1 Criterios de Inclusión:

Un sujeto debe cumplir los siguientes criterios para ser incluido en el estudio:

1. Edad ≥ 75 años o edad entre 65-74 años con al menos una de las comorbilidades siguientes:
   a. Diagnóstico de hipertensión arterial bajo tratamiento farmacológico.
   b. Diagnóstico conocido de diabetes en tratamiento con algunas de las drogas disponibles (Apéndice I).
   c. Obesidad (IMC -Índice de masa corporal- ≥ a 30 kg/m2),
   d. Diagnóstico de enfermedad pulmonar obstructiva crónica (EPOC) en tratamiento con algunas de las drogas disponibles (Apéndice I).
   e. Enfermedad cardiovascular establecida definida como a) diagnóstico conocido de enfermedad coronaria, b) historia de enfermedad

cerebrovascular isquémica o hemorrágica, o c) ICC (definida como FE < 40%).

f. Enfermedad renal crónica (definida como reducción del FG por debajo de 60 ml/min/1,73 m^2).

2. Presentar hace menos de 48 horas: (A)Temperatura axilar ≥37,5°C o equivalente febril (definido por sensación de frío y/o escalofríos y/o sudoración inexplicada), combinado con (a) tos seca y/o (b) dificultad respiratoria y/o (c) odinofagia y/o (d) anosmia/disgeusia y/o (e) alguno de los siguientes síntomas: fatiga, anorexia, mialgias o rinorrea.
3. Diagnóstico de SARS-CoV2 confirmado por RT-PCR
4. Ser capaz, según juicio médico, de comprender y cumplir con los procedimientos del estudio y de consentir o no su participación.
5. Proveer consentimiento informado por sí mismo.

5.1.2 Criterios de Exclusión

Un sujeto que cumple cualquiera de los siguientes criterios será excluido del estudio:

1. Que presente al momento del ingreso ENFERMEDAD RESPIRATORIA SEVERA definida como (a) frecuencia respiratoria ≥30 por minuto y/o (b) saturación de oxígeno en aire ambiental <93%.
2. INSUFICIENCIA CARDIACA en clase funcional III y IV (según clasificación funcional de la New York Heart Association).
3. Diagnóstico conocido de INSUFICIENCIA RENAL CRÓNICA en estadios de filtrado G4 y G5 (según clasificación KDIGO).
4. Diagnóstico previo de HIPOGAMMAGLOBULINEMIAS PRIMARIAS (congénitas y hereditarias).
5. Diagnóstico previo de GAMMAPATÍAS MONOCLONALES (mieloma múltiple, macroglobulinemia de Waldenström, amiloidosis primaria, enfermedad de las cadenas pesadas, entre otras).
6. Diagnóstico previo de DEFICIENCIA SELECTIVA DE IgA.
7. Diagnóstico previo de SÍNDROMES MIELODISPLÁSICOS. [clasificación OMS: trombocitopenia refractaria (TR), anemia refractaria (AR), etc.]
8. Diagnóstico previo de SÍNDROMES LINFOPROLIFERATIVOS CRÓNICOS. (clasificación OMS: linfomas periféricos de linfocitos B, linfomas de linfocitos T y células NK, Linfoma de Hodgkin).
9. HIPERSENSIBILIDAD CONOCIDA a la administración de inmunoglobulinas, plasma, anticuerpos monoclonales y/o vacunas.
10. Cáncer activo, definido por estar recibiendo o haber recibido o estar recibiendo quimioterapia, radioterapia o tratamientos con drogas nuevas de diseño o monoclonales en los últimos seis meses.
11. Infección conocida por HIV, HBV o HCV.
12. Administración crónica (definida como más de 14 días corridos) de inmunosupresores u otras drogas que modifican el sistema inmune **al momento del enrolamiento** o dentro de los 6 meses previos a la administración de la medicación del estudio. Una dosis inmunosupresora de glucocorticoides se definirá como una dosis sistémica ≥10mg de prednisona por día o su equivalente.
13. Antecedente de transplante de órgano sólido.
14. Enfermedad hepática crónica conocida con diagnóstico de cirrosis estadio II-III-IV.
15. Enfermedad pulmonar crónica con requerimiento de oxígeno.
16. Cualquier otra condición física, psiquiátrica o social que pueda, a criterio del investigador, aumentar los riesgos por la participación en el estudio a los participantes o que puedan conducir a la recolección de datos de seguridad incompletos o inexactos.

5.2. Procedimientos del estudio (Tabla 2)

5.2.a. Población participante y proceso de identificación de potenciales sujetos.

Sujetos entre 65-74 años con al menos una comorbilidad y todos los ≥ 75 años que presenten hace menos de 48 hs alguno de los siguientes síntomas: (**a**) temperatura ≥37,5°C o equivalente febril (definido por sensación de frío o escalofríos o sudoración inexplicada), combinado con (**b**) tos seca y/o disnea y/o anosmia/disgeusia y/o odinofagia y/o fatiga y/o anorexia y/o mialgias y/o rinorrea.

Dichos candidatos serán invitados a contactarse de inmediato con el fin de evaluar su participación a través de los números designados por las organizaciones intervinientes.

Aquellos pacientes que cumplan con los criterios de inclusión y no cumplan ninguno de los criterios de exclusión arriba mencionados serán invitados a participar en la fase de pesquisa del estudio en el cual, en caso de aceptar (plasmando su conformidad a través de la firma del consentimiento informado de pesquisa - ANEXO), se obtendrá una muestra de secreción respiratoria por medio de hisopados nasofaríngeo y orofaríngeo (de acuerdo al procedimiento y normativa implementada por el Ministerio de Salud) para detectar ARN de SARS-CoV2 por la prueba de cadena de la polimerasa (RT-PCR).

Dicha muestra será procesada y analizada por los laboratorios intervinientes designados para las instituciones participantes, y que actualmente proveen este mismo servicio diagnostico diariamente, utilizando el mismo test de RT-PCR para evaluar la presencia de ARN de SARS-CoV2. Esta determinación se realizará lo antes posible (en un máximo de 24 horas) y, tal como hasta hoy, bajo todas las normas de bioseguridad indicadas por las autoridades sanitarias. Las muestras se conservarán para posterior testeo por RT-PCR de co-infecciones con influenza A y B, virus sincicial respiratorio y otros patógenos virales de invierno en la Fundación INFANT.

5.2.b. Enrolamiento para la participación en el estudio

En caso de detectarse en la muestra respiratoria ARN de SARS-CoV2, se informará al candidato sobre los detalles del estudio y se verificará su elegibilidad nuevamente. El candidato podrá decidir no participar de la investigación según su libre albedrío y sin consecuencia alguna de ningún tipo. En caso de que el sujeto esté interesado en participar en el estudio, y tras su consentimiento atestado con la firma del consentimiento informado de participación (ANEXO), se procederá a asignarle un número de identificación único. Una vez asignado su código alfanumérico, se procederá a obtener los signos vitales y realizar un examen físico completo para obtener la siguiente información demográfica y clínica [1-3, 25, 47-51]:

- Sexo
- Edad
- Medicaciones habituales y de los últimos 15 días.
- Antecedentes de tabaquismo
- Comorbilidades de interés primario: hipertensión arterial, diabetes, enfermedad coronaria, insuficiencia cardíaca, antecedentes de ACV e IAM, EPOC, nefropatía crónica, y obesidad**.**
- Comorbilidades secundarias: asma, antecedentes de cáncer, enfermedades hepáticas, y enfermedades neurológicas**.**

5.2.c. Asignación aleatoria

Todos los participantes con elegibilidad confirmada serán asignados aleatoriamente a un grupo de tratamiento. La asignación aleatoria de sujetos participantes se realizará utilizando un sistema electrónico por el encargado de aleatorización del estudio. Una vez aleatorizado el paciente, el encargado de la asignación se comunicará con un miembro del equipo de Medicina Transfusional Central del estudio quien procederá a extraer la bolsa opaca de tratamiento indicada del freezer del Laboratorio Central. El equipo de Medicina Transfusional procederá a llevar dicha bolsa en frío al hospital asignado. Allí completará la preparación del producto enmascarado y administrará el tratamiento indicado al paciente participante utilizando para su infusión un acceso venoso previamente obtenido por un miembro del equipo del hospital. Solo este equipo (el encargado de aleatorización y el encargado de Medicina Transfusional Central de administrar el tratamiento) conocerán el producto a administrar a cada paciente (equipo no ciego). Ni el paciente ni los investigadores tendrán conocimiento del tratamiento administrado, realizando un estudio de doble ciego. El equipo no ciego llevará un registro de las asignaciones de producto y sus administraciones que será guardado de manera confidencial. En la eventual necesidad de una ruptura de ciego se podrá recurrir a dichos registros.

5.2.d. Preparación y administración del artículo de prueba

La preparación y administración del plasma de convaleciente o placebo (solución fisiológica) se realizará acorde a las NORMAS ADMINISTRATIVAS Y TÉCNICAS RM 797/13 – 139/14 – 1507/15 Dirección de Sangre y Hemoderivados Ministerio de Salud de la Nación. (http://www.msal.gob.ar/disahe/images/stories/pdf/normas-hemoterapia.pdf).

Una vez enmascarado el producto, el equipo de Medicina Transfusional lo administrará en forma endovenosa lenta al paciente durante un mínimo de 3 horas y hasta 4 horas

de acuerdo a las normas. Luego de la administración se monitoreará la ocurrencia de reacciones locales en el sitio de inyección y sistémicas por 12 horas. *Este es un estudio de mínimo riesgo, ya que la administración de plasma y de solución salina (placebo en este estudio) son de hábito diario en la práctica médica.* En el caso de una emergencia médica, cuando se tenga conocimiento de que la asignación de tratamiento puede influir en la atención médica del paciente, el investigador o la persona designada pueden solicitar que se rompa el ciego para el sujeto que está experimentando la emergencia. Sin embargo, antes del quiebre de ciego el investigador debe realizar todos los esfuerzos razonables de ponerse en contacto con la persona designada para discutir la decisión de quebrar el ciego. Se espera que el investigador proporcione una razón para la necesidad de romper el ciego, en base a un cambio significativo en la atención médica inmediata o de corto plazo del participante que resultará del conocimiento de la asignación del tratamiento.

5.2.e. Toma de muestra de sangre para titulación de IgG anti-S SARS CoV2 en suero.

A las 24 horas de completada la infusión del tratamiento, se obtendrá una muestra de 5 ml de sangre venosa de todos los participantes para la titulación en suero de IgG anti-S SARS-CoV2, a realizarse en la Fundación INFANT por método ELISA (COVIDAR IgG, Leloir/CONICET). El suero se preservará a -20°C hasta su traslado en frío por un sistema de transporte autorizado para manejo de muestras biológicas a la Fundación.

5.2.f. Seguimiento clínico diario

Se realizará un control diario a partir del Dia 0, y por lo menos durante 15 días desde la infusión y hasta 25 días para aquellos sujetos que continúan hospitalizados a partir del día 15. Aquellos pacientes que sean dados de alta previo al día 15, serán monitoreados por un equipo de médicos domiciliarios entrenados para tal fin que trabajarán en colaboración con los centros de investigación. La siguiente información clínica se recolectará diariamente (utilizando un cuestionario diseñado para tal fin) por personal del estudio y **sin interferir con la atención médica del paciente ni alterar las normas recomendadas por las autoridades sanitarias para el manejo de los pacientes con COVID-19**: (a) frecuencia respiratoria (mirando como excursiona el tórax durante 30 segundos), (b) saturación de oxígeno, (c) temperatura, (d) frecuencia cardiaca central, (e) tos y duración, (f) dolor de garganta y duración, (g) sensación de fiebre/escalofríos, (h) necesidad de provisión de oxígeno suplementario y duración, (i) necesidad de cuidados intensivos y duración, (j) necesidad de asistencia respiratoria no invasiva o invasiva y duración, (k) evidencia de SDMO: según criterios de injuria renal

aguda, criterios de elevación de enzimas hepáticas y criterios de miocardiopatía aguda (detallados en sección 2.2), (l) sobrevida.

Tabla 2. Cronograma de procedimientos del estudio.

Día del Estudio	-1 Pesquisa	0 Día 0	Seguimiento Diario
Consentimiento informado de pesquisa para la evaluación de antecedentes, condición clínica y diagnóstico *SARS-CoV2*	X		
Toma de hisopado nasofaríngeo para confirmación diagnóstica de SARS-CoV2 por RT-PCR	X		
Consentimiento informado de participación en el estudio		X	
Revisión de historia médica		X	X
Signos vitales		X	
Confirmación de elegibilidad		X	
Medicamentos concomitantes		X	X
Asignación aleatoria de tratamiento		X	
Administración de la intervención		X	
Monitoreo de la transfusión		X	
Vigilancia de eventos adversos		X*	(X)
Toma de muestra de sangre luego de completada la infusión			Única muestra a las 24 hs
Vigilancia de síntomas respiratorios		X	X

Se considerará que el paciente completa su participación al llegar el día 15 (si el paciente ya está dado de alta), al alta hospitalaria entre el día 15 y el día 25 o al cumplirse el día 25 de continuar hospitalizado.

6. Comité Independiente de Monitoreo de Datos

Un Comité Independiente de Monitoreo de Datos supervisará la seguridad de los sujetos durante todo el estudio. El CIMD incluirá, como mínimo, miembros con experiencia en el manejo de medicina interna, enfermedades infecciosas, y un bio-estadístico con experiencia específica en el diseño, análisis y monitoreo de seguridad de estudios clínicos. El CIMD operará bajo un plan aprobado y tendrá la responsabilidad de monitorear las medidas de resultado / puntos finales, eventos adversos (EA) y eventos adversos serios (EAS), y recomendar la finalización del estudio si aparece en algún momento durante el estudio que los participantes (o un subgrupo de participantes) se encuentran en riesgo indebido como resultado de su participación. El CIMD se reunirá (por teleconferencia) semanalmente para revisar el acumulado de datos sobre seguridad y eficacia y realizará un análisis interino de los datos. El CIMD emitirá recomendaciones escritas en base a sus reuniones acerca de la continuidad del estudio. Las actas de cada reunión se registrarán en minutas documentadas en base a una agenda de trabajo preestablecida. Cualquier información de salud protegida específica del participante revisado por el CIMD se mantendrá completamente confidencial. Las sesiones serán cerradas sin acceso a terceros.

7. Monitoreo de Seguridad

El investigador en cada institución y a nivel general supervisará la seguridad del paciente del estudio en su(s) sitio(s) según los requisitos de este protocolo y de acuerdo con las Buenas Prácticas Clínicas (GCP) actuales. El investigador monitoreará los datos de seguridad en todos los sitios de estudio. El monitoreo de seguridad se realizará de manera continua (por ejemplo, revisión individual de EAS, EAs y puntos finales) y de forma acumulada periódica.

Evento adverso (EA)

Un EA es cualquier acontecimiento médico desfavorable en un paciente al que se le administró un fármaco del estudio que puede tener o no una relación causal con el fármaco del estudio. Por lo tanto, una EA es cualquier signo desfavorable e involuntario (incluido el hallazgo anormal de laboratorio), síntoma o enfermedad que se asocia temporalmente con el uso de un medicamento del estudio, independientemente de si se considera relacionado con el medicamento del estudio.

Un EA también incluye cualquier empeoramiento (es decir, cualquier cambio clínicamente significativo en la frecuencia y / o intensidad) de una afección preexistente que se asocia temporalmente con el uso del producto en investigación.

La progresión de COVID-19 no se considerará un EA si es claramente coherente con el patrón de progresión típico de la enfermedad

Si existe alguna incertidumbre acerca de que un EA se deba solo a la progresión de COVID-19, se informará como un EA o EAS como se describe en la sección respectiva.

Evento adverso serio (EAS)

Un EAS, por definición, es cualquier evento médico desfavorable que a cualquier dosis:

- Resulte en la muerte: incluye todas las muertes, incluso aquellas que parecen no tener relación alguna con el fármaco del estudio (por ejemplo, un accidente automovilístico en el que un paciente es pasajero).
- Es potencialmente mortal: en opinión del investigador, el paciente corre un riesgo inmediato de muerte en el momento del evento. Esto no incluye un AE que si hubiera ocurrido en una forma más severa, podría haber causado la muerte.
- Requiere hospitalización o prolongación de la hospitalización existente. La hospitalización se define como el ingreso a un hospital o sala de emergencias por más de 24 horas. La prolongación de la hospitalización existente se define como una estadía en el hospital que es más larga de lo previsto originalmente para el evento, o se prolonga debido al desarrollo de un nuevo EA según lo determinado por el investigador o el médico tratante.
- Resulta en discapacidad/incapacidad persistente o significativa (interrupción sustancial de la capacidad de uno para llevar a cabo funciones normales de la vida).
- Es un evento médico importante: los eventos médicos importantes pueden no poner en peligro la vida de inmediato o provocar la muerte u hospitalización, pero pueden poner en peligro al paciente o pueden requerir intervención para prevenir uno de los otros resultados graves enumerados anteriormente (por ejemplo, tratamiento intensivo en una emergencia o en casa para broncoespasmo alérgico; discrasias sanguíneas que no resultan en hospitalización).

En el caso específico de este estudio se considerarán como EA o EAS, según la descripción detallada en la sección 11.2, aquellos que se inicien dentro de las 12 horas posteriores a la administración del tratamiento y los agravamientos clínicos y muertes asociadas con estos eventos. No se considerarán EA o EAS aquellos eventos clínicos que se inicien luego de las 12 horas de iniciación del tratamiento, que constituirán parte de la evolución clínica de los pacientes enrolados infectados con SARS CoV2.

Periodo de Recolección de Eventos Adversos

El período de informe EA / EAS comienza cuando el participante se incluye inicialmente en el estudio (fecha de firma del consentimiento informado de participación) y recibe la infusión y continuará para los eventos que se inicien en las siguientes 12 horas desde su inicio (ver sección 11.2). Durante el seguimiento posterior a las 12 horas iniciales de la administración del producto de investigación, se monitoreará la evolución clínica asociada a los criterios de valoración primario y secundarios.

8. Abandono Prematuro del Estudio

Los sujetos podrán abandonar el estudio en cualquier momento si así lo deseasen, pero serán igualmente monitoreados durante el periodo estipulado para garantizar su seguridad.

9. Reemplazo de Pacientes

Aquellos pacientes que decidan abandonar el estudio antes de la administración de la droga serán reemplazados, de ser necesario, para asegurar un número adecuado de pacientes evaluables.

10. Justificación del tamaño muestral y análisis estadístico

Existe una incertidumbre significativa en el tamaño del efecto esperado de la intervención, y considerando que se espera que el ensayo se complete en un período de tiempo relativamente corto, el estudio está diseñado para tener un análisis intermedio cuando los resultados del 50% de los sujetos hayan sido adquiridos.

Dada la relativa complejidad de implementar esta intervención, la diferencia mínimamente importante clínicamente se establece en una reducción relativa del 40%, para una tasa de resultado esperada del 50% en el grupo control que se reduce al 30% en el grupo de intervención. Un tamaño de muestra total de 210 sujetos (105 por brazo

de prueba) tendrá una potencia del 80%, a un nivel de significancia (alfa) de 0.05 utilizando una prueba z de dos lados con corrección de continuidad. Estos resultados suponen que se realizan 2 pruebas secuenciales utilizando la función de gasto O'Brien-Fleming para determinar los límites de la prueba, como se describe en la tabla a continuación.

Look	Time	Lower Bndry	Upper Bndry	Nominal Alpha	Power
1	0.50	-2.96259	2.96259	0.003	0.168
2	1.00	-1.96857	1.96857	0.049	0.806

Bajo la estrategia de análisis primario, usaremos la distribución de límite de producto de Kaplan-Meier para comparar los grupos de tratamiento durante el tiempo necesario para alcanzar el resultado primario. También se informará una estimación del riesgo relativo y el intervalo de confianza del 95%.

11. Artículo de prueba y medicina transfusional

11.1. Donación voluntaria de plasma de convaleciente

Todos los procedimientos se harán acorde al PLAN ESTRATÉGICO PARA REGULAR EL USO DE PLASMA DE PACIENTES RECUPERADOS DE COVID-19 CON FINES TERAPÉUTICOS. (IF-2020-26315442-APN-SCS#MS)

https://www.boletinoficial.gob.ar/detalleAviso/primera/227976/20200418

El plasma de convaleciente se obtendrá invitando a participar como donante voluntario a pacientes que hayan padecido la enfermedad COVID-19 y se hayan recuperado satisfactoriamente en la Ciudad Autónoma y Provincia de Buenos Aires siguiendo los criterios de donación establecidos por las autoridades. Si el paciente desea donar, de forma voluntaria y altruista firmara el consentimiento de donación de plasma (ANEXO).

Los donantes serán identificados por las autoridades ministeriales e institucionales si se trata de un organismo privado, contactados, e invitados a donar en uno de los cinco Bancos de Sangre participantes de este estudio:

a) Instituto de Hemoterapia de la Provincia de La Plata
b) Hospital Militar Central
c) Fundación Hemocentro Buenos Aires
d) Fundación Hematológica Sarmiento
e) CEMIC

Para poder donar plasma, el paciente debe cumplir con las condiciones determinadas a la fecha (https://www.boletinoficial.gob.ar/detalleAviso/primera/227976/20200418) o seguir la actualización de ellas que realice el Ministerio.

Titulación de anticuerpos anti-SARS CoV2

Tras el proceso de la donación de plasma por aféresis o hemodonación, adicionalmente a las muestras que se toman para controles de rutina del banco de sangre, se obtendrá un tubo seco de 5 mL de sangre entera rotulados con la identificación dada al donante, identificación del Banco de Sangre y etiqueta que identifica la finalidad del estudio "PCC19" para la realización del título de anticuerpos. Estos se realizarán mediante el ensayo de ELISA anti-proteína S de SARS CoV2, que a luz de los datos existentes sobre protección contra el virus permiten una extrapolación indirecta de la capacidad de neutralización del suero, optimizado por el Instituto Leloir a cargo de la Dra. Gamarnik, y actualmente utilizado por los equipos de salud nacionales para estudiar prevalencia de inmunidad. Asimismo, de ser posible, se correlacionará este dato con el título de anticuerpos neutralizantes contra un pseudovirus codificando la proteína S optimizado por el mismo laboratorio.

El tubo será almacenado en un lugar designado dentro del Banco y enviado en un transporte autorizado de muestras biológicas al laboratorio de la Fundación INFANT (con más de 18 años de experiencia en realización de ensayos de estas características) donde se realizará la técnica de ELISA y la titulación de anticuerpos neutralizantes.

Los títulos obtenidos por ELISA de S serán luego clasificados y aquellos que estén por encima de 1:1.000 seleccionados para proveer plasma de convaleciente para este estudio.

Los plasmas de alto título adicionales serán almacenados asimismo para enviar al Centro de Hemoderivados de Córdoba (UNC) que producirá gammaglobulina enriquecida con anticuerpos anti-SARS-CoV2.

Plasmaféresis (Instituto de Hemoterapia de la Provincia de La Plata, Hospital Militar Central, Fundación Hemocentro Buenos Aires, y Fundación Hematológica Sarmiento)

La donación de plasma se efectuará a través de un procedimiento de aféresis con equipos e insumos descartables aprobados para tal fin, durante el cual se recomienda extraer un volumen no mayor al 15% de la volemia del donante. El anticoagulante a

utilizar será ACD-A o similar. En los casos en que no se realizare la reposición del volumen, la extracción de plasma no deberá superar los 600 ml por procedimiento.
Se deberá respetar el intervalo de 48 hs. entre cada procedimiento, y no superar las 2 donaciones en una semana o 24 donaciones en un periodo de 12 meses.
Las unidades de PCC19 se podrán separar en alícuotas de 300ml respetando el circuito cerrado y siguiendo las indicaciones del procedimiento operativo estándar vigente.

Hemodonación (CEMIC)

1-La obtención de plasma se realizará con un equipo Cobe Spectra. Se extraerán 1,5 a 2 L de plasma de acuerdo al peso y tolerancia al procedimiento del donante. En caso de inaccesibilidad venosa u oposición del donante, se extraerá entre 400 y 500 ml de sangre entera (hemodonación clásica)
2-El reemplazo de volumen se efectuará con solución fisiológica y de albúmina.
3-Durante el procedimiento el plasma será derivado a bolsas de transferencia de similar volumen cada una (aproximadamente 500ml). Se denominará Bolsa 1 a la inicialmente obtenida, Bolsa 2 la media y Bolsa 3 la final.
4-Las bolsas recolectadas serán rotuladas como detallado abajo
5-Se congelarán en el ultrafreezer vertical Righi de -56°C (rotulado como Freezer # I, identificado con rótulo de plasma de convaleciente COVID-19, en el Banco de Sangre) separadas en estantes por tipo de bolsa (1, 2 o 3).
6-El plasma de convaleciente permanecerá almacenado hasta su uso o caducidad (1 año), con criterios de seguridad apropiados.
7-El descarte se efectuará bajo normas de seguridad que se estipulen.
8- Se guardarán alícuotas de suero/plasma para futuras determinaciones congelado a -80°C, en tubos de Eppendorf del PC de las diferentes etapas, y congelados y almacenados a -80°C: Previo al procedimiento de aféresis de las bolsas 1, 2 y 3 (previo al congelamiento) luego del descongelamiento de las bolsas 1, 2 y 3.

Etiquetado

Todas las unidades de PC COVID-19 deben cumplir con el etiquetado requerido para el plasma fresco congelado de cada Banco de Sangre y además deberán tener una clara identificación, en la que deberá constar:

- "Tipo de Producto: PC COVID-19"
- "Resultado de título de anticuerpos para SARS-Cov-2" (si están disponibles)
- "PRECAUCIÓN: producto de uso exclusivo para investigación"
- "PROTOCOLO: Fundación INFANT – Suero enriquecido con anticuerpos anti SARS-CoV2"

Cadena de Frío de PCCOVID-19

1. Las unidades se almacenarán debidamente separadas del resto de las unidades de plasma habilitadas para uso transfusional, en un lugar claramente identificado para tal fin.

2. Las unidades de PCC19 se almacenarán a temperatura inferior a -25C, la cual permite un almacenamiento de 36 meses y entre -18C y -25C para 3 meses de almacenamiento.

3. El transporte de las unidades se realizará de forma tal que se garantice fehacientemente el mantenimiento de la cadena de frío.

4. La conservación de las unidades de plasma una vez descongeladas deberá realizarse entre 2 y 6ºC hasta las 24 horas de finalizado el descongelamiento. Pasado ese tiempo, se deberán descartar.

Trazabilidad

El Banco de Sangre y el Servicio de Transfusión de la Institución solicitante implementarán un sistema de registros que garantice la trazabilidad entre donantes y receptores. En esta situación especial, además, deberán disponer de un registro específico por tratarse de una terapia transfusional administrada en un contexto experimental.

11.2. Administración de la intervención

Una vez evaluados los signos vitales y verificada la elegibilidad, el equipo no ciego de Medicina Transfusional Central será notificado del resultado del proceso de asignación aleatoria y se trasladará al hospital asignado con el producto de tratamiento enmascarado y en frío. Al arribar procederá nuevamente verificar el código de tratamiento asignado con el miembro de laboratorio de Medicina Transfusional del hospital correspondiente (ver 5.2.c).

Como placebo, se utilizarán 250 ml de solución salina al 0,9% estéril enmascarada y administrada de la misma forma y velocidad que el plasma. Para evitar sesgos y mantener el ciego del estudio, el plasma y la solución salina al 0,9% serán enmascarados, utilizando una bolsa opaca y cinta que no permitirán diferenciar de qué producto se trata. El miembro de Medicina Transfusional Central será quien entregue al

miembro del equipo local para que administre la intervención en conjunto con el equipo central. De esta manera tanto los miembros de Medicina Transfusional Central como los miembros de Medicina Transfusional de los hospitales serán no ciegos, mientras que todo el resto del equipo delegado en funciones en el estudio en cada Centro de Investigación como los pacientes serán ciegos a la intervención.

Para preparar el plasma, se descongelará la bolsa de 250 ml a 37°C, según procedimientos operativos del Departamento de Medicina Transfusional del Hospital. Se infundirá al receptor en forma lenta (en no menos de 3 horas y hasta 4 horas) de acuerdo a las condiciones hemodinámicas del paciente y se monitorearán por 12 horas y registrarán los efectos adversos tempranos y tardíos atribuibles a la transfusión.

Monitoreo de eventos adversos asociados a la transfusión de plasma

Sobrecarga circulatoria asociada a transfusión (TACO)

La sobrecarga circulatoria asociada a transfusión (transfusion-associated circulatory overload, TACO) es la complicación pulmonar más frecuente y es un factor de riesgo independiente para morbimortalidad hospitalaria, con mayor incidencia en pacientes críticos [58]. La frecuencia estimada de TACO varía del 1% a 5% según el sistema de hemovigilancia sea [59], hasta los 8% en pacientes post quirúrgicos de avanzada, y 11% en pacientes críticos [60 61 62]. Los factores de riesgo incluyen enfermedad cardíaca, pulmonar o renal, edad ≥70 años y un balance de fluidos positivo, pre transfusional [63 64]. La mayoría de los casos de TACO se previenen disminuyendo la velocidad de transfusión y la instauración de las medidas habituales para sobrecarga hídrica en poblaciones susceptibles. La sobrecarga constituye un EA solicitado, pero de no mejorar en el curso de 120 minutos después de la infusión o de requerir -a juicio de los profesionales responsables- el paso del paciente a cuidados intensivos por mala progresión clínica a causa de dicha sobrecarga, deberá informarse de inmediato como un EAS.

Criterios diagnósticos de TACO [19]

Durante o hasta 12 horas posteriores a la transfusión, TACO se caracteriza por la presencia de un total de 3 o más de los criterios listados:

A. Compromiso respiratorio agudo o que empeora

B. Evidencia de edema pulmonar agudo o que empeora basado en la clínica y / o imágenes radiográficas del tórax y / u otra evaluación no invasiva de la función cardíaca (ecocardiograma)

C. Evidencia de cambios cardiovasculares no explicados por la condición médica subyacente del paciente, incluido: taquicardia, hipertensión, presión de pulso

ensanchada, distensión venosa yugular, silueta cardíaca agrandada y / o edema periférico
D. Evidencia de sobrecarga de líquidos, incluyendo cualquiera de los siguientes: un balance positivo de líquidos; respuesta a la terapia diurética, o diálisis combinada con mejoría clínica; y variación del peso del paciente
E. Aumento del nivel de péptido natriurético de tipo B (por ejemplo, BNP o NT-pro BNP) por encima del rango de referencia específico del grupo de edad y mayor de 1,5 veces el valor de pre transfusión.

Injuria Pulmonar Aguda Asociada a Transfusión (TRALI)

Es un síndrome de dificultad respiratoria aguda, será considerado un EAS y ocurre durante o dentro de las seis horas posteriores a la administración de la transfusión. Estudios prospectivos de TRALI en diversas encontraron tasas de incidencia muy bajas (0,0008% a 0,001% de pacientes transfundidos) [19] después de la implementación de estrategias para prevenir la transfusión de componentes de la sangre obtenido de donantes femeninas multíparas. En nuestro estudio no se transfundirá plasma convaleciente de mujeres multíparas.
El tratamiento del paciente con TRALI incluye la interrupción inmediata de la transfusión.

Criterios diagnósticos de TRALI: [28]

TRALI Tipo I: pacientes que no tienen factores de riesgo de SDRA y cumplen con los siguientes criterios:
A. i. Inicio agudo
ii. Hipoxemia (PaO_2 / FiO_2 ≤ 300 o SpO_2 <90% en aire ambiente).
iii. Evidencia clara de edema pulmonar bilateral en imágenes (radiografía de tórax, tac o ecografía)
iv. No hay evidencia de hipertrofia ventricular izquierda o, si está presente, no es la principal contribuyente de la hipoxemia
B. Inicio durante o dentro de las 6 horas de la transfusión
C. Sin relación temporal con un factor de riesgo alternativo para SDRA
TRALI Tipo II: pacientes que tienen factores de riesgo de SDRA (pero que no han sido diagnosticados con SDRA) o que tienen SDRA leve existente (Pa / Fi de 200-300), pero cuyo estado respiratorio se deteriora y se considera que se debe a una transfusión basado en:
a. Los resultados descritos en las categorías a y b de TRALI Tipo I, y
b. Estado respiratorio estable en las 12 horas previas a la transfusión

Reacciones Alérgicas – Anafilácticas

Las reacciones alérgicas ocurren en general durante o dentro de las 4 horas posteriores a la transfusión y están más frecuentemente asociadas a la transfusión de plaquetas (302 cada 100 000 unidades de plaquetas) [29]. Los síntomas son causados por mediadores como la histamina, liberados en la activación de mastocitos y basófilos [30]. En general la presentación clínica es leve (erupción cutánea, prurito, urticaria, y angioedema localizado) y constituye un EA solicitado. Las reacciones transfusionales alérgicas leves en general resuelven con la administración del tratamiento habitual para reacciones alérgicas, pudiendo reiniciar la infusión de la unidad. La transfusión debe suspenderse si los síntomas reaparecen. La incidencia de reacciones anafilácticas es de 8/100,000 unidades de plaquetas transfundidas. Las reacciones más severas generalmente se presentan con broncoespasmo, dificultad respiratoria e hipotensión y constituyen un EAS y debe ser reportado como tal inmediatamente [31-35].

Reacciones transfusionales hemolíticas agudas

Las reacciones de transfusionales hemolíticas agudas (RTHA) pueden ocurrir cuando se transfunden glóbulos rojos incompatibles o en menor frecuencia, grandes cantidades de plasma incompatible con el ABO del paciente. El mecanismo fisiopatológico central es la hemólisis intravascular y se considerará un EAS. Se presenta con fiebre repentina y escalofríos, dolor retroperitoneal y disnea, hemoglobinuria y hasta coagulación intravascular diseminada, insuficiencia renal aguda y shock. Dado que la fiebre y los escalofríos pueden ser los únicos signos tempranos, es importante controlar al paciente durante la transfusión y detenerla transfusión inmediatamente si hay algún cambio en los signos vitales o ante la aparición de síntomas inesperados. El tratamiento se basa en medidas de sostén para mitigar los síntomas. La identificación adecuada del paciente y el cumplimiento de todos los procesos relacionados con el manejo de muestras pre-transfusionales y con la administración de la transfusión, son esenciales para prevenir la RTHA [36].

Infecciones Transmisibles por Transfusión [39]

El riesgo de transmisión de enfermedades infecciosas por transfusiones se ha reducido dramáticamente, secundario a los grandes avances en el testeo de las unidades, inactivación de patógenos para unidades de plasma y sus componentes [51] y a la implementación de rigurosos métodos de selección de donantes. En nuestro medio, las muestras son testeadas para HBV, HCV, HIV, HTLV y *Trypanosoma cruzi* [52]. En Estados Unidos, el riesgo de adquirir HBV y HIV por transfusión es de 1:280.000 y 1:1.467.000, respectivamente [53 54]. Gracias al congelamiento de las muestras de plasma, la contaminación de las mismas por patógenos bacterianos y CMV es extremadamente rara. Hay solo una decena de casos entre los millones de transfusiones realizadas, reportados en Alemania y Canadá de transmisión bacteriana. Se estima que la fuente potencial de esta contaminación habrían sido los baños de

agua utilizados para el descongelamiento de las unidades. Esto es fácilmente evitable con la limpieza y esterilización correctas de los descongeladores [39].

12. Consideraciones éticas

Declaración de Buena Práctica Clínica

Este estudio se llevará a cabo de conformidad con el protocolo y con las siguientes consideraciones:

- los principios éticos que tienen su origen en la Declaración de Helsinki,
- las pautas vigentes de las buenas prácticas clínicas (Good Clinical Practice, GCP) del Consejo Internacional de Armonización (International Council of Harmonisation, ICH),
- las leyes y regulaciones vigentes.

El protocolo, los formularios de Consentimiento Informado (FCI) y otros documentos relevantes han sido revisados y aprobados por Fundación INFANT, las autoridades participantes y enviados al Comité de Ética (CE) para su evaluación.

Comité de ética (CE):

Un CE debidamente constituido, como se describe en las pautas de ICH para GCP, debe revisar y aprobar:

- El protocolo, FCI y cualquier otro material que se proporcione a los participantes antes de que cualquier sujeto pueda ingresar en el estudio
- Cualquier enmienda o modificación al protocolo de estudio o al FCI antes de la implementación, a menos que el cambio sea necesario para eliminar un peligro inmediato para los pacientes, en cuyo caso el CE debe ser informado lo antes posible

Además, debe ser informado de cualquier evento que pueda afectar la seguridad de los pacientes o la realización continua del estudio clínico.

INFANT debe recibir una copia de la carta de aprobación del CE antes de enviar los suministros de medicamentos al investigador de cada hospital. La carta de aprobación debe incluir el título del estudio, los documentos revisados y la fecha de la revisión.

El investigador debe mantener en el archivo los registros de la revisión del CE y la aprobación de todos los documentos del estudio

Proceso de Consentimiento Informado

El FCI utilizado por el investigador será el aprobado por el CE correspondiente.

Es responsabilidad del investigador o profesional delegado obtener el consentimiento informado por escrito de cada sujeto antes de su participación en el estudio y después de que los objetivos, procedimientos y riesgos potenciales del estudio se han explicado completamente en un lenguaje que el sujeto pueda entender. El FCI debe estar firmado y fechado por el investigador o personal delegado que realizó el proceso de toma de consentimiento.

El investigador o personal delegado le explicará al participante la naturaleza del estudio y responderá todas las preguntas sobre el estudio. Les informará que su participación es voluntaria. El participante deberá firmar el formulario de consentimiento informado (FCI) antes de que se realice cualquier actividad específica del estudio.

A los participantes que pueden entender pero que no pueden escribir y/o leer se les leerá el CI en presencia de un testigo imparcial, que firmará y fechará el FCI para confirmar que se obtuvo el consentimiento informado.

Se firmarán dos ejemplares. El investigador debe conservar un ejemplar como parte del registro del estudio del paciente, y se debe entregar el otro ejemplar firmado al participante.

13. Confidencialidad y Protección de Datos Personales

El investigador tomará todas las medidas apropiadas para garantizar que se mantenga el anonimato de cada sujeto del estudio en los registros para investigación transmitidos fuera del centro de salud. Los documentos originales y esenciales del estudio deben mantenerse en estricta confidencialidad en cada centro de investigación por el equipo del estudio.

Los datos personales de los participantes se almacenarán en el centro del estudio en un formato impreso y/o electrónico protegidos por contraseña o en un cuarto bajo llave, para garantizar el acceso exclusivo del personal autorizado del estudio.

Para proteger los derechos y las libertades de las personas físicas en relación con el tratamiento de datos personales, se asignará a los participantes un código alfanumérico único y específico. Los registros o conjuntos de datos de los participantes que se transfieran contendrán el código alfanumérico; los nombres de los participantes no se transferirán. Todos los demás datos identificables transferidos entre los investigadores se identificarán mediante este código único y específico del participante. El centro del estudio mantendrá una lista confidencial de los participantes que participaron en el

estudio bajo estricta seguridad (protegidos por contraseña o en un cuarto bajo llave), vinculando el código alfanumérico de cada participante con su identidad real.

14. Documentación del Estudio

Los registros y los documentos, incluidos los FCI firmados, respecto a la realización de este estudio, serán conservados por el investigador durante 15 años después de la finalización del estudio, a menos que las regulaciones locales o las políticas institucionales requieran un período de conservación más prolongado.
El investigador de cada institución participante deberá consultar con INFANT antes de descartar o destruir cualquier documento esencial del estudio después de la finalización o interrupción del estudio. En caso de ser aprobado, los registros deben destruirse de manera que se garantice la confidencialidad.

15. Monitoreo de estudio

15.1. Monitoreo de sitios de estudio

El monitor del estudio visitará cada sitio antes de inscribir al primer paciente y periódicamente durante el estudio de acuerdo con el Plan de Monitoreo del Estudio Aprobado.

El monitor recibirá semanalmente de cada uno de los centros un informe con el número de pacientes en periodo de pesquisa y enrolados y verificará que el envió de datos se encuentre al día y completo, realizando de ser necesario seguimiento a cada uno de los centros.

Cada centro contará con una persona designada por el Investigador a verificar procesos realizados bajo protocolo y datos originales y se documentará dicha verificación por escrito.

Las visitas de monitoreo y las actividades de monitoreo centralizado se realizarán de acuerdo con todos los requisitos reglamentarios aplicables y normas vigentes en Argentina. Se entiende que el monitor contactará a cada investigador y a su equipo responsable regularmente y se le permitirá verificar la generación de los distintos registros del estudio.

Será responsabilidad del monitor inspeccionar los sistemas de captura de datos a intervalos regulares durante todo el estudio para verificar el cumplimiento del protocolo y la integridad, precisión y consistencia de los datos; y adhesión al ICH GCP y normativa local sobre la realización de investigaciones clínicas. El monitor debe tener

acceso a informes de laboratorio, medicación de estudio, registros asociados con él, y otros registros médicos necesario para verificar las entradas en el EDC.

Se asignará un **monitor no ciego** cuyo rol estará limitado a auditar los datos de logística manejo y registro del tratamiento de estudio de acuerdo con el protocolo aprobado y las instrucciones de tratamiento:

- recepción y condiciones de almacenaje
- randomización y administración
- retorno o destrucción/ reconciliación final

15.2. Requisitos del documento fuente

Se requiere que los investigadores preparen y mantengan registros de pacientes adecuados y precisos (documentos fuente).

El investigador debe mantener todos los documentos fuente en el archivo de los datos volcados al formulario del estudio (CRF). Algunos datos generados del estudio podrán volcarse directamente en el sistema de EDC (captura directa de datos), previa aprobación de dicho proceso por los Comités de Ética intervinientes. Los formularios de informes de casos y los documentos fuente deben estar disponibles en todo momento.

15.3. Requisitos del formulario de informe de caso

Los datos del estudio obtenidos en el curso del estudio serán registrados en formularios de informes de casos (CRF) y enviados a INFANT en formato scan. Una vez recibidos serán archivados y procesados mediante el ingresados al del sistema EDC por personal capacitado de INFANT. Todos los CRF requeridos deben completarse para cada paciente inscrito en el estudio. El investigador debe conservar una copia del libro de casos de CRF de cada paciente como parte del registro del estudio y debe estar disponible en todo momento para su inspección por parte de representantes autorizados del patrocinador y las autoridades reguladoras.

16.. Auditorias e inspecciones

Este estudio puede estar sujeto a una auditoría o inspección de garantía de calidad. Si esto ocurre, el investigador es responsable de:

- Brindar acceso a todas las instalaciones, datos de estudio y documentos necesarios para la inspección o auditoría.
- Comunicar cualquier información que surja de la inspección de las autoridades reguladoras a INFANT de inmediato.
- Tomar todas las medidas apropiadas solicitadas por INFANT para resolver los problemas encontrados durante la auditoría o inspección.

Los documentos sujetos a auditoría o inspección incluyen, entre otros, todos los documentos fuente, CRF, registros médicos, correspondencia, FCI, archivos del CE, documentación de certificación y control de calidad de laboratorios de apoyo, y registros relevantes para el estudio que se mantienen Instalaciones de farmacia. Las condiciones de almacenamiento del material de estudio también están sujetas a inspección. Además, los representantes del patrocinador pueden observar la conducta de cualquier aspecto del estudio clínico o sus actividades de apoyo tanto dentro como fuera de la institución del investigador.

En todos los casos, se debe respetar la confidencialidad de los datos.

ANEXO

INSUFICIENCIA CARDIACA
ESCALA NYHA (NEW YORK HEART ASSOCIATION)
VALORACIÓN FUNCIONAL DE INSUFICIENCIA CARDÍACA.

CLASIFICACIÓN FUNCIONAL	

NYHA	
Clase I	Sin limitación de la actividad física. El ejercicio físico normal no causa fatiga, palpitaciones o disnea.
Clase II	Ligera limitación de la actividad física. Sin síntomas en reposo. La actividad ordinaria ocasiona fatiga, palpitaciones o disnea.
Clase III	Marcada limitación de la actividad física. Sin síntomas en reposo. Actividad física menor que la ordinaria ocasiona fatiga, palpitaciones o disnea.
Clase IV	Incapacidad para llevar a cabo cualquier actividad física; los síntomas de insuficiencia cardíaca están presentes incluso en reposo y aumentan con cualquier actividad física.

CIRROSIS (CONSENSO HIPERTENSION PORTAL BAVENO IV)

ESTADIOS DE CIRROSIS	
Estadío 1	Ausencia de varices esofágicas y de ascitis
Estadío 2	Varices esofágicas sin antecedente de hemorragia y sin ascitis.
Estadío 3	Presencia de ascitis con o sin varices esofágicas.
Estadío 4	Hemorragia gastrointestinal por hipertensión portal, con o sin ascitis.

ENFERMEDAD RENAL CLASIFCIACION KDIGO.

GRADO	FILTRACIÓN GLOMERULAR ML/MIN/1,73 M2	DESCRIPCION
GRADO 1	> 90 G5	Normal o elevado
GRADO 2	60-89	Ligeramente disminuido

GRADO 3a	45-59	Ligera a moderadamente disminuido
GRADO 3b	30-44	Moderada a gravemente disminuido
GRADO 4	15-29	Gravemente disminuido
GRADO 5	< 15	Fallo renal

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EVALUACIÓN DE LA EFICACIA DE LA ADMINISTRACIÓN DE PLASMA DE CONVALECIENTE DE COVID-19 EN LA DISMINUCIÓN DE LA PROGRESIÓN A ENFERMEDAD SEVERA EN ADULTOS MAYORES CON SÍNTOMAS LEVES POR SARS-COV2

Investigador Principal Hospital Central de San Isidro: Dr. Ramiro Larrea
Investigador Principal Hospital Dr. Carlos Bocalandro: Dr. Aníbal Rondan
Investigador Principal Hospital Simplemente Evita: Dra. Valeria Fernández Viña
Investigador Principal Hospital Evita Pueblo: Dra. Sandra Azcárate
Investigador Principal Hospital San Juan de Dios: Dra. Ivonne Ritou
Investigador Principal Centros COVID-PAMI: Dr. Gonzalo Perez Marc
Investigador Principal del Programa: Dr. Fernando P. Polack (INFANT)

Co-Investigadores: Dra. Romina Libster (INFANT/CONICET), Dr. Gonzalo Pérez Marc (HMC), Dr. Diego Wappner (SMG), Dr. Jorge Lantos (Los Arcos), Dr. Ricardo Valentini (CEMIC), Dr. Federico Etchenique (Ecco), Dr. Maximiliano De Zan (OSECAC), Dr. Gabriel Leberzstein (OSECAC), Dr. Miguel González (Finochietto), Dra. Andrea Gamarnik (Leloir/CONICET), Dr. Jorge Geffner (UBA/CONICET), Bioq. Silvina Coviello (INFANT), Dr. Mauricio Caballero (INFANT/CONICET), Dr. Damián Alvarez Paggi (INFANT/CONICET), Dr. Sebastián Esperante (INFANT/CONICET), Dr. Federico Dimase (HMC), Dra. Susana Pastor Argüello (HMC), Dr. Juan Molinos (Clínica Olivos), Dr. Pablo Cruz (Centro Gallego), Dra. María Dolores Silveyra (Sanatorio Anchorena), Dr. Alfonso Raggio (Sanatorio Antártida), Dr. Juan Sebastián Riera (Ministerio de Salud de la Provincia de Buenos Aires), Dr. Enio García (Ministerio de Salud de la Provincia de Buenos Aires), Dr. Juan Canela (Ministerio de Salud de la Provincia de Buenos Aires), Dr. Mario Rovere (Ministerio de Salud de la Provincia de Buenos Aires), Dr. Fernando Althabe (OMS), Dr. Eduardo Bergel (IECS),

Asesores: Dr. Daniel Stamboulian (FUNCEI)

1. INTRODUCCIÓN

SARS-CoV2 es un virus nuevo y particularmente agresivo para individuos de edad avanzada, quienes representan entre el 73 y 90% de los casos fatales en distintas regiones del mundo [28, 30, 40]. La mortalidad, la necesidad de cuidados intensivos, la ventilación mecánica, el requerimiento de oxígeno, y las hospitalizaciones por enfermedad respiratoria aumentan marcadamente con el avance de la edad en los pacientes [2, 3, 29, 32, 46]. De hecho, la frecuencia de muerte por enfermedad por SARS-CoV2 (covid-19) es del 8% en los pacientes entre 70 y 80 años, y aumenta a 14,8% en los mayores de 80 [23]. Específicamente en pacientes hospitalizados mayores de 75 años, la mortalidad es de 29,4% [24], y en la terapia intensiva asciende a un alarmante 43,5% [25]. Varias comorbilidades asociadas con enfermedad vascular y/o pulmonar agravan el pronóstico de los infectados aun en pacientes menores de 70, incluyendo hipertensión arterial, diabetes, obesidad y enfermedad pulmonar obstructiva crónica (EPOC) [3,23,30,31]. A la fecha, el virus ha causado más de 290.000 muertes en el mundo, más de 300 de ellas en Argentina donde se encuentra contenido a través de una estrategia transitoria de cuarentena cuasi-universal [4]. No existe aún ningún tratamiento específico disponible. Los resultados de los ensayos de eficacia para vacunas contra SARS-CoV2 se conocerán dentro de mínimamente 10-14 meses.

El SARS-CoV2 es un virus envuelto que contiene ARN monocatenario en sentido positivo unido a una nucleoproteína (proteína N), dentro de una cápside compuesta por proteínas de la matriz (proteína M). La envoltura posee glicoproteínas en forma de espinas (proteína S) que se unen al receptor celular ACE2 en humanos y generan anticuerpos neutralizantes [13]. La primo infección por SARS-CoV2, como otras enfermedades respiratorias, genera una respuesta de anticuerpos con producción temprana de IgM seguida de IgG específica contra las proteínas virales [14]. La detección de anticuerpos neutralizantes del virus es frecuente, y alcanza niveles altos de hasta 1:21,500 $PRNT_{50}$, mayormente excediendo títulos de 1:500 después de 28 días del inicio de síntomas en pacientes leves [41]. Aproximadamente 5% de los pacientes presentan niveles de anticuerpos neutralizantes <1:40, especialmente los más jóvenes [41]. Un estudio de infección primaria vía respiratoria en macacos Rhesus, utilizando 10^6 pfu de SARS-CoV2 seguido de un segundo desafío intratraqueal usando el mismo virus y dosis 28 días más tarde, demostró ausencia de reinfección tras una extensa evaluación por RT-PCR de tejidos post-necropsia [42]. Los títulos neutralizantes antes del segundo inóculo variaban entre 1:8-1:16 $PRNT_{50}$ [42]. **Estos hallazgos - limitados por**

cierto, dada la novedad del problema- sugieren que aún bajos títulos de anticuerpos neutralizantes podrían prevenir la enfermedad severa por el virus.

Proteger a las poblaciones más vulnerables al SARS-CoV2 es imperioso, en el contexto de un germen altamente infeccioso (R_0 estimado entre 2 y 3,28) [27, 33, 34]. Su contagiosidad desborda rápidamente la capacidad sanitaria de países desarrollados en distintas regiones del mundo [5] y amenaza los recursos sanitarios de países en vías de desarrollo [6]. Regiones de Italia, España y Estados Unidos se han visto desbordadas por la pandemia, que representa una seria amenaza para Argentina, en coincidencia con el inicio de la circulación anual de otros patógenos pulmonares, como la gripe común y el virus sincicial respiratorio [26]. Evidentemente, resultaría imposible dar respuesta a una avalancha de pacientes graves [7], y toda estrategia tendiente a disminuir las infecciones y el desarrollo de enfermedad severa **se alinea directamente con el objetivo médico de salvar vidas y con las necesidades sanitarias del país para poder brindar la mejor atención posible a aquellos pacientes que lo necesiten**.

La profilaxis post-exposición a virus y el tratamiento en fases tempranas de enfermedad, a través de defensas obtenidas en plasma de convalecientes, es una práctica extendida con antecedentes exitosos en la historia de la medicina a nivel nacional y global. Ya en 1960, Brunell y col. lograron prevenir la varicela clínica en hermanos con padres enfermos, usando inmunoglobulinas anti-varicela zoster obtenidas del plasma de pacientes previamente infectados [8]. Hoy mismo, por ejemplo, la inmunoglobulina enriquecida para sarampión se utiliza en personas no vacunadas que estuvieron en contacto con un enfermo durante los 6 días previos con una eficacia cercana al 100% [9, 52]; un producto similar enriquecido para el virus de varicela zoster se administra en embarazadas, recién nacidos, e inmunosuprimidos no vacunados en contacto con infectados dentro de las 96 horas disminuyendo un 90% la incidencia de enfermedad grave [10, 53, 54]; la inmunoglobulina antitetánica suplementa la vacunación en víctimas de heridas sucias con inmunización primaria incompleta [43]; la gammaglobulina contra hepatitis B se utiliza como prevención para recién nacidos de madres infectadas con una eficacia del 75% [44, 55]; y la gammaglobulina antirrábica es ~100% efectiva en la profilaxis posterior a la agresión de un animal sospechoso [11,56]. **Las intervenciones utilizando inmunidad humana derivada del plasma de convalecientes han demostrado ser seguras, han prevenido innumerables casos de enfermedad severa, y han preservado vidas en todo el mundo.**

El objetivo principal de nuestro estudio es evaluar la eficacia del plasma de convaleciente en reducir la progresión a enfermedad severa en personas entre 65-74 años con al menos una comorbilidad y en todos los ≥ 75 años que se presenten con sintomatología leve de menos de 48 hs de evolución al momento del inicio de la pesquisa y reciban diagnóstico temprano de COVID-19. *Nuestra hipótesis central es que una dosis única de plasma de convaleciente comparada contra placebo (solución salina al 0,9%), y administrada hasta 72 horas después del inicio de los síntomas por SARS-Cov2 (o sea, hasta 24 horas después del límite de tiempo para presentarse a pesquisa y testeo), prevendrá la progresión a una enfermedad respiratoria severa en sujetos entre 65-74 años con al menos una comorbilidad y en los ≥ 75 años independientemente de presencia de comorbilidad basal.*

2. OBJETIVOS DEL ESTUDIO

2.1. Objetivo Primario

Evaluar la eficacia del plasma de convaleciente, a partir de 12 horas de la administración, en reducir la progresión a enfermedad respiratoria severa en personas entre 65-74 años con al menos una comorbilidad y en todos los ≥ de 75 años con sintomatología leve y diagnóstico temprano de COVID-19 hasta los 15 días de administración del tratamiento (16-18 días de enfermedad considerando el periodo sintomático pre-enrolamiento),

2.2. Objetivos Secundarios

Los Objetivos Secundarios incluyen determinar si la administración de plasma de convaleciente hasta los 15 días o a partir de entonces hasta un máximo de *25 días de la administración de tratamiento si continuase internado* consigue:

- Disminuir la necesidad de soporte de oxígeno con oxigenoterapia máxima (mascara de reservorio de O2) y/o utilización de soporte respiratorio no invasivo (soporte de VNI incluyendo CPAP) y/o admisión a UTI y/o requerimiento de ventilación mecánica invasiva por SARS-CoV2 en pacientes entre 65-74 años con al menos una comorbilidad y en todos los ≥ 75 años
- Disminuir la enfermedad crítica definida como (a) presencia de falla respiratoria aguda (PaO2/FiO2 ≤ 200 mm Hg.) y/o (b) shock (definido por necesidades de soporte con drogas vasoactivas para mantener P.A.M. igual o mayor a 65 mm. Hg), y/o (c) síndrome de disfunción multiorgánica (SDMO): injuria renal aguda (definida por aumento de creatinina por dos o más veces con respecto al basal o aumento de creatinina 0.3 mg/dl), elevación de

enzimas hepáticas (transaminasas) mayor a tres veces el valor superior normal, miocardiopatía aguda (definida por elevación de troponina por encima del nivel normal y/o nuevas alteraciones electrocardiográficas o ecocardiográficas para daño miocárdico) por SARS-Cov2 en pacientes entre 65-74 años con al menos una comorbilidad y en todos los ≥ 75 años a causa de COVID-19.

- Disminuir la mortalidad por SARS-CoV2 en pacientes entre 65-74 años con al menos una comorbilidad y en todos los ≥ 75 años a causa de COVID-19.
- Disminuir la duración de soporte de oxigeno debido a covid-19 en pacientes hipoxémicos.
- Describir la seguridad de la administración de plasma de convaleciente en pacientes entre 65-74 años con al menos una comorbilidad y en todos los ≥ 75 años con COVID-19.
- Explorar la concentración de IgG anti-S de SARS CoV2 en plasma de los participantes asociada con ausencia de enfermedad respiratoria severa obtenidas a las 24 horas de la infusión.

2.3. Objetivos Exploratorios

- Explorar si, en lugar de proteger contra la enfermedad respiratoria severa, la administración de plasma de convaleciente retarda la aparición de dicha enfermedad.
- Explorar los efectos del plasma de convaleciente sobre la respuesta inmune humoral primaria contra la infección por SARS CoV2. a los 90 días de enrolamiento
- Explorar si los efectos en enfermedad respiratoria, cardiovascular y mortalidad a largo plazo fueron afectados por la intervención a los 12 meses de enrolamiento.
- Explorar la correlación entre carga viral determinada por RT-PCR al diagnóstico y la respuesta a tratamiento con plasma.

3. CRITERIOS DE VALORACIÓN DE EFICACIA

3.1.1. Criterio Primario de Valoración de Eficacia

Enfermedad respiratoria severa por SARS-CoV2, confirmada por detección de ARN viral por RT-PCR, y definida por la presencia de cualquiera de las dos siguientes variables en forma no excluyente: (a) frecuencia respiratoria ≥30 por minuto, (b) saturación de oxígeno en aire ambiental <93% [20,21]. El endpoint primario se determinará a partir de 12 horas del inicio de la infusión hasta 15 días desde la administración del tratamiento.

3.1.2. Criterios Secundarios de Valoración de Eficacia *(hasta los 15 días o, a partir de entonces, hasta un máximo de 25 días de la administración de tratamiento si continuase internado)*

- Necesidad de soporte de oxígeno con oxigenoterapia máxima (mascara de reservorio de O2) y/o soporte respiratorio no invasivo (soporte de VNI incluyendo CPAP) y/o admisión a UTI y/o requerimiento de ventilación mecánica invasiva, por SARS-Cov2.
- Enfermedad crítica definida como (a) presencia de falla respiratoria aguda ($PaO2/FiO_2$ ≤ 200 mmHg.) y/o (b) shock, y/o (c) síndrome de disfunción multiorgánica (SDMO) según criterios detallados en sección 2.2: injuria renal aguda, elevación de enzimas hepáticas, miocardiopatía aguda, por SARS-Cov2.
- Mortalidad por covid-19.
- <u>Combinación</u> de los criterios secundarios de valoración de eficacia #1 (necesidad de soporte de oxigeno con…) y/o #2 (enfermedad critica definida…) y/o #3 (mortalidad por covid-19).
- Duración del requerimiento de soporte de oxigeno en pacientes con covid-19 debido a saturación en aire ambiental <93%.

4. HIPÓTESIS Y JUSTIFICACIÓN

4.1. Hipótesis

Nuestra hipótesis central es que una dosis de plasma de convaleciente comparada contra placebo, y administrada hasta 72 horas desde el inicio de los síntomas leves, prevendrá la progresión a enfermedad respiratoria severa por covid-19 en pacientes

entre 65-74 años con al menos una comorbilidad y en todos los ≥ 75 años que se presenten con menos de 48 horas de evolución al proceso de pesquisa y con sintomatología leve.

4.2. Justificación

La eficacia de una preparación terapéutica contra el SARS-CoV2 económicamente accesible analizada mediante un estudio aleatorizado, doble ciego, en pacientes vulnerables permitiría escalar de inmediato su aplicabilidad a nivel nacional e internacional mediante campañas masivas de donación de plasma de convalecientes a la espera de soluciones definitivas tales como medicamentos exitosos, anticuerpos monoclonales, o vacunas [17]. Inclusive, de existir protección parcial concentrada en el tracto respiratorio inferior [18], *esta misma estrategia podría hipotéticamente permitir la inmunización de los sujetos mediante la replicación controlada del germen en el tracto respiratorio alto* (como en el caso de la administración pasiva de anticuerpos contra el virus sincicial respiratorio en lactantes [19]).

5. DISEÑO DEL ESTUDIO

Un estudio aleatorizado, doble-ciego, controlado con placebo para testear la eficacia del plasma de convaleciente, administrado hasta 72 horas después del inicio de síntomas, con el fin de evitar la progresión hacia una enfermedad respiratoria severa. El estudio se llevará a cabo en sujetos entre 65-74 años con al menos una comorbilidad y en todos los ≥ 75 años que se presenten con sintomatología leve de menos de 48 horas de evolución al momento de la pesquisa (definida en sección 5.1) y diagnóstico precoz de covid-19. El estudio se realizará durante un período de observación mínimo de 15 días en el que los participantes permanecerán bajo control médico diario por protocolo para determinar el criterio de valoración primario. El período de monitoreo se extenderá a partir de entonces, hasta un máximo de 25 días de la administración de tratamiento, si continuase internado, para analizar los criterios de valoración de eficacia secundarios.

Se proyecta que el estudio incorpore un máximo estimado de 210 pacientes (ver 9.0 Tamaño muestral). Los participantes serán aleatorizados en una proporción de 1:1.

Tabla 1. Asignaciones de Tratamiento

Grupo de Tratamiento	Rango de sujetos asignados por rama	Artículo de Prueba	Volumen de Dosificación intravenoso	Día de Administración de la intervención
A	105	Placebo		

		(solución salina al 0,9%)	250 cc	Día 0
B	105	Plasma de convaleciente		

Todos los participantes recibirán una dosis única endovenosa (EV) - acorde a las NORMAS ADMINISTRATIVAS Y TÉCNICAS RM 797/13 – 139/14 – 1507/15 Dirección de Sangre y Hemoderivados Ministerio de Salud de la Nación (por http://www.msal.gob.ar/disahe/images/stories/pdf/normas-hemoterapia.pdf) el Día 0 con el artículo de prueba asignado, plasma de convaleciente o placebo (ver Tabla 1). Para cada sujeto, la participación en el estudio se extenderá un mínimo de 15 días o hasta la resolución de síntomas desde la administración del artículo de prueba con un máximo de 25 días. Los sujetos participantes serán monitoreados durante y después de la administración del artículo de prueba para evaluar eventos de seguridad esperables y no esperables luego de la administración de plasma. Un Comité de Monitoreo de Datos y Seguridad supervisará el enrolamiento, la eficacia y la seguridad de los participantes a lo largo del estudio.

El estudio se llevará a cabo en el Hospital San Juan de Dios, el Hospital Simplemente Evita, el Hospital Dr. Carlos Bocalandro, el Hospital Evita Pueblo, el Hospital Central de San Isidro y el Sanatorio Antártida de la Provincia de Buenos Aires en estrecha coordinación con los efectores sanitarios del Ministerio de Salud provincial y en el Hospital Militar Central, el Sanatorio de Los Arcos, CEMIC, el Centro de Investigación OSECAC, el Sanatorio Finochietto, el Centro Gallego de Buenos Aires, el Sanatorio Anchorena y la Clínica Olivos garantizando que no se interferirá con los cuidados y las normas de atención de pacientes dispuestas para la notificación y manejo de esta enfermedad.

EQUIPO MOVIL-COVID. Dado el contexto de la situación covid-19 en el AMBA con la reducción de disponibilidad de camas y la sobrecarga del personal hospitalario sumado al aumento exponencial de los casos graves, los pacientes levemente sintomáticos pero sin requerimientos de oxígeno y provenientes de geriátricos encuentran extraordinariamente difícil (casi imposible) su internación en los hospitales. Por tanto, para facilitar la incorporación de los principales beneficiarios potenciales de esta intervención al estudio (es decir, los ancianos mas vulnerables) y dada la enorme necesidad de salud publica existente para proveer alternativas terapéuticas contra este flagelo, se agregara una unidad COVID-Móvil que monitoreará participantes voluntarios en Centros COVID-PAMI donde la administración del producto de investigación (hoy

demostrado claramente como seguro en publicaciones de más de 20.000 pacientes) se realizará bajo las mismas normas y por el mismo equipo que en todos los otros sitios de investigación y el equipo COVID-Móvil registrara la evolución de dichos participantes que se encuentran bajo el cuidado de médicos y personal de salud del PAMI *in situ*. Todo traslado de estos pacientes a centros de mayor complejidad por la evolución natural de su enfermedad será decisión de los médicos tratantes del PAMI, y el equipo de investigación móvil se limitará a continuar recabando datos de su progreso clínico de la misma forma que lo hace hoy cuando un paciente es trasladado o recibe un alta temprana en otra institución.

5.1. Criterios de elegibilidad

5.1.1 Criterios de Inclusión:

Un sujeto debe cumplir los siguientes criterios para ser incluido en el estudio:

1. Edad ≥ 75 años o edad entre 65-74 años con al menos una de las comorbilidades siguientes:
   a. Diagnóstico de hipertensión arterial bajo tratamiento farmacológico.
   b. Diagnóstico conocido de diabetes en tratamiento con algunas de las drogas disponibles (Apéndice I).
   c. Obesidad (IMC -Índice de masa corporal- ≥ a 30 kg/m2),
   d. Diagnóstico de enfermedad pulmonar obstructiva crónica (EPOC) en tratamiento con algunas de las drogas disponibles (Apéndice I).
   e. Enfermedad cardiovascular establecida definida como a) diagnóstico conocido de enfermedad coronaria, b) historia de enfermedad cerebrovascular isquémica o hemorrágica, o c) ICC (definida como FE < 40%).
   f. Enfermedad renal crónica (definida como reducción del FG por debajo de 60 ml/min/1,73 m^2).
2. Presentar <u>hace menos de 48 horas</u>: (A)Temperatura axilar ≥37,5°C o equivalente febril (definido por sensación de frío y/o escalofríos y/o sudoración inexplicada), <u>combinado con</u> (a) tos seca y/o (b) dificultad respiratoria y/o (c) odinofagia y/o (d) anosmia/disgeusia y/o (e) alguno de los siguientes síntomas: fatiga, anorexia, mialgias o rinorrea.
3. Diagnóstico de SARS-Cov2 confirmado por RT-PCR

4. Ser capaz, según juicio médico, de comprender y cumplir con los procedimientos del estudio y de consentir o no su participación.
5. Proveer consentimiento informado por sí mismo.
6. Pacientes con vulnerabilidad cognitiva con apoyo en la toma de decisión por su representante según corresponda. (ver sección 12)

5.1.2 Criterios de Exclusión

Un sujeto que cumple cualquiera de los siguientes criterios será excluido del estudio:

1. Que presente al momento del ingreso ENFERMEDAD RESPIRATORIA SEVERA definida como (a) frecuencia respiratoria ≥30 por minuto y/o (b) saturación de oxígeno en aire ambiental <93%.
2. INSUFICIENCIA CARDIACA en clase funcional III y IV (según clasificación funcional de la New York Heart Association).
3. Diagnóstico conocido de INSUFICIENCIA RENAL CRÓNICA en estadios de filtrado G4 y G5 (según clasificación KDIGO).
4. Diagnóstico previo de HIPOGAMMAGLOBULINEMIAS PRIMARIAS (congénitas y hereditarias).
5. Diagnóstico previo de GAMMAPATÍAS MONOCLONALES (mieloma múltiple, macroglobulinemia de Waldenström, amiloidosis primaria, enfermedad de las cadenas pesadas, entre otras).
6. Diagnóstico previo de DEFICIENCIA SELECTIVA DE IgA.
7. Diagnóstico previo de SÍNDROMES MIELODISPLÁSICOS. [clasificación OMS: trombocitopenia refractaria (TR), anemia refractaria (AR), etc.]
8. Diagnóstico previo de SÍNDROMES LINFOPROLIFERATIVOS CRÓNICOS. (clasificación OMS: linfomas periféricos de linfocitos B, linfomas de linfocitos T y células NK, Linfoma de Hodgkin).
9. HIPERSENSIBILIDAD CONOCIDA a la administración de inmunoglobulinas, plasma, anticuerpos monoclonales y/o vacunas.
10. Cáncer activo, definido por estar recibiendo o haber recibido o estar recibiendo quimioterapia, radioterapia o tratamientos con drogas nuevas de diseño o monoclonales en los últimos seis meses.
11. Infección conocida por HIV, HBV o HCV.
12. Administración crónica (definida como más de 14 días corridos) de inmunosupresores u otras drogas que modifican el sistema inmune **al momento del enrolamiento** o dentro de los 6 meses previos a la administración de la medicación del estudio. Una dosis inmunosupresora de glucocorticoides se

definirá como una dosis sistémica ≥10mg de prednisona por día o su equivalente.

13. Antecedente de transplante de órgano sólido.
14. Enfermedad hepática crónica conocida con diagnóstico de cirrosis estadio II-III-IV.
15. Enfermedad pulmonar crónica con requerimiento de oxígeno.
16. Cualquier otra condición física, psiquiátrica o social que pueda, a criterio del investigador, aumentar los riesgos por la participación en el estudio a los participantes o que puedan conducir a la recolección de datos de seguridad incompletos o inexactos.
17. Pacientes que estén recibiendo cualquier tipo de terapia anticoagulante sea por vía oral; familia de los dicumarínicos (Warfarina como Acenocumarol) o anticoagulantes de acción directa (ACOD) (Rivaroxaban, Dabigatran, Apixaban) así como tampoco aquellos que estén recibiendo heparina en cualquiera de sus tipos con fines de terapia anticoagulante.

5.2. Procedimientos del estudio (Tabla 2)

5.2.a. Población participante y proceso de identificación de potenciales sujetos.

Sujetos entre 65-74 años con al menos una comorbilidad y todos los ≥ 75 años que presenten hace menos de 48 hs alguno de los siguientes síntomas: (**a**) temperatura ≥37,5°C o equivalente febril (definido por sensación de frío o escalofríos o sudoración inexplicada), combinado con (**b**) tos seca y/o disnea y/o anosmia/disgeusia y/o odinofagia y/o fatiga y/o anorexia y/o mialgias y/o rinorrea.

Dichos candidatos serán invitados a contactarse de inmediato con el fin de evaluar su participación a través de los números designados por las organizaciones intervinientes.

Aquellos pacientes que cumplan con los criterios de inclusión y no cumplan ninguno de los criterios de exclusión arriba mencionados serán invitados a participar en la fase de pesquisa del estudio en el cual, en caso de aceptar (plasmando su conformidad a través de la firma del consentimiento informado de pesquisa - ANEXO), se obtendrá una muestra de secreción respiratoria por medio de hisopados nasofaríngeo y orofaríngeo (de acuerdo al procedimiento y normativa implementada por el Ministerio de Salud) para detectar ARN de SARS-CoV2 por la prueba de cadena de la polimerasa (RT-PCR).

Dicha muestra será procesada y analizada por los laboratorios intervinientes designados para las instituciones participantes, y que actualmente proveen este mismo servicio diagnostico diariamente, utilizando el mismo test de RT-PCR para evaluar la presencia de ARN de SARS-CoV2. Esta determinación se realizará lo antes posible (en

un máximo de 24 horas) y, tal como hasta hoy, bajo todas las normas de bioseguridad indicadas por las autoridades sanitarias. Las muestras se conservarán para posterior testeo por RT-PCR de co-infecciones con influenza A y B, virus sincicial respiratorio y otros patógenos virales de invierno en la Fundación INFANT.

Aquellos pacientes que ya cuenten con un resultado positivo (+) y considerado válido podrán ser invitados a participar de la fase de pesquisa del estudio y no serán hisopados nuevamente.

5.2.b. Enrolamiento para la participación en el estudio

En caso de detectarse en la muestra respiratoria ARN de SARS-CoV2, se informará al candidato sobre los detalles del estudio y se verificará su elegibilidad nuevamente. El candidato podrá decidir no participar de la investigación según su libre albedrío y sin consecuencia alguna de ningún tipo. En caso de que el sujeto esté interesado en participar en el estudio, y tras su consentimiento atestado con la firma del consentimiento informado de participación (ANEXO), se procederá a asignarle un número de identificación único. Una vez asignado su código alfanumérico, se procederá a obtener los signos vitales y realizar un examen físico completo para obtener la siguiente información demográfica y clínica [1-3, 25, 47-51]:

- Sexo
- Edad
- Medicaciones habituales y de los últimos 15 días.
- Antecedentes de tabaquismo
- Comorbilidades de interés primario: hipertensión arterial, diabetes, enfermedad coronaria, insuficiencia cardíaca, antecedentes de ACV e IAM, EPOC, nefropatía crónica, y obesidad**.**
- Comorbilidades secundarias: asma, antecedentes de cáncer, enfermedades hepáticas, y enfermedades neurológicas**.**

5.2.c. Asignación aleatoria

Todos los participantes con elegibilidad confirmada serán asignados aleatoriamente a un grupo de tratamiento. La asignación aleatoria de sujetos participantes se realizará utilizando un sistema electrónico por el encargado de aleatorización del estudio. Una vez aleatorizado el paciente, el encargado de la asignación se comunicará con un miembro del equipo de Medicina Transfusional Central del estudio quien procederá a extraer la bolsa opaca de tratamiento indicada del freezer del Laboratorio Central. El

equipo de Medicina Transfusional procederá a llevar dicha bolsa en frío al hospital asignado. Allí completará la preparación del producto enmascarado y administrará el tratamiento indicado al paciente participante utilizando para su infusión un acceso venoso previamente obtenido por un miembro del equipo del hospital. Solo este equipo (el encargado de aleatorización y el encargado de Medicina Transfusional Central de administrar el tratamiento) conocerán el producto a administrar a cada paciente (equipo no ciego). Ni el paciente ni los investigadores tendrán conocimiento del tratamiento administrado, realizando un estudio de doble ciego. El equipo no ciego llevará un registro de las asignaciones de producto y sus administraciones que será guardado de manera confidencial. En la eventual necesidad de una ruptura de ciego se podrá recurrir a dichos registros.

5.2.d. Preparación y administración del artículo de prueba

La preparación y administración del plasma de convaleciente o placebo (solución fisiológica) se realizará acorde a las NORMAS ADMINISTRATIVAS Y TÉCNICAS RM 797/13 – 139/14 – 1507/15 Dirección de Sangre y Hemoderivados Ministerio de Salud de la Nación. (http://www.msal.gob.ar/disahe/images/stories/pdf/normas-hemoterapia.pdf).

Una vez enmascarado el producto, el equipo de Medicina Transfusional lo administrará en forma endovenosa lenta al paciente durante un mínimo de 1,5 horas y hasta 2 horas de acuerdo a las normas. Luego de la administración se monitoreará la ocurrencia de reacciones locales en el sitio de inyección y sistémicas por 12 horas. *Este es un estudio de mínimo riesgo, ya que la administración de plasma y de solución salina (placebo en este estudio) son de hábito diario en la práctica médica.* En el caso de una emergencia médica, cuando se tenga conocimiento de que la asignación de tratamiento puede influir en la atención médica del paciente, el investigador o la persona designada pueden solicitar que se rompa el ciego para el sujeto que está experimentando la emergencia. Sin embargo, antes del quiebre de ciego el investigador debe realizar todos los esfuerzos razonables de ponerse en contacto con la persona designada para discutir la decisión de quebrar el ciego. Se espera que el investigador proporcione una razón para la necesidad de romper el ciego, en base a un cambio significativo en la atención médica inmediata o de corto plazo del participante que resultará del conocimiento de la asignación del tratamiento.

5.2.e. Toma de muestra de sangre para titulación de IgG anti-S SARS CoV2 en suero.

A las 24 horas de completada la infusión del tratamiento, se obtendrá una muestra de 5 ml de sangre venosa de todos los participantes para la titulación en suero de IgG anti-S SARS-CoV2, a realizarse en la Fundación INFANT por método ELISA (COVIDAR IgG, Leloir/CONICET). El suero se preservará a -20°C hasta su traslado en frío por un sistema de transporte autorizado para manejo de muestras biológicas a la Fundación.

Ventana de toma de muestra: +/- 4 horas. La muestra podrá tomarse en un plazo mínimo de 20 hs y uno máximo de 28 horas post-finalización de la administración del Producto de Investigación.

5.2.f. Seguimiento clínico diario

Se realizará un control diario a partir del Dia 0, y por lo menos durante 15 días desde la infusión y hasta 25 días para aquellos sujetos que continúan hospitalizados a partir del día 15. Aquellos pacientes que sean dados de alta previo al día 15, serán monitoreados por un equipo de médicos domiciliarios entrenados para tal fin que trabajarán en colaboración con los centros de investigación. La siguiente información clínica se recolectará diariamente (utilizando un cuestionario diseñado para tal fin) por personal del estudio y **sin interferir con la atención médica del paciente ni alterar las normas recomendadas por las autoridades sanitarias para el manejo de los pacientes con COVID-19**: (a) frecuencia respiratoria (mirando como excursiona el tórax durante 30 segundos), (b) saturación de oxígeno, (c) temperatura, (d) frecuencia cardiaca central, (e) tos y duración, (f) dolor de garganta y duración, (g) sensación de fiebre/escalofríos, (h) necesidad de provisión de oxígeno suplementario y duración, (i) necesidad de cuidados intensivos y duración, (j) necesidad de asistencia respiratoria no invasiva o invasiva y duración, (k) evidencia de SDMO: según criterios de injuria renal aguda, criterios de elevación de enzimas hepáticas y criterios de miocardiopatía aguda (detallados en sección 2.2), (l) sobrevida.

Tabla 2. Cronograma de procedimientos del estudio.

Día del Estudio	-1 Pesquisa	0 Día 0	Seguimiento Diario
Consentimiento informado de pesquisa para la evaluación de antecedentes, condición clínica y diagnóstico *SARS-CoV2*	X		

Toma de hisopado nasofaríngeo para confirmación diagnóstica de SARS-CoV2 por RT-PCR	X(1)		
Consentimiento informado de participación en el estudio		X	
Revisión de historia médica		X	X
Signos vitales		X	
Confirmación de elegibilidad		X	
Medicamentos concomitantes		X	X
Asignación aleatoria de tratamiento		X	
Administración de la intervención		X	
Monitoreo de la transfusión		X	
Vigilancia de eventos adversos		X*	(X)
Toma de muestra de sangre luego de completada la infusión			Única muestra a las 24 hs (+/- 4 hs)
Vigilancia de síntomas respiratorios		X	X

(1) Este procedimiento no será requerido si se encuentra un resultado disponible por un método valido al momento de pesquisar el paciente

Se considerará que el paciente completa su participación al llegar el día 15 (si el paciente ya está dado de alta), al alta hospitalaria entre el día 15 y el día 25 o al cumplirse el día 25 de continuar hospitalizado.

6. Comité Independiente de Monitoreo de Datos

Un Comité Independiente de Monitoreo de Datos supervisará la seguridad de los sujetos durante todo el estudio. El CIMD incluirá, como mínimo, miembros con experiencia en el manejo de medicina interna, enfermedades infecciosas, y un bio-estadístico con experiencia específica en el diseño, análisis y monitoreo de seguridad de estudios clínicos. El CIMD operará bajo un plan aprobado y tendrá la responsabilidad de monitorear las medidas de resultado / puntos finales, eventos adversos (EA) y eventos adversos serios (EAS), y recomendar la finalización del estudio si aparece en algún momento durante el estudio que los participantes (o un subgrupo de participantes) se encuentran en riesgo indebido como resultado de su

participación. El CIMD se reunirá (por teleconferencia) semanalmente para revisar el acumulado de datos sobre seguridad y eficacia y realizará un análisis interino de los datos. El CIMD emitirá recomendaciones escritas en base a sus reuniones acerca de la continuidad del estudio. Las actas de cada reunión se registrarán en minutas documentadas en base a una agenda de trabajo preestablecida. Cualquier información de salud protegida específica del participante revisado por el CIMD se mantendrá completamente confidencial. Las sesiones serán cerradas sin acceso a terceros.

7. Monitoreo de Seguridad

El investigador en cada institución y a nivel general supervisará la seguridad del paciente del estudio en su(s) sitio(s) según los requisitos de este protocolo y de acuerdo con las Buenas Prácticas Clínicas (GCP) actuales. El investigador monitoreará los datos de seguridad en todos los sitios de estudio. El monitoreo de seguridad se realizará de manera continua (por ejemplo, revisión individual de EAS, EAs y puntos finales) y de forma acumulada periódica.

Evento adverso (EA)

Un EA es cualquier acontecimiento médico desfavorable en un paciente al que se le administró un fármaco del estudio que puede tener o no una relación causal con el fármaco del estudio. Por lo tanto, una EA es cualquier signo desfavorable e involuntario (incluido el hallazgo anormal de laboratorio), síntoma o enfermedad que se asocia temporalmente con el uso de un medicamento del estudio, independientemente de si se considera relacionado con el medicamento del estudio.

Un EA también incluye cualquier empeoramiento (es decir, cualquier cambio clínicamente significativo en la frecuencia y / o intensidad) de una afección preexistente que se asocia temporalmente con el uso del producto en investigación.

La progresión de covid-19 no se considerará un EA si es claramente coherente con el patrón de progresión típico de la enfermedad

Si existe alguna incertidumbre acerca de que un EA se deba solo a la progresión de covid-19, se informará como un EA o EAS como se describe en la sección respectiva.

Evento adverso serio (EAS)

Un EAS, por definición, es cualquier evento médico desfavorable que a cualquier dosis:

- Resulte en la muerte: incluye todas las muertes, incluso aquellas que parecen no tener relación alguna con el fármaco del estudio (por ejemplo, un accidente automovilístico en el que un paciente es pasajero).
- Es potencialmente mortal: en opinión del investigador, el paciente corre un riesgo inmediato de muerte en el momento del evento. Esto no incluye un AE que si hubiera ocurrido en una forma más severa, podría haber causado la muerte.
- Requiere hospitalización o prolongación de la hospitalización existente. La hospitalización se define como el ingreso a un hospital o sala de emergencias por más de 24 horas. La prolongación de la hospitalización existente se define como una estadía en el hospital que es más larga de lo previsto originalmente para el evento, o se prolonga debido al desarrollo de un nuevo EA según lo determinado por el investigador o el médico tratante.
- Resulta en discapacidad/incapacidad persistente o significativa (interrupción sustancial de la capacidad de uno para llevar a cabo funciones normales de la vida).
- Es un evento médico importante: los eventos médicos importantes pueden no poner en peligro la vida de inmediato o provocar la muerte u hospitalización, pero pueden poner en peligro al paciente o pueden requerir intervención para prevenir uno de los otros resultados graves enumerados anteriormente (por ejemplo, tratamiento intensivo en una emergencia o en casa para broncoespasmo alérgico; discrasias sanguíneas que no resultan en hospitalización).

En el caso específico de este estudio se considerarán como EA o EAS, según la descripción detallada en la sección 11.2, aquellos que se inicien dentro de las 12 horas posteriores a la administración del tratamiento y los agravamientos clínicos y muertes asociadas con estos eventos. No se considerarán EA o EAS aquellos eventos clínicos que se inicien luego de las 12 horas de iniciación del tratamiento, que constituirán parte de la evolución clínica de los pacientes enrolados infectados con SARS CoV2.

Periodo de Recolección de Eventos Adversos

El período de informe EA / EAS comienza cuando el participante se incluye inicialmente en el estudio (fecha de firma del consentimiento informado de participación) y recibe la infusión y continuará para los eventos que se inicien en las siguientes 12 horas desde su inicio (ver sección 11.2). Durante el seguimiento posterior a las 12 horas iniciales de

la administración del producto de investigación, se monitoreará la evolución clínica asociada a los criterios de valoración primario y secundarios.

8. Abandono Prematuro del Estudio

Los sujetos podrán abandonar el estudio en cualquier momento si así lo deseasen, pero serán igualmente monitoreados durante el periodo estipulado para garantizar su seguridad.

9. Reemplazo de Pacientes

Aquellos pacientes que decidan abandonar el estudio antes de la administración de la droga serán reemplazados, de ser necesario, para asegurar un número adecuado de pacientes evaluables.

10. Justificación del tamaño muestral y análisis estadístico

Existe una incertidumbre significativa en el tamaño del efecto esperado de la intervención, y considerando que se espera que el ensayo se complete en un período de tiempo relativamente corto, el estudio está diseñado para tener un análisis intermedio cuando los resultados del 50% de los sujetos hayan sido adquiridos.

Dada la relativa complejidad de implementar esta intervención, la diferencia mínimamente importante clínicamente se establece en una reducción relativa del 40%, para una tasa de resultado esperada del 50% en el grupo control que se reduce al 30% en el grupo de intervención. Un tamaño de muestra total de 210 sujetos (105 por brazo de prueba) tendrá una potencia del 80%, a un nivel de significancia (alfa) de 0.05 utilizando una prueba z de dos lados con corrección de continuidad. Estos resultados suponen que se realizan 2 pruebas secuenciales utilizando la función de gasto O'Brien-Fleming para determinar los límites de la prueba, como se describe en la tabla a continuación.

Look	Time	Lower Bndry	Upper Bndry	Nominal Alpha	Power
1	0.50	-2.96259	2.96259	0.003	0.168
2	1.00	-1.96857	1.96857	0.049	0.806

Bajo la estrategia de análisis primario, usaremos la distribución de límite de producto de Kaplan-Meier para comparar los grupos de tratamiento durante el tiempo necesario para alcanzar el resultado primario. También se informará una estimación del riesgo relativo y el intervalo de confianza del 95%.

Por recomendación del Comité Independiente de Monitoreo de Seguridad, se realizará además un análisis estratificado por edad (65-74 años y ≥75 años) y se ajustará el análisis estadístico por aquellos factores de riesgo cuya distribución entre grupos pueda afectar el resultado.

11. Artículo de prueba y medicina transfusional

11.1. Donación voluntaria de plasma de convaleciente

Todos los procedimientos se harán acorde al PLAN ESTRATÉGICO PARA REGULAR EL USO DE PLASMA DE PACIENTES RECUPERADOS DE COVID-19 CON FINES TERAPÉUTICOS. (IF-2020-26315442-APN-SCS#MS)

https://www.boletinoficial.gob.ar/detalleAviso/primera/227976/20200418

El plasma de convaleciente se obtendrá invitando a participar como donante voluntario a pacientes que hayan padecido la enfermedad covid-19 y se hayan recuperado satisfactoriamente en la Ciudad Autónoma y Provincia de Buenos Aires siguiendo los criterios de donación establecidos por las autoridades. Si el paciente desea donar, de forma voluntaria y altruista firmara el consentimiento de donación de plasma (ANEXO).

Los donantes serán identificados por las autoridades ministeriales e institucionales si se trata de un organismo privado, contactados, e invitados a donar en uno de los cinco Bancos de Sangre participantes de este estudio:

a) Instituto de Hemoterapia de la Provincia de La Plata
b) Hospital Militar Central
c) Fundación Hemocentro Buenos Aires
d) Fundación Hematológica Sarmiento
e) CEMIC

Para poder donar plasma, el paciente debe cumplir con las condiciones determinadas a la fecha (https://www.boletinoficial.gob.ar/detalleAviso/primera/227976/20200418) o seguir la actualización de ellas que realice el Ministerio.

Titulación de anticuerpos anti-SARS Cov2

Tras el proceso de la donación de plasma por aféresis o hemodonación, adicionalmente a las muestras que se toman para controles de rutina del banco de sangre, se obtendrá un tubo seco de 5 mL de sangre entera rotulados con la identificación dada al donante, identificación del Banco de Sangre y etiqueta que identifica la finalidad del estudio "PCC19" para la realización del título de anticuerpos. Estos se realizarán mediante el ensayo de ELISA anti-proteína S de SARS CoV2, que a luz de los datos existentes sobre protección contra el virus permiten una extrapolación indirecta de la capacidad de neutralización del suero, optimizado por el Instituto Leloir a cargo de la Dra. Gamarnik, y actualmente utilizado por los equipos de salud nacionales para estudiar prevalencia de inmunidad. Asimismo, de ser posible, se correlacionará este dato con el título de anticuerpos neutralizantes contra un pseudovirus codificando la proteína S optimizado por el mismo laboratorio.

El tubo será almacenado en un lugar designado dentro del Banco y enviado en un transporte autorizado de muestras biológicas al laboratorio de la Fundación INFANT (con más de 18 años de experiencia en realización de ensayos de estas características) donde se realizará la técnica de ELISA y la titulación de anticuerpos neutralizantes.

Los títulos obtenidos por ELISA de S serán luego clasificados y aquellos que estén por encima de 1:1.000 seleccionados para proveer plasma de convaleciente para este estudio.

Los plasmas de alto título adicionales serán almacenados asimismo para enviar al Centro de Hemoderivados de Córdoba (UNC) que producirá gammaglobulina enriquecida con anticuerpos anti-SARS-CoV2.

Plasmaféresis (Instituto de Hemoterapia de la Provincia de La Plata, Hospital Militar Central, Fundación Hemocentro Buenos Aires, y Fundación Hematológica Sarmiento)

La donación de plasma se efectuará a través de un procedimiento de aféresis con equipos e insumos descartables aprobados para tal fin, durante el cual se recomienda extraer un volumen no mayor al 15% de la volemia del donante. El anticoagulante a utilizar será ACD-A o similar. En los casos en que no se realizare la reposición del volumen, la extracción de plasma no deberá superar los 600 ml por procedimiento.
Se deberá respetar el intervalo de 48 hs. entre cada procedimiento, y no superar las 2 donaciones en una semana o 24 donaciones en un periodo de 12 meses.
Las unidades de PCC19 se podrán separar en alícuotas de 300ml respetando el circuito cerrado y siguiendo las indicaciones del procedimiento operativo estándar vigente.

Hemodonación (CEMIC)

1-La obtención de plasma se realizará con un equipo Cobe Spectra. Se extraerán 1,5 a 2 L de plasma de acuerdo al peso y tolerancia al procedimiento del donante. En caso de inaccesibilidad venosa u oposición del donante, se extraerá entre 400 y 500 ml de sangre entera (hemodonación clásica)
2-El reemplazo de volumen se efectuará con solución fisiológica y de albúmina.
3-Durante el procedimiento el plasma será derivado a bolsas de transferencia de similar volumen cada una (aproximadamente 500ml). Se denominará Bolsa 1 a la inicialmente obtenida, Bolsa 2 la media y Bolsa 3 la final.
4-Las bolsas recolectadas serán rotuladas como detallado abajo
5-Se congelarán en el ultrafreezer vertical Righi de -56°C (rotulado como Freezer # I, identificado con rótulo de plasma de convaleciente COVID-19, en el Banco de Sangre) separadas en estantes por tipo de bolsa (1, 2 o 3).
6-El plasma de convaleciente permanecerá almacenado hasta su uso o caducidad (1 año), con criterios de seguridad apropiados.
7-El descarte se efectuará bajo normas de seguridad que se estipulen.
8- Se guardarán alícuotas de suero/plasma para futuras determinaciones congelado a -80°C, en tubos de Eppendorf del PC de las diferentes etapas, y congelados y almacenados a -80°C: Previo al procedimiento de aféresis de las bolsas 1, 2 y 3 (previo al congelamiento) luego del descongelamiento de las bolsas 1, 2 y 3.

Etiquetado

Todas las unidades de PC COVID-19 deben cumplir con el etiquetado requerido para el plasma fresco congelado de cada Banco de Sangre y además deberán tener una clara identificación, en la que deberá constar:

- "Tipo de Producto: PC COVID-19"
- "Resultado de título de anticuerpos para SARS-Cov-2" (si están disponibles)
- "PRECAUCIÓN: producto de uso exclusivo para investigación"
- "PROTOCOLO: Fundación INFANT – Suero enriquecido con anticuerpos anti SARS-CoV2"

Cadena de Frío de PCCOVID-19

1. Las unidades se almacenarán debidamente separadas del resto de las unidades de plasma habilitadas para uso transfusional, en un lugar claramente identificado para tal fin.

2. Las unidades de PCC19 se almacenarán a temperatura inferior a -25 C, la cual permite un almacenamiento de 36 meses y entre -18C y -25 para 3 meses de almacenamiento.

3. El transporte de las unidades se realizará de forma tal que se garantice fehacientemente el mantenimiento de la cadena de frío.

4. La conservación de las unidades de plasma una vez descongeladas deberá realizarse entre 2 y 6ºC hasta las 24 horas de finalizado el descongelamiento. Pasado ese tiempo, se deberán descartar.

Trazabilidad

El Banco de Sangre y el Servicio de Transfusión de la Institución solicitante implementarán un sistema de registros que garantice la trazabilidad entre donantes y receptores. En esta situación especial, además, deberán disponer de un registro específico por tratarse de una terapia transfusional administrada en un contexto experimental.

11.2. Administración de la intervención

Una vez evaluados los signos vitales y verificada la elegibilidad, el equipo no ciego de Medicina Transfusional Central será notificado del resultado del proceso de asignación aleatoria y se trasladará al hospital asignado con el producto de tratamiento enmascarado y en frío. Al arribar procederá nuevamente verificar el código de tratamiento asignado con el miembro de laboratorio de Medicina Transfusional del hospital correspondiente (ver 5.2.c).

Como placebo, se utilizarán 250 ml de solución salina al 0,9% estéril enmascarada y administrada de la misma forma y velocidad que el plasma. Para evitar sesgos y mantener el ciego del estudio, el plasma y la solución salina al 0,9% serán enmascarados, utilizando una bolsa opaca y cinta que no permitirán diferenciar de qué producto se trata. El miembro de Medicina Transfusional Central será quien entregue al miembro del equipo local para que administre la intervención en conjunto con el equipo central. De esta manera tanto los miembros de Medicina Transfusional Central como los miembros de Medicina Transfusional de los hospitales serán no ciegos, mientras que todo el resto del equipo delegado en funciones en el estudios en cada Centro de Investigación como los pacientes serán ciegos a la intervención.

Para preparar el plasma, se descongelará la bolsa de 250 ml a 37°C, según procedimientos operativos del Departamento de Medicina Transfusional del Hospital.

Se infundirá al receptor en forma lenta (en no menos de 1.5 horas y hasta 2 horas) de acuerdo a las condiciones hemodinámicas del paciente y se monitorearán por 12 horas y registrarán los efectos adversos tempranos y tardíos atribuibles a la transfusión.

Ventana nocturna para pasaje del producto de investigación: entre las 20.00 hs y las 8.00 hs, se tolerará una ventana de +8 horas para el pasaje del Producto de investigación. Siendo posible un máximo de 80 hs (72+8) de comienzo de síntomas al momento del inicio de la infusión. Esta excepción sólo será permitida en este rango horario nocturno.

Monitoreo de eventos adversos asociados a la transfusión de plasma

Sobrecarga circulatoria asociada a transfusión (TACO)

La sobrecarga circulatoria asociada a transfusión (transfusion-associated circulatory overload, TACO) es la complicación pulmonar más frecuente y es un factor de riesgo independiente para morbimortalidad hospitalaria, con mayor incidencia en pacientes críticos [58]. La frecuencia estimada de TACO varía del 1% a 5% según el sistema de hemovigilancia sea [59], hasta los 8% en pacientes post quirúrgicos de avanzada, y 11% en pacientes críticos [60 61 62]. Los factores de riesgo incluyen enfermedad cardíaca, pulmonar o renal, edad ≥70 años y un balance de fluidos positivo, pre transfusional [63 64]. La mayoría de los casos de TACO se previenen disminuyendo la velocidad de transfusión y la instauración de las medidas habituales para sobrecarga hídrica en poblaciones susceptibles. La sobrecarga constituye un EA solicitado, pero de no mejorar en el curso de 120 minutos después de la infusión o de requerir -a juicio de los profesionales responsables- el paso del paciente a cuidados intensivos por mala progresión clínica a causa de dicha sobrecarga, deberá informarse de inmediato como un EAS.

Criterios diagnósticos de TACO [19]

Durante o hasta 12 horas posteriores a la transfusión, TACO se caracteriza por la presencia de un total de 3 o más de los criterios listados:

A. Compromiso respiratorio agudo o que empeora

B. Evidencia de edema pulmonar agudo o que empeora basado en la clínica y / o imágenes radiográficas del tórax y / u otra evaluación no invasiva de la función cardíaca (ecocardiograma)

C. Evidencia de cambios cardiovasculares no explicados por la condición médica subyacente del paciente, incluido: taquicardia, hipertensión, presión de pulso ensanchada, distensión venosa yugular, silueta cardíaca agrandada y / o edema periférico

D. Evidencia de sobrecarga de líquidos, incluyendo cualquiera de los siguientes: un balance positivo de líquidos; respuesta a la terapia diurética, o diálisis combinada con mejoría clínica; y variación del peso del paciente

E. Aumento del nivel de péptido natriurético de tipo B (por ejemplo, BNP o NT-pro BNP) por encima del rango de referencia específico del grupo de edad y mayor de 1,5 veces el valor de pre transfusión.

Injuria Pulmonar Aguda Asociada a Transfusión (TRALI)

Es un síndrome de dificultad respiratoria aguda, será considerado un EAS y ocurre durante o dentro de las seis horas posteriores a la administración de la transfusión. Estudios prospectivos de TRALI en diversas encontraron tasas de incidencia muy bajas (0,0008% a 0,001% de pacientes transfundidos) [19] después de la implementación de estrategias para prevenir la transfusión de componentes de la sangre obtenido de donantes femeninas multíparas. En nuestro estudio no se transfundirá plasma convaleciente de mujeres multíparas.

El tratamiento del paciente con TRALI incluye la interrupción inmediata de la transfusión.

Criterios diagnósticos de TRALI: [28]

TRALI Tipo I: pacientes que no tienen factores de riesgo de SDRA y cumplen con los siguientes criterios:

A. i. Inicio agudo

ii. Hipoxemia (PaO_2 / FiO_2 ≤ 300 o SpO_2 <90% en aire ambiente).

iii. Evidencia clara de edema pulmonar bilateral en imágenes (radiografía de tórax, tac o ecografía)

iv. No hay evidencia de hipertrofia ventricular izquierda o, si está presente, no es la principal contribuyente de la hipoxemia

B. Inicio durante o dentro de las 6 horas de la transfusión

C. Sin relación temporal con un factor de riesgo alternativo para SDRA

TRALI Tipo II: pacientes que tienen factores de riesgo de SDRA (pero que no han sido diagnosticados con SDRA) o que tienen SDRA leve existente (Pa / Fi de 200-300), pero cuyo estado respiratorio se deteriora y se considera que se debe a una transfusión basado en:

a. Los resultados descritos en las categorías a y b de TRALI Tipo I, y

b. Estado respiratorio estable en las 12 horas previas a la transfusión

Reacciones Alérgicas – Anafilácticas

Las reacciones alérgicas ocurren en general durante o dentro de las 4 horas posteriores a la transfusión y están más frecuentemente asociadas a la transfusión de plaquetas (302 cada 100 000 unidades de plaquetas) [29]. Los síntomas son causados

por mediadores como la histamina, liberados en la activación de mastocitos y basófilos [30]. En general la presentación clínica es leve (erupción cutánea, prurito, urticaria, y angioedema localizado) y constituye un EA solicitado. Las reacciones transfusionales alérgicas leves en general resuelven con la administración del tratamiento habitual para reacciones alérgicas, pudiendo reiniciar la infusión de la unidad. La transfusión debe suspenderse si los síntomas reaparecen. La incidencia de reacciones anafilácticas es de 8/100,000 unidades de plaquetas transfundidas. Las reacciones más severas generalmente se presentan con broncoespasmo, dificultad respiratoria e hipotensión y constituyen un EAS y debe ser reportado como tal inmediatamente [31-35].

Reacciones transfusionales hemolíticas agudas

Las reacciones de transfusionales hemolíticas agudas (RTHA) pueden ocurrir cuando se transfunden glóbulos rojos incompatibles o en menor frecuencia, grandes cantidades de plasma incompatible con el ABO del paciente. El mecanismo fisiopatológico central es la hemólisis intravascular y se considerará un EAS. Se presenta con fiebre repentina y escalofríos, dolor retroperitoneal y disnea, hemoglobinuria y hasta coagulación intravascular diseminada, insuficiencia renal aguda y shock. Dado que la fiebre y los escalofríos pueden ser los únicos signos tempranos, es importante controlar al paciente durante la transfusión y detenerla transfusión inmediatamente si hay algún cambio en los signos vitales o ante la aparición de síntomas inesperados. El tratamiento se basa en medidas de sostén para mitigar los síntomas. La identificación adecuada del paciente y el cumplimiento de todos los procesos relacionados con el manejo de muestras pre-transfusionales y con la administración de la transfusión, son esenciales para prevenir la RTHA [36].

Infecciones Transmisibles por Transfusión [39]

El riesgo de transmisión de enfermedades infecciosas por transfusiones se ha reducido dramáticamente, secundario a los grandes avances en el testeo de las unidades, inactivación de patógenos para unidades de plasma y sus componentes [51] y a la implementación de rigurosos métodos de selección de donantes. En nuestro medio, las muestras son testeadas para HBV, HCV, HIV, HTLV y *Trypanosoma cruzi* [52]. En Estados Unidos, el riesgo de adquirir HBV y HIV por transfusión es de 1:280.000 y 1:1.467.000, respectivamente [53 54]. Gracias al congelamiento de las muestras de plasma, la contaminación de las mismas por patógenos bacterianos y CMV es extremadamente rara. Hay solo una decena de casos entre los millones de transfusiones realizadas, reportados en Alemania y Canadá de transmisión bacteriana. Se estima que la fuente potencial de esta contaminación habrían sido los baños de agua utilizados para el descongelamiento de las unidades. Esto es fácilmente evitable con la limpieza y esterilización correctas de los descongeladores [39].

12. Consideraciones éticas

Declaración de Buena Práctica Clínica

Este estudio se llevará a cabo de conformidad con el protocolo y con las siguientes consideraciones:

- los principios éticos que tienen su origen en la Declaración de Helsinki,
- las pautas vigentes de las buenas prácticas clínicas (Good Clinical Practice, GCP) del Consejo Internacional de Armonización (International Council of Harmonisation, ICH),
- las leyes y regulaciones vigentes.

El protocolo, los formularios de Consentimiento Informado (FCI) y otros documentos relevantes han sido revisados y aprobados por Fundación INFANT, las autoridades participantes y enviados al Comité de Ética (CE) para su evaluación.

Comité de ética (CE):

Un CE debidamente constituido, como se describe en las pautas de ICH para GCP, debe revisar y aprobar:

- El protocolo, FCI y cualquier otro material que se proporcione a los participantes antes de que cualquier sujeto pueda ingresar en el estudio
- Cualquier enmienda o modificación al protocolo de estudio o al FCI antes de la implementación, a menos que el cambio sea necesario para eliminar un peligro inmediato para los pacientes, en cuyo caso el CE debe ser informado lo antes posible

Además, debe ser informado de cualquier evento que pueda afectar la seguridad de los pacientes o la realización continua del estudio clínico.

INFANT debe recibir una copia de la carta de aprobación del CE antes de enviar los suministros de medicamentos al investigador de cada hospital. La carta de aprobación debe incluir el título del estudio, los documentos revisados y la fecha de la revisión.

El investigador debe mantener en el archivo los registros de la revisión del CE y la aprobación de todos los documentos del estudio

Proceso de Consentimiento Informado

El FCI utilizado por el investigador será el aprobado por el CE correspondiente.

Es responsabilidad del investigador o profesional delegado obtener el consentimiento informado por escrito de cada sujeto antes de su participación en el estudio y después de que los objetivos, procedimientos y riesgos potenciales del estudio se han explicado completamente en un lenguaje que el sujeto pueda entender. El FCI debe estar firmado y fechado por el investigador o personal delegado que realizó el proceso de toma de consentimiento.

El investigador o personal delegado le explicará al participante la naturaleza del estudio y responderá todas las preguntas sobre el estudio. Les informará que su participación es voluntaria. El participante deberá firmar el formulario de consentimiento informado (FCI) antes de que se realice cualquier actividad específica del estudio.

A los participantes que pueden entender pero que no pueden escribir y/o leer se les leerá el CI en presencia de un testigo imparcial, que firmará y fechará el FCI para confirmar que se obtuvo el consentimiento informado.

Se firmarán dos ejemplares. El investigador debe conservar un ejemplar como parte del registro del estudio del paciente, y se debe entregar el otro ejemplar firmado al participante.

- Pacientes con vulnerabilidad cognitiva:
  Podrán ser incluidos previa toma de consentimiento por parte de su representante según corresponda:
  a. Pacientes que posean una declaración jurídica de incapacidad: deberá ser quien haya sido designado como curador siempre que exista esa declaración
  b. Pacientes que puedan tomar una decisión por si mismos previa asistencia de un "apoyo" según las disposiciones del Código Civil: por lo general el paciente puede designar a quien lo ayude a decidir.
  c. Pacientes sin declaración judicial de incapacidad y que tampoco hayan designado un apoyo o representante: resultará de aplicación la ley de derechos de los pacientes.
  Los medios para acreditar la representación pueden consistir en cualquier documento que acredite la designación como curador (si aplica) o bien cualquier directiva anticipada del paciente en donde establezca quién lo representa en temas de salud, o documentos que acrediten el parentesco según la Ley 26529.

13. Confidencialidad y Protección de Datos Personales

El investigador tomará todas las medidas apropiadas para garantizar que se mantenga el anonimato de cada sujeto del estudio en los registros para investigación transmitidos fuera del centro de salud. Los documentos originales y esenciales del estudio deben

mantenerse en estricta confidencialidad en cada centro de investigación por el equipo del estudio.

Los datos personales de los participantes se almacenarán en el centro del estudio en un formato impreso y/o electrónico protegidos por contraseña o en un cuarto bajo llave, para garantizar el acceso exclusivo del personal autorizado del estudio.

Para proteger los derechos y las libertades de las personas físicas en relación con el tratamiento de datos personales, se asignará a los participantes un código alfanumérico único y específico. Los registros o conjuntos de datos de los participantes que se transfieran contendrán el código alfanumérico; los nombres de los participantes no se transferirán. Todos los demás datos identificables transferidos entre los investigadores se identificarán mediante este código único y específico del participante. El centro del estudio mantendrá una lista confidencial de los participantes que participaron en el estudio bajo estricta seguridad (protegidos por contraseña o en un cuarto bajo llave), vinculando el código alfanumérico de cada participante con su identidad real.

14. Documentación del Estudio

Los registros y los documentos, incluidos los FCI firmados, respecto a la realización de este estudio, serán conservados por el investigador durante 15 años después de la finalización del estudio, a menos que las regulaciones locales o las políticas institucionales requieran un período de conservación más prolongado.
El investigador de cada institución participante deberá consultar con INFANT antes de descartar o destruir cualquier documento esencial del estudio después de la finalización o interrupción del estudio. En caso de ser aprobado, los registros deben destruirse de manera que se garantice la confidencialidad.

15. Monitoreo de estudio

15.1. Monitoreo de sitios de estudio

El monitor del estudio visitará cada sitio antes de inscribir al primer paciente y periódicamente durante el estudio de acuerdo con el Plan de Monitoreo del Estudio Aprobado.

El monitor recibirá semanalmente de cada uno de los centros un informe con el número de pacientes en periodo de pesquisa y enrolados y verificará que el envió de datos se encuentre al día y completo, realizando de ser necesario seguimiento a cada uno de los centros.

Cada centro contará con una persona designada por el Investigador a verificar procesos realizados bajo protocolo y datos originales y se documentará dicha verificación por escrito.

Las visitas de monitoreo y las actividades de monitoreo centralizado se realizarán de acuerdo con todos los requisitos reglamentarios aplicables y normas vigentes en Argentina. Se entiende que el monitor contactará a cada investigador y a su equipo responsable regularmente y se le permitirá verificar la generación de los distintos registros del estudio.

Será responsabilidad del monitor inspeccionar los sistemas de captura de datos a intervalos regulares durante todo el estudio para verificar el cumplimiento del protocolo y la integridad, precisión y consistencia de los datos; y adhesión al ICH GCP y normativa local sobre la realización de investigaciones clínicas. El monitor debe tener acceso a informes de laboratorio, medicación de estudio, registros asociados con él, y otros registros médicos necesario para verificar las entradas en el EDC.

Se asignará un **monitor no ciego** cuyo rol estará limitado a auditar los datos de logística manejo y registro del tratamiento de estudio de acuerdo con el protocolo aprobado y las instrucciones de tratamiento:

- recepción y condiciones de almacenaje
- randomización y administración
- retorno o destrucción/ reconciliación final

15.2. Requisitos del documento fuente

Se requiere que los investigadores preparen y mantengan registros de pacientes adecuados y precisos (documentos fuente).

El investigador debe mantener todos los documentos fuente en el archivo de los datos volcados al formulario del estudio (CRF). Algunos datos generados del estudio podrán volcarse directamente en el sistema de EDC (captura directa de datos), previa aprobación de dicho proceso por los Comités de Ética intervinientes. Los formularios de informes de casos y los documentos fuente deben estar disponibles en todo momento.

15.3. Requisitos del formulario de informe de caso

Los datos del estudio obtenidos en el curso del estudio serán registrados en formularios de informes de casos (CRF) y enviados a INFANT en formato scan. Una vez recibidos serán archivados y procesados mediante el ingresados al del sistema EDC por personal capacitado de INFANT. Todos los CRF requeridos deben completarse para cada paciente inscrito en el estudio. El investigador debe conservar una copia del libro de casos de CRF de cada paciente como parte del registro del estudio y debe estar disponible en todo momento para su inspección por parte de representantes autorizados del patrocinador y las autoridades reguladoras.

16.. Auditorias e inspecciones

Este estudio puede estar sujeto a una auditoría o inspección de garantía de calidad. Si esto ocurre, el investigador es responsable de:

- Brindar acceso a todas las instalaciones, datos de estudio y documentos necesarios para la inspección o auditoría.
- Comunicar cualquier información que surja de la inspección de las autoridades reguladoras a INFANT de inmediato.
- Tomar todas las medidas apropiadas solicitadas por INFANT para resolver los problemas encontrados durante la auditoría o inspección.

Los documentos sujetos a auditoría o inspección incluyen, entre otros, todos los documentos fuente, CRF, registros médicos, correspondencia, FCI, archivos del CE, documentación de certificación y control de calidad de laboratorios de apoyo, y registros relevantes para el estudio que se mantienen Instalaciones de farmacia. Las condiciones de almacenamiento del material de estudio también están sujetas a inspección. Además, los representantes del patrocinador pueden observar la conducta de cualquier aspecto del estudio clínico o sus actividades de apoyo tanto dentro como fuera de la institución del investigador.

En todos los casos, se debe respetar la confidencialidad de los datos.

ANEXO

INSUFICIENCIA CARDIACA
ESCALA NYHA (NEW YORK HEART ASSOCIATION)
VALORACIÓN FUNCIONAL DE INSUFICIENCIA CARDÍACA.

CLASIFICACIÓN FUNCIONAL NYHA	
Clase I	Sin limitación de la actividad física. El ejercicio físico normal no causa fatiga, palpitaciones o disnea.
Clase II	Ligera limitación de la actividad física. Sin síntomas en reposo. La actividad ordinaria ocasiona fatiga, palpitaciones o disnea.
Clase III	Marcada limitación de la actividad física. Sin síntomas en reposo. Actividad física menor que la ordinaria ocasiona fatiga, palpitaciones o disnea.
Clase IV	Incapacidad para llevar a cabo cualquier actividad física; los

	síntomas de insuficiencia cardíaca están presentes incluso en reposo y aumentan con cualquier actividad física.

CIRROSIS (CONSENSO HIPERTENSION PORTAL BAVENO IV)

ESTADIOS DE CIRROSIS	
Estadío 1	Ausencia de varices esofágicas y de ascitis
Estadío 2	Varices esofágicas sin antecedente de hemorragia y sin ascitis.
Estadío 3	Presencia de ascitis con o sin varices esofágicas.
Estadío 4	Hemorragia gastrointestinal por hipertensión portal, con o sin ascitis.

ENFERMEDAD RENAL CLASIFCIACION KDIGO.

GRADO	FILTRACIÓN GLOMERULAR ML/MIN/1,73 M2	DESCRIPCION
GRADO 1	> 90 G5	Normal o elevado
GRADO 2	60-89	Ligeramente disminuido
GRADO 3a	45-59	Ligera a moderadamente disminuido
GRADO 3b	30-44	Moderada a gravemente disminuido
GRADO 4	15-29	Gravemente disminuido
GRADO 5	< 15	Fallo renal

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EVALUATION OF THE EFFICACY OF COVID-19 CONVALESCENT PLASMA ADMINISTRATION IN REDUCING THE PROGRESSION TO SEVERE DISEASE IN OLDER ADULTS WITH MILD SYMPTOMS DUE TO SARS-CoV2

Dr. Carlos Bocalandro Hospital Principal Investigator: Dr. Aníbal Rondan
Principal Investigator Simply Evita Hospital: Dra. Valeria Fernández Viña
Evita Pueblo Hospital Principal Investigator: Dra. Maria Clarisa Barolin
San Juan de Dios Hospital Principal Investigator: Dra. Ivonne Ritou
Principal Investigator of the Program: Dr. Fernando P. Polack (INFANT)

Co- Investigators: Dra. Romina Libster (INFANT / CONICET), Dr. Gonzalo Pérez Marc (HMC), Dr. Diego Wappner (SMG), Dr. Jorge Lantos (Los Arcos), Dr. Ricardo Valentini (CEMIC), Dr. Federico Etchenique (Ecco), Dr. Mariano Girasolli (OSECAC), Dr. Gabriel Leberzstein (OSECAC) , Dr. Miguel González (Finochietto), Dr. Andrea Gamarnik (Leloir / CONICET), Dr. Jorge Geffner (UBA / CONICET), Bioq. Silvina Coviello (INFANT), Dr. Mauricio Caballero (INFANT / CONICET) , Dr. Damián Alvarez Paggi (INFANT / CONICET), Dr. Sebastián Esperante (INFANT / CONICET) , Dr. Federico Dimase (HMC), Dr. Susana Pastor Argüello (HMC) , Dr. Juan Sebastián Riera (Ministry of Health of the Province of Buenos Aires), Dr. Enio García (Ministry of Health of the Province of Buenos Aires), Dr. Juan Canela (Ministry of Health of the Province of Buenos Aires), Dr. Mario Rovere (Ministry of Health of the Province of Buenos Aires) , Dr. Fernando Althabe (WHO), Dr. Eduardo Bergel (IECS).

Advisors: Dr. Daniel Stamboulian (FUNCEI)

1. INTRODUCTION

SARS-CoV2 is a new and particularly aggressive virus for elderly individuals, who represent between 73% and 90% of fatal cases in different regions of the world [28, 30, 40]. Mortality, the need for intensive care, mechanical ventilation, oxygen requirements, and hospitalizations for respiratory disease increase markedly with advancing age in patients [2, 3, 29, 32, 46]. In fact, the frequency of death from disease due to SARS-CoV2 (COVID-19) is 8% in patients between 70 and 80 years old, and increases to 14.8% in those over 80 [23]. Specifically in hospitalized patients older than 75 years, mortality is 29.4% [24], and in intensive care it amounts to an alarming 43.5% [25]. Several comorbidities associated with vascular and / or pulmonary disease worsen the prognosis of those infected even in patients younger than 70, including arterial hypertension, diabetes, obesity, and chronic obstructive pulmonary disease (COPD) [3,23,30,31]. To date, the virus has caused more than 290,000 deaths worldwide, more than 300 of them in Argentina which is contained through a transitional strategy quarantine quasi-universal [4]. There is no specific treatment available yet. The results of the efficacy trials for SARS-CoV2 vaccines will be known within a minimum of 10-14 months.

SARS-CoV2 is an enveloped virus that contains single stranded RNA in the positive sense bound to a nucleoprotein (protein N), within a capsid composed of matrix proteins (protein M). The envelope contains spine-shaped glycoproteins (protein S) that bind to the cellular receptor ACE2 in humans and generate neutralizing antibodies [13]. Primary SARS-CoV2 infection, like other respiratory diseases, generates an antibody response with early production of IgM followed by specific IgG against viral proteins [14]. Detection of virus neutralizing antibodies is common, reaching high levels of up to 1: 21,500 $PRNT_{50}$, mostly exceeding 1: 500 titers after 28 days of symptom onset in mild patients [41]. Approximately 5% of patients have neutralizing antibody levels <1:40, especially the younger ones [41]. A study of primary respiratory tract infection in rhesus macaques, using 10^6 pfu of SARS-CoV2 followed by a second intratracheal challenge using the same virus and doses 28 days later, demonstrated the absence of reinfection after an extensive evaluation by RT-PCR in tissues post-necropsy [42]. Neutralizing titers before the second inoculum ranged from 1:8-1:16 $PRNT_{50}$ [42]. **These findings - limited indeed, given the novelty of the problem - suggest that even low neutralizing antibody titers could prevent severe disease due to the virus.**

Protecting the populations most vulnerable to SARS-CoV2 is imperative, in the context of a highly infectious pathogen (R_0 estimated between 2 and 3.28) [27, 33, 34]. Its contagiousness rapidly overwhelms the health capacity of developed countries in different regions of the world [5] and threatens the health resources of developing countries [6]. Regions of Italy, Spain and the United States have been overwhelmed by the pandemic, which represents a serious threat to Argentina, coinciding with the beginning of the annual circulation of other lung pathogens, such as the common flu and respiratory syncytial virus [26]. Obviously, it would be

impossible to respond to an avalanche of critically ill patients [7], and any strategy aimed at reducing infections and the development of severe disease **is directly aligned with the medical objective of saving lives and with the health needs of the country in order to provide the best possible care for those patients who need it**.

Post-exposure prophylaxis to viruses and treatment in early stages of disease, through defenses obtained in convalescent plasma, is a widespread practice with successful antecedents in the history of medicine at a national and global level. As early as 1960, Brunell et al. managed to prevent clinical varicella in siblings with sick parents, using anti-varicella zoster immunoglobulins obtained from the plasma of previously infected patients [8]. Today, for example, enriched immunoglobulin for measles is used in unvaccinated people who were in contact with a patient for the previous 6 days with an efficacy close to 100% [9, 52]; a similar product enriched for varicella zoster virus is administered to unvaccinated pregnant women, newborns, and immunosuppressed patients in contact with infected persons within 96 hours, reducing the incidence of severe disease by 90% [10, 53, 54]; tetanus immunoglobulin supplements vaccination in soiled wound victims with incomplete primary immunization [43]; gamma globulin against hepatitis B is used as prevention for newborns of infected mothers with an efficacy of 75% [44, 55]; and rabies gamma globulin is ~ 100% effective in the prophylaxis of post-injury due to a rabid animal [11,56]. **Interventions using human immunity derived from convalescent plasma have been shown to be safe, have prevented countless cases of severe disease, and have preserved lives around the world.**

The main objective of our study is to evaluate the efficacy of convalescent plasma in reducing the progression to severe disease in people between 65-74 years with at least one comorbidity and in all those ≥75 years of age who present with mild symptoms of less than 48 hs of evolution at the time of screening and with an early diagnosis of COVID-19. *Our central hypothesis is that a single dose convalescent plasma compared against placebo (saline at 0.9%) administered up to 72 hours after the onset of symptoms by SARS-COV2, prevent progression to severe respiratory disease in subjects 65-74 years with at least one comorbidity and in ≥ 75 years irrespective of the presence of comorbidities.*

2. OBJECTIVES OF THE STUDY

2.1. Primary objective

To evaluate the efficacy of convalescent plasma, starting 12 hours after administration, in reducing the progression to severe respiratory disease in people between 65-74 years with at least one comorbidity and in all those ≥75 years with mild symptoms and a diagnosis of early COVID-19 until 15 days of administration of

treatment (16-18 days of disease considering the pre-symptomatic period before enrollment).

2.2. Secondary Objectives

The Secondary Objectives include determining if the administration of convalescent plasma up to 15 days or thereafter up to a maximum of *25 days of the administration of treatment in those still hospitalized*:

- Reduces the need for oxygen support with maximal oxygen therapy (O_2 reservoir mask) and/or use of non-invasive respiratory support (NIV support including CPAP) and/or admission to ICU and/or requirement of invasive mechanical ventilation due to SARS-CoV2 in patients between 65-74 years with at least one comorbidity and in all those ≥75 years.
- Reduces critical illness defined as (a) presence of acute respiratory failure (PaO2 / FiO2 ≤ 200 mm Hg.) and / or (b) shock (defined by need of vasoactive drugs to maintain MAP equal to or greater than 65 mm Hg) , and / or (c) multi-organ dysfunction syndrome (MODS): acute kidney injury (defined by a creatinine increase two or more times from baseline or a creatinine increase of 0.3 mg / dl) , elevated liver enzymes (transaminases) greater than three times the upper normal value , acute cardiomyopathy (defined by troponin elevation above the normal level and/or new electrocardiographic or echocardiographic changes of myocardial damage) in patients 65-74 years with at least one comorbidity and in all those ≥ 75 years due to COVID-19.
- Reduces mortality due to SARS-CoV2 in patients between 65-74 years with at least one comorbidity and in all those ≥ 75 years due to COVID-19.
- Decreases the length of oxygen support due to hypoxemia associated with COVID-19.
- Describe the safety of convalescent plasma administration in patients between 65-74 years with at least one comorbidity and in all those ≥75 years with COVID-19.
- Explore the concentration of IgG anti-S SARS COV2 in plasma of participants associated with the absence of severe respiratory disease obtained at 24 hours of infusion.

2.3. Exploratory Objectives

- Explore whether, rather than protect against the severe respiratory disease, administration of convalescent plasma delays the onset of the disease.
- Explore the effects of convalescent plasma on primary humoral immune response against infection by SARS COV2 at 90 days post-illness.

- Explore whether the effects on respiratory and cardiovascular disease and long-term mortality were affected by the intervention at 12 months of enrollment.
- Explore the correlation between viral load determined by RT-PCR at diagnosis and the response to plasma treatment.

3. EFFICACY ASSESSMENT CRITERIA

3.1.1. Primary Efficacy Assessment Criterion

Severe respiratory disease due to SARS-CoV2, confirmed by detection of viral RNA by RT-PCR, and defined by the presence of any of the following two variables in a non-exclusive way: (a) respiratory rate ≥30 per minute, (b) oxygen saturation in room air <93% [20,21]. The primary endpoint will be determined from 12 hours of the start of the infusion until 15 days since administering treatment.

3.1.2. Secondary Efficacy Assessment Criteria *(up to 15 days or, thereafter, up to a maximum of 25 days after the administration of treatment if continued hospitalization)*

- Need for oxygen support with maximum oxygen therapy (O_2 reservoir mask) and/or non-invasive respiratory support (NIV support including CPAP) and/or admission to ICU and/or requirement of invasive mechanical ventilation, due to SARS-CoV2.
- Critical illness defined as (a) presence of acute respiratory failure (PaO2 / FiO_2 ≤ 200 mmHg.) and/or (b) shock, and/or (c) multi-organ dysfunction syndrome (MODS) according to criteria detailed in section 2.2: acute kidney injury, elevated liver enzymes, acute cardiomyopathy, due to SARS- Cov2.
- Mortality due to COVID-19.

4. HYPOTHESIS AND JUSTIFICATION

4.1. Hypothesis

Our central hypothesis is that a convalescent plasma dose compared to placebo, and administered up to 72 hours from the onset of mild symptoms, will prevent progression to severe respiratory disease due to COVID-19 in patients between 65-74 years with at least one comorbidity and in all those ≥75 years who present with less than 48 hours of evolution and with mild symptoms.

4.2. Justification

The efficacy of an economically accessible therapeutic preparation against SARS-CoV2 analyzed by means of a randomized, double-blind study in vulnerable patients would

allow its applicability to be immediately scaled up nationally and internationally through massive plasma donation campaigns in convalescent patients awaiting definitive solutions such as successful drugs, monoclonal antibodies, or vaccines [17]. Even if there is concentrated partial protection in the lower respiratory tract [18], *this same strategy could hypothetically allow immunization of subjects through controlled replication of the germ in the upper respiratory tract* (as in the case of passive administration of antibodies against respiratory syncytial virus in infants [19]).

5. STUDY DESIGN

A randomized, double-blind, placebo-controlled study to test the efficacy of convalescent plasma, administered up to 72 hours after the onset of symptoms, to prevent progression to severe respiratory disease. The study will be conducted in subjects aged 65-74 years at the least one comorbidity and all ≥ 75 years who presented with mild symptoms of less than 48 hours at the time of screening (as defined in section 5.1) and early diagnosis of COVID-19. Subjects will be followed for a minimum observation period of 15 days in which participants will remain under medical supervision daily to determine the primary endpoint. Monitoring will extend thereafter, up to 25 days if subjects remain symptomatic and hospitalized, to analyze secondary endpoints.

The study is projected to incorporate an estimated maximum of 210 patients (see 9.0 Sample size). Participants will be randomized in a 1:1 ratio.

Table 1. Treatment Assignments

Treatment Group	Range of subjects assigned by branch	Test Article	Intravenous Dosing Volume	Intervention Administration Day
A	105	Placebo (0.9% saline solution)	250 cc	Day 0
B	105	Convalescent plasma		

All participants will receive a single intravenous dose (EV) - according to the ADMINISTRATIVE AND TECHNICAL REGULATIONS RM 797/13 - 139/14 - 1507/15 Directorate of Blood and Blood Products Ministry of Health of the Nation (at http: // www. msal.gob.ar/disahe/images/stories/pdf/normas-hemoterapia.pdf) on Day 0 with the assigned test article, convalescent plasma or placebo (see Table 1). For each subject, participation in the study will last a minimum of 15 days or until the resolution of symptoms from the administration of the test article with a maximum of 25 days. Participating subjects will be monitored during and after administration of the test article to assess expected and unexpected safety events after plasma administration. A

Data and Safety Monitoring Board will oversee the enrollment, efficacy, and safety of the participants throughout the study.

The study will be conducted at the San Juan de Dios Hospital, the Simply Evita Hospital, the Dr. Carlos Bocalandro Hospital, the Evita Pueblo Hospital, in close coordination with health effectors of the provincial Ministry of Health and the Hospital Central Militar, the Sanatorio of Los Arcos, CEMIC, and the Research Center OSECAC and will not interfere with the care and standards of patient care established for notification and management of this disease.

5.1. Eligibility criteria

5.1.1 Inclusion Criteria:

A subject must meet the following criteria to be included in the study:

1. Age ≥ 75 years or age between 65-74 years with at least one of the following comorbidities:
   a. Diagnosis of arterial hypertension under pharmacological treatment.
   b. Known diagnosis of diabetes in treatment with one or more of the available drugs (Appendix I).
   c. Obesity (BMI -Body mass index- ≥ 30 kg / m2),
   d. Chronic obstructive pulmonary disease (COPD) treated with any of the available drugs (Appendix I).
   e. Cardiovascular disease defined as a) known diagnosis of coronary heart disease, b) history of ischemic stroke or hemorrhagic, or c) CHF (defined as EF < 40%).
   f. Chronic kidney disease (defined as a reduction in GFR below 60 ml/min/1.73 m^2).
2. Present <u>for less than 48 hs</u> : (A) axillary temperature ≥ 37,5°C or fever equivalence (defined as feeling cold and/or chills and/or unexplained sweating) , <u>combined with</u> (a) dry cough and / or (b) difficulty breathing and / or (c) odynophagia and / or (d) anosmia and/or (e) dysgeusia and / or (e) any of the following symptoms: fatigue, anorexia, myalgia or rhinorrhea .
3. SARS-CoV2 diagnosis confirmed by RT-PCR
4. Being able, according to medical judgment, to understand and comply with the study procedures and to consent or not to their participation.
5. Provide informed consent.

5.1.2 Exclusion Criteria

A subject who meets <u>any</u> of the following criteria will be excluded from the study:

1. Present at the time of inclusion SEVERE RESPIRATORY DISEASE defined as (a) respiratory rate ≥30 per minute and / or (b) oxygen saturation in ambient air <93%.
2. HEART FAILURE in functional class III and IV (according to the functional classification of the New York Heart Association).
3. Known diagnosis of CHRONIC KIDNEY INSUFFICIENCY in filtration stages G4 and G5 (according to KDIGO classification).
4. Previous diagnosis of PRIMARY HYPOGAMMAGLOBULINEMIA (congenital and hereditary).
5. Previous diagnosis of MONOCLONAL GAMMOPATHIES (multiple myeloma, Waldenström macroglobulinemia, primary amyloidosis, heavy chain disease, among others).
6. Previous diagnosis of SELECTIVE DEFICIENCY OF IgA.
7. Previous diagnosis of MYELODYSPLASIC SYNDROMES. [WHO classification: refractory thrombocytopenia (TR), refractory anemia (RA), etc.]
8. Previous diagnosis of CHRONIC LYMPHOPROLIFERATIVE SYNDROMES. (WHO classification: peripheral B lymphocyte lymphomas, T lymphocyte and NK cell lymphomas, Hodgkin lymphoma).
9. KNOWN HYPERSENSITIVITY to the administration of immunoglobulins, plasma, monoclonal antibodies and / or vaccines.
10. Active cancer, defined as receiving or having received or receiving chemotherapy, radiotherapy, or new designer or monoclonal drug treatments in the last six months.
11. Known HIV, HBV, or HCV infection.
12. Chronic administration (defined as more than 14 calendar days) of immunosuppressants or other drugs that modify the immune system at the time of enrollment or within the 6 months prior to administration of study medication. An immunosuppressive dose of glucocorticoids will be defined as a systemic dose of ≥10mg of prednisone per day or its equivalent.
13. Solid organ transplant.
14. Known chronic liver disease diagnosed with stage II-III-IV cirrhosis.
15. Chronic lung disease with oxygen requirement.
16. Any other physical, psychiatric or social condition that may, at the discretion of the investigator, increase the risks of participation in the study for the participant or that may lead to the collection of incomplete or inaccurate safety data.

5.2. Study procedures (Table 2)

5.2.a. Participating population and identification process of potential subjects.

Subjects 65-74 years with at least one comorbidity and all ≥ 75 years who present for less than 48 hours the following symptoms: (**a**) temperature ≥ 37,5°C or fever equivalence (defined by feeling cold or chills or unexplained sweating) , <u>combined with</u> (**b**) dry cough and / or dyspnea and / or anosmia / dysgeusia and / or odynophagia and / or fatigue and / or anorexia and / or myalgias and / or rhinorrhea .

Those patients who meet the inclusion criteria and do not meet any of the aforementioned exclusion criteria will be invited to participate in the research phase of the study in which, if they accept (expressing their agreement by signing the informed consent - research ANNEX), a sample of respiratory secretions is obtained by swabbing the nasopharynx and oropharynx (according to the procedure and regulations of the Argentinean Ministry of Health) to assay for RNA of SARS-COV2 by reverse transcriptase-polymerase chain reaction (RT-PCR).

The sample will be processed and analyzed by the laboratory designated for participating institutions daily, using the same RT-PCR test to assess the presence of RNA of SARS-COV2. This determination will be made as soon as possible (within a maximum of 24 hours) and under all the biosecurity standards indicated by the health authorities. The samples will be kept for later testing by RT-PCR for co-infections with influenza A and B, respiratory syncytial virus and other winter viral pathogens at the INFANT Foundation.

5.2.b. Enrollment for participation in the study

If SARS-CoV2 RNA is detected in the respiratory sample, the candidate will be informed about the details of the study and eligibility will be verified again. The candidates may decide not to participate in the investigation by their free will and without any consequence whatsoever. In the event that the subject is interested in participating in the study, and after their consent is attested with the signing of the informed consent for participation (ANNEX), a unique identification number will be assigned. Once its alphanumeric code has been assigned, vital signs will be obtained and a complete physical examination will be performed to obtain the following demographic and clinical information [1-3, 25, 47-51]:

- Sex
- Age
- Usual medications and those of the last 15 days.
- History of smoking
- Comorbidities of primary interest: arterial hypertension, diabetes, coronary heart disease, heart failure, history of stroke and AMI, COPD, chronic kidney disease, and obesity.
- Secondary comorbidities: asthma, history of cancer, liver diseases, and neurological diseases.

5.2.c. Random assignment

All participants with confirmed eligibility will be randomly assigned to a treatment group. The randomization of participating subjects will be conducted by the person in charge of randomizing the study using an electronic system. Once the patient is randomized, the person in charge of the allocation will communicate with a member of the Transfusion Medicine Central Team in the study who will remove the opaque bag treatment indicated in the freezer of the Central Laboratory. The

Transfusion Medicine team will proceed to take the cold bag to the hospital. There, he/she will complete the preparation of the masked product and administer the indicated treatment to the participating patient, using a venous access previously obtained by a member of the hospital team for the infusion. Only the person responsible for randomization and the physician in the Transfusion Medicine Central Team administering treatment will know the product administered to each patient (unblind). Neither the patient nor the researchers will have knowledge of the administered treatment, conducting a double-blind study. The unblinded team will keep a record of the product assignments and their administrations that will be kept confidential. In the eventual need to open the blind, such records may be used.

5.2.d. Preparation and administration of the test article

The preparation and administration of the convalescent plasma or placebo (physiological solution) will be performed according to the ADMINISTRATIVE AND TECHNICAL REGULATIONS RM 797/13 - 139/14 - 1507/15 Directorate of Blood and Hemoderivatives Ministry of Health of the Nation. (http://www.msal.gob.ar/disahe/images/stories/pdf/normas-hemoterapia.pdf).

Once masked, the team of Transfusion Medicine will administer the product intravenously for 3 hours and up to 4 hours. After administration, local reactions at the injection site and systemic reactions will be monitored for 12 hours. *This is a minimal risk study, since the administration of plasma and saline (placebo in this study) are a daily habit in medical practice.* In the event of a medical emergency, when it is known that the treatment assignment may influence the medical care of the patient, the investigator or designee may request that the subject be unblinded for the emergency. However, prior to breaking the blind the investigator must make all reasonable efforts to discuss the decision to break the blind. The investigator is expected to provide a reason for the need to break the blind, based on a significant change in the participant's immediate or short-term medical care that will result from knowledge of the treatment assignment.

5.2.e. Taking a blood sample for titration of IgG anti-S SARS CoV2 in serum.

At 24 hours of completion of infusion of the treatment, a sample of 5 ml of venous blood will be obtained from all participants for titration of serum IgG anti-S SARS-COV2 and held at the Foundation INFANT. The assay will be performed by the ELISA method (COVIDAR IgG, Leloir / CONICET and Genetech IgG and sNT). Serum will be preserved to -20 °C and transferred by a shuttle authorized for sample handling system transport biological the Foundation.

5. 2. f. Daily clinical monitoring

We will perform one control daily from Day 0 and at least 15 days from the infusion and up to 25 days for those subjects who remain hospitalized with symptoms after day 15. Patients who are discharged prior to the day 15 will be monitored at home by a team of physicians trained for this purpose working in collaboration with the research

centers. The following clinical information will be collected daily (using a questionnaire designed for this purpose) by study personnel and **without interfering with the patient's medical care or altering the standards recommended by the health care authorities for the management of patients with COVID-19** : (a) respiratory rate (looking at the chest excursion for 30 seconds) , (b) oxygen saturation, (c) temperature, (d) central heart rate , (e) cough and duration, (f) sore throat and duration , (g) feeling of fever / chills, (h) need for supplemental oxygen provision and duration, (i) need for intensive care and duration, (j) need for non-invasive or invasive respiratory support and duration, (k) evidence of SDMO : according to criteria for acute kidney injury , criteria for elevated liver enzymes and criteria for acute cardiomyopathy (detailed in section 2.2) , (l) survival.

Table 2. Schedule of study procedures.

Study Day	**-1 Research**	**0 Day 0**	**Daily follow up**
Informed consent for the evaluation of history, clinical condition and *SARS-COV2 diagnosis*	X		
Nasopharyngeal swab collection for confirmation of SARS-CoV2 by RT-PCR	X		
Informed consent to participate in the study		X	
Medical history review		X	X
Vital signs		X	
Eligibility confirmation		X	
Concomitant medications		X	X
Random assignment of treatment		X	
Administration of the intervention		X	
Monitoring of transfusion		X	
Surveillance of adverse events		X *	(X)
Taking a blood sample after the infusion is complete			24 hours
Surveillance of respiratory symptoms		X	X

We consider that the patient completes its participation when reaching day 15 (if the patient is already discharged), at the time of discharge between days 15 and 25, or at the expiration of day 25 if he/she continues hospitalized.

6. Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will monitor the safety of the subjects throughout the study. The DSMB includes at least experienced members in managing internal medicine, infectious diseases, and a biostatistician with specific experience in the design, analysis and safety of clinical trials. The DSMB will operate under an approved plan and will have the responsibility to monitor the outcomes/end points, adverse events (AE) and serious adverse events (SAE), and recommend termination of the study if it appears at any point during the study that participants (or a subset of participants) are at undue risk as a result of their participation. The DSMB will meet (by teleconference) weekly to review the accumulated data on safety and efficacy and will conduct an interim analysis of the data. The DSMB will issue written recommendations based on its meetings regarding the continuity of the study. The minutes of each meeting will be recorded in documented minutes based on a pre-established work schedule. Any participant-specific protected health information reviewed by the DSMB will be kept completely confidential. Sessions will be closed without access to third parties.

7. Security Monitoring

The researcher at each institution and at a general level will supervise the safety of the study patient at his/her site(s) according to the requirements of this protocol and in accordance with current Good Clinical Practices (GCP). The investigator will monitor safety data at all study sites. Security monitoring will be carried out on an ongoing basis (for example, individual review of EA S, EAs and endpoints) and on a periodic cumulative basis.

Adverse event (AE)

An AE is any unfavorable medical event in a patient who was administered a study drug that may or may not have a causal relationship to the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease that is temporarily associated with the use of a study drug, regardless of whether it is considered related to the study drug.

An AE also includes any worsening (ie, any clinically significant change in frequency and / or intensity) of a pre-existing condition that is temporarily associated with the use of the investigational product.

COVID-19 progression will not be considered an AE if it is clearly consistent with the typical progression pattern of the disease

If there is any uncertainty that an AE is due to COVID-19 progression only, it will be reported as an AE or SAE, as described in the appropriate protocol section.

Serious adverse event (SAE)

A SAE, by definition, is any unfavorable medical event that at any dose:

- Results in death: Includes all deaths, even those that appear to be unrelated to the study drug (for example, a car accident in which a patient is a passenger).
- It is life threatening: In the opinion of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE which, if it had occurred in a more severe form, could have caused death.
- Requires hospitalization or extension of existing hospitalization. Hospitalization is defined as admission to a hospital or emergency room for more than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than originally planned for the event, or prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant disability (substantial disruption of one's ability to carry out normal life functions).
- It is a major medical event - Major medical events may not immediately endanger life or result in death or hospitalization, but may endanger the patient or may require intervention to prevent one of the other serious outcomes listed above (for example, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias that do not result in hospitalization).

In the case specific of this study we will consider AE or SAE , according to the detailed description in section 11.2, those that are initiated within 12 hours after administration of the IP and clinical exacerbations and deaths associated with these events. We will not consider as AE and SAEs those events occurring after 12 hours of initiation of treatment, that are consistent with the clinical course in patients infected with SARS COV2.

Adverse Event Collection Period

The reporting period for AE/SAE begins when the participant was initially included in the study (date of signature of informed consent for participation) and receives the infusion and continues for events that occur in the next 12 hours (see section 11.2) . During the follow up period, after the initial 12 hours of IP administration subjects will be monitored for the clinical outcome associated with primary and secondary endpoints.

8. Leaving the Study Prematurely

Subjects may leave the study at any time if they wish, but we will make every effort to monitor them during the stipulated period to guarantee their safety.

9. Patient Replacement

Those patients who decide to drop out of the study prior to drug administration will be replaced, if necessary, to ensure an adequate number of evaluable patients.

10. Justification of the sample size and statistical analysis

There is significant uncertainty in the expected effect size of the intervention, and considering that the trial is expected to be completed in a relatively short period of time, the study is designed to have an interim analysis when the results of 50% of the subjects have been acquired.

Given the relative complexity of implementing this intervention, the minimally clinically important difference is established in a relative reduction of 40%, for an expected result rate of 50% in the control group that is reduced to 30% in the intervention group. A total sample size of 210 subjects (105 per test arm) will have 80% power, at a significance level (alpha) of 0.05 using a two-sided z-test with continuity correction. These results assume that 2 sequential tests are performed using the O'Brien-Fleming expenditure function to determine the limits of the test, as described in the table below.

Look	Time	Lower Bndry	Upper Bndry	Nominal Alpha	Power
1	0.50	-2.96259	2.96259	0.003	0.168
2	1.00	-1.96857	1.96857	0.049	0.806

Under the primary analysis strategy, we will use the Kaplan-Meier product cutoff distribution to compare treatment groups over time required to reach the primary outcome. An estimate of the relative risk and the 95% confidence interval will also be reported.

11. Test article and transfusion medicine

11.1. Voluntary donation of convalescent plasma

All procedures will be done in accordance with the STRATEGIC PLAN TO REGULATE THE USE OF PLASMA BY COVID-19 RECOVERED PATIENTS FOR THERAPEUTIC PURPOSES. (IF-2020-26315442-APN-SCS # MS)

https://www.boletinoficial.gob.ar/detalleAviso/primera/227976/20200418

Convalescent plasma will be obtained by inviting patients who experienced COVID-19 and have recovered satisfactorily in the Autonomous City and Province of Buenos Aires to participate as a voluntary donor, following the donation criteria established by

the authorities. If the patient wishes to donate, they will voluntarily and altruistically sign the plasma donation consent (ANNEX).

Donors will be identified by the ministerial and institutional authorities (if it is a private body), contacted, and invited to donate in one of the five Blood Banks participating in this study:

a) Institute of Hemotherapy of the Province of La Plata
b) Central Military Hospital
c) Hemocentro Buenos Aires Foundation
d) Sarmiento Hematology Foundation
e) CEMIC

In order to donate plasma, the patient must comply with the conditions determined to date (https://www.boletinoficial.gob.ar/detalleAviso/primera/227976/20200418) or follow updates from the Ministry of Health.

Anti-SARS Cov2 antibody titration

After donating plasma by apheresis or hemodonation, in addition to the samples obtained for routine blood bank controls, a dry tube of 5 mL of whole blood will be obtained, labeled with the identification given to the donor, identification of the Blood Bank and label that identifies the purpose of the "PCC19" study to perform the antibody titer. These will be assayed using the SARS CoV2 anti-protein S ELISA test, which in light of the existing data on protection against the virus allows an indirect extrapolation of the serum's neutralization capacity, optimized by the Leloir Institute in charge of Dr. Gamarnik, and currently used by health teams in Argentina to study immunity prevalence. Likewise, if possible, data will be correlated with the neutralizing antibody titer against a pseudovirus encoding protein S optimized by the same laboratory.

Tubes will be stored in a designated location within the Bank and shipped in an approved biological sample shipment to the INFANT Foundation (over 18 years of experience in testing) for assaying ELISAs and neutralizing antibodies.

The titers obtained by S ELISA will then be classified and those that are above 1: 1,000 selected to provide convalescent plasma for this study.

The additional high titer plasmas will also be stored to be sent to the Córdoba Blood Products Center (UNC), which will produce gammaglobulin enriched with anti-SARS-CoV2 antibodies.

Plasmapheresis (Institute of Hemotherapy of the Province in La Plata, Central Military Hospital, Hemocentro Buenos Aires Foundation, and Sarmiento Hematology Foundation)

Plasma donation will be conducted through an apheresis procedure with equipment and disposable supplies approved for this purpose, during which it is recommended to extract a volume no greater than 15% of the donor's blood volume. The anticoagulant to

be used will be ACD-A or similar. In cases where volume replacement is not performed, plasma extraction should not exceed 600 ml per procedure.
The 48 hours interval must be respected between each procedure, not to exceed 2 donations in a week or 24 donations in a 12-month period.
The PCC19 units can be separated into 250ml aliquots, respecting the closed circuit and following the indications of the current standard operating procedure.

Hemodonation (CEMIC)

1-Plasma will be obtained with a Cobe Spectra equipment. 1.5 to 2 L of plasma will be extracted according to the donor's weight and tolerance to the procedure. In case of venous inaccessibility or opposition from the donor, between 400 and 500 ml of whole blood will be drawn (classic hemodonation)
2-The volume replacement will use NS and albumin solution.
3-During the procedure the plasma will be transferred to transfer bags of similar volume each (approximately 500ml).
4-The bags will be labeled as detailed below.
5-They will be frozen in the -56°C Righi vertical ultrafreezer (labeled Freezer # I, identified with COVID-19 convalescent plasma label in the Blood Bank) separated on shelves by bag type (1, 2 or 3).
6-The convalescent plasma will remain stored until its use or expiration (1 year), with appropriate safety criteria.
7-Disposal will be conducted under stipulated security regulations.
8- Stored aliquots of serum / plasma frozen for future determinations at -80°C in Eppendorf tubes.

Labelled
All units of PC COVID-19 must comply with the labeling required for fresh frozen plasma from each Blood Bank and must also have a clear identification, which must include:

- "Product Type: PC COVID-19"
- "Result of antibody titer for SARS-CoV-2" (if available)
- "CAUTION: product for research use only"
- "PROTOCOL: INFANT Foundation - Serum enriched with anti SARS-CoV2 antibodies"

Cold Chain of PCCOVID-19

1. The units are stored properly separated from the remaining plasma units and labelled for transfusional use in a place clearly identified for this purpose.

2. The PCC19 units will be stored at temperatures below -25°C, which allows a storage of 36 months and between -18°C and -25°C for 3 months of storage.

3. The units will be transported in a way to maintain the cold chain reliably.

4. Plasma units should be stored between 2 ºC and 6ºC until 24 hours after thawing. After then, they should be discarded.

Traceability

The Blood Bank and the Transfusion Service of the requesting Institution will implement a registry system that guarantees traceability between donors and recipients. In this special situation, they must also have a specific registry as this is a transfusion therapy administered in an experimental context.

11.2. Administration of the intervention

After assessing vital signs and verifying eligibility, the unblinded team from the Medical Transfusion Center will be notified of the result of the randomization process and drive to the assigned hospital with the masked treatment product cold. On arrival, they will proceed again to check the code assigned for treatment with a member of the laboratory of Transfusion Medicine of the hospital (see 5.2.c).

Placebo will be a 250 ml of normal saline (0.9%) sterile, masked and administered in the same way and speed as plasma. To avoid bias and maintain the study blinded, plasma and saline 0.9% will be masked using an opaque bag and tape that will not allow to differentiate both products. Members of the Medical Transfusion Central Team will conduct the intervention with a member of the local team. Thus, both members of the Transfusion Medicine Central Team and the respective member of Transfusion Medicine at the hospitals will not be blind, while the rest of the team with delegated functions in the studies in each Center and the patients will be blind to the intervention.

To prepare the plasma, 250 ml bags will be thawed at 37 °C, according to the operating procedures of the Department of Transfusion Medicine at the Hospital. Plasma will be infused slowly (at least 3 hours and up to 4 hours) according to the hemodynamics of the patient and monitored for 12 hours and adverse effects early and late attributable to transfusion recorded.

Monitoring of adverse events associated with plasma transfusion

Transfusion-associated circulatory overload (TACO)

Transfusion-associated circulatory overload (TACO) is the most common pulmonary complication and is an independent risk factor for hospital morbidity and mortality, with a higher incidence in critically ill patients [58]. The estimated frequency of TACO varies from 1% to 5% depending on the hemovigilance system [59], up to 8% in advanced post-surgical patients, and 11% in critically ill patients [60 61 62]. Risk factors include heart, lung, or kidney disease, age ≥70 years, and a positive, pre-transfusion fluid balance [63-64]. Most cases of TACO are prevented by slowing the transfusion rate and establishing the usual measures for fluid overload in susceptible populations. Overload constitutes a requested AE, but if it does not improve within 120 minutes after the infusion or requires - in the opinion of the responsible professionals -

transfer of the patient to intensive care due to poor clinical progression, should be reported immediately as a SAE.

Diagnostic criteria for TACO [19]
During or up to 12 hours after the transfusion, TACO is characterized by the presence of a total of 3 or more of these criteria:
A. Acute or worsening respiratory compromise
B. Evidence of acute or worsening pulmonary edema based on clinical and / or chest radiographic images and / or other noninvasive assessment of cardiac function (echocardiogram)
C. Evidence of cardiovascular changes not explained by the patient's underlying medical condition, including: tachycardia, hypertension, widened pulse pressure, jugular venous distention, enlarged cardiac silhouette, and/or peripheral edema.
D. Evidence of fluid overload, including any of the following: a positive fluid balance; response to diuretic therapy, or dialysis combined with clinical improvement; and variation of the patient's weight.
E. Increased level of B-type natriuretic peptide (eg, BNP or NT-pro BNP) above the age-specific reference range and greater than 1.5 times the pre-transfusion value.

Transfusion Associated Acute Pulmonary Injury (TRALI)
This is an acute respiratory distress syndrome, it will be considered a SAE and it occurs during or within six hours after the administration of the transfusion. Prospective studies of TRALI reported very low incidence rates (0.0008% to 0.001% of transfused patients) [19] after the implementation of strategies to prevent the transfusion of blood components obtained from multiparous female donors. In our study, multiparous women will not be invited to donate plasma.
Treatment of a patient with TRALI involves immediate interruption of the transfusion.

TRALI diagnostic criteria: [28]
TRALI Type I: patients who do not have risk factors for ARDS and meet the following criteria:
A. i. Acute onset
ii. Hypoxemia ($Pa\ O_2$ / $Fi\ O_2 \leq 300$ or $SpO_2 < 90\%$ in room air).
iii. Pulmonary edema with clear evidence of bilateral images (CXR, CT or ultrasound)
iv. There is no evidence of left ventricular hypertrophy or, if present, it is not the main contributor to hypoxemia.
B. Initiation during or within 6 hours of transfusion.
C. Temporarily unrelated to an alternative risk factor for ARDS.
TRALI Type II: patients who have risk factors for ARDS (but have not been diagnosed with ARDS) or who have existing mild ARDS (Pa / Fi 200-300), but whose respiratory status is deteriorating and is considered to be due to a transfusion based on:
a. The results described in categories a and b of TRALI Type I, and
b. Stable respiratory status within 12 hours prior to transfusion

Allergic - Anaphylactic Reactions

Allergic reactions generally occur during or within 4 hours of transfusion and are most frequently associated with platelet transfusions (302 per 100,000 platelet units) [29]. Symptoms are caused by mediators such as histamine, released in mast cell and basophil activation [30]. Frequently, the clinical presentation is mild (rash, pruritus, urticaria, and angioedema are localized) and they are a solicited AE. Mild allergic transfusion reactions generally resolve with the administration of the usual treatment for allergic reactions, being able to restart the infusion of the unit. The transfusion should be stopped if symptoms reappear. The incidence of anaphylactic reactions is 8 / 100,000 units of transfused platelets. The most severe reactions generally present with bronchospasm, respiratory distress, and hypotension and constitute a SAE and should be reported as such immediately [31-35].

Acute hemolytic transfusion reactions

Acute hemolytic transfusion reactions (ATRs) can occur when incompatible red blood cells are transfused or, less frequently, large amounts of plasma incompatible with the patient's ABO are transfused. The central pathophysiological mechanism is intravascular hemolysis and is considered a SAE. It presents with sudden fever and chills, retroperitoneal pain and dyspnea, hemoglobinuria and even disseminated intravascular coagulation, acute renal failure, and shock. Since fever and chills may be the only early signs, it is important to monitor the patient during the transfusion and stop the transfusion immediately if there is any change in vital signs or unexpected symptoms appear. Treatment is based on supportive measures to alleviate symptoms. Proper patient identification and adherence to all procedures related to handling pretransfusion specimens and administration of transfusions are essential to prevent ATRs [36].

Transfusion Communicable Infections [39]

The risk of transmission of infectious diseases through transfusions has been dramatically reduced, secondary to the great advances in unit testing, and pathogen inactivation for plasma units and their components [51] and the implementation of rigorous donor selection methods. In our environment, the samples are tested for HBV, HCV, HIV, HTLV and *Trypanosoma cruzi* [52]. In the United States, the risk of acquiring HBV and HIV by transfusion is 1:280,000 and 1:1,467,000, respectively [53 54]. Due to freezing of plasma samples, contamination by bacterial pathogens and CMV is extremely rare. There are only a dozen cases among the millions of transfusions reported in Germany and Canada of bacterial transmission. It is estimated that the potential source of this contamination would have been the water baths used to defrost the units. This is easily avoidable with proper cleaning and sterilization of defrosters [39].

12. Ethical considerations

Statement of Good Clinical Practice

This study will be conducted in accordance with the protocol and with the following considerations:

- the ethical principles that have their origin in the Declaration of Helsinki,
- the current Good Clinical Practice (GCP) guidelines from the International Council of Harmonization (ICH),
- current laws and regulations.

The protocol, the Informed Consent forms (ICF) and other relevant documents have been reviewed and approved by INFANT Foundation, the participating authorities and sent to the Ethics Committee (EC) for evaluation.

Ethics Committee (EC):

A properly constituted EC, as outlined in the ICH guidelines for GCP, must review and approve:

- The protocol, ICF and any other materials that are provided to the participants before any subject can enter the study
- Any amendment or modification to the study protocol or to the CRF prior to implementation, unless the change is necessary to eliminate an immediate danger to patients, in which case the EC should be informed as soon as possible

In addition, they must be informed of any event that may affect the safety of patients or the continued conduct of the clinical study.

INFANT should receive a copy of the approval letter from the EC before sending drug supplies to the investigator at each hospital. The approval letter should include the title of the study, the documents reviewed, and the date of the review.

The investigator must keep on file the records of the EC review and approval of all study documents

Informed Consent Process

The ICF used by the researcher will be approved by the corresponding EC.

It is the responsibility of the investigator or delegated professional to obtain the written informed consent from each subject prior to their participation in the study and after the objectives, procedures, and potential risks of the study have been fully explained in language that the subject can understand. The ICF must be signed and dated by the researcher or delegated personnel who performed the consenting process.

The investigator or delegated staff will explain the nature of the study to the participant and answer all questions about the study. He/she will inform them that their participation is voluntary. The participant must sign the informed consent form (ICF) before any specific study activity takes place.

Participants who can understand but cannot write and / or read will have the IC read to them in the presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was obtained.

Two copies will be signed. The investigator should keep one copy as part of the patient's study record, and the other signed copy should be given to the participant.

13. Confidentiality and Protection of Personal Data

The investigator will take all appropriate measures to ensure that the anonymity of each study subject is maintained in research records transmitted outside the health center. The original and essential documents of the study must be kept in strict confidence at each research center by the study team.

The personal data of the participants will be stored in the study center in a password-protected print and/or electronic format or in a locked room, to guarantee the exclusive access of authorized study personnel.

To protect the rights and freedoms of natural persons in relation to the processing of personal data, a unique and specific alphanumeric code will be assigned to the participants. The records or data sets of the participants that are transferred will contain the alphanumeric code; the names of the participants will not be transferred. All other identifiable data transferred between researchers will be identified by this unique, participant-specific code. The study center will maintain a confidential list of participants who participated in the study under strict security (password protected or in a locked room), linking the alphanumeric code of each participant with their real identity.

14. Study Documentation

Records and documents, including signed FCIs, regarding the conduct of this study will be retained by the investigator for 15 years after study completion, unless local regulations or institutional policies require a longer retention period.
The investigator from each participating institution should consult with INFANT before discarding or destroying any essential study documents after study completion or interruption. If approved, records must be destroyed in a way that ensures confidentiality.

15. Study monitoring

15.1. Monitoring of study sites

The study monitor will visit each site prior to enrolling the first patient and periodically during the study in accordance with the Approved Study Monitoring Plan.

The monitor receives weekly reports from each of the centers with the number of patients in a period of research and enrolled.

Monitoring visits and centralized monitoring activities will be carried out in accordance with all applicable regulatory requirements and standards in force in Argentina. It is understood that the monitor will contact each researcher and

their responsible team regularly and will be allowed to verify the generation of the different study records.

It will be the monitor's responsibility to inspect the data capture systems at regular intervals throughout the study to verify compliance with the protocol and the integrity, precision and consistency of the data; and adherence to the ICH GCP and local regulations on conducting clinical research. The monitor should have access to laboratory reports, study medication, records associated with it, and other medical records necessary to verify the entries in the EDC.

An unblinded **monitor** will be assigned whose role will be limited to auditing the logistic data, management and study treatment registration according to the approved protocol and treatment instructions:

- reception and storage conditions
- randomization and administration
- return or destruction / final reconciliation

15.2. Source document requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents).

The researcher must keep all the source documents in the file of the data submitted to the study form (CRF). Some data generated from the study may be entered directly into the EDC system (direct data capture), after approval of the process by the Ethics Committees involved. Case report forms and source documents must be available at all times.

15.3. Case Report Form Requirements

Study data obtained in the course of the study will be recorded in case report forms (CRF) and sent to INFANT in scan format. Once received, they will be archived and processed by entering the EDC system by trained INFANT personnel. All required CRFs must be completed for each patient enrolled in the study. The investigator should retain a copy of each patient's CRF case book as part of the study record and should be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

16. Audits and inspections

This study may be subject to a quality assurance audit or inspection. If this occurs, the investigator is responsible for:

- Provide access to all facilities, study data and documents necessary for inspection or audit.

- Communicate any information arising from the inspection of the regulatory authorities to INFANT immediately.
- Take all appropriate measures requested by INFANT to resolve the problems found during the audit or inspection.

Documents subject to audit or inspection include, but are not limited to, all source documents, CRF, medical records, correspondence, FCI, CE files, supporting laboratory quality control and certification documentation, and relevant records for the study being conducted. they maintain pharmacy facilities. The storage conditions of study material are also subject to inspection. Additionally, sponsor representatives may observe the conduct of any aspect of the clinical trial or its support activities both within and outside of the investigator's institution.

In all cases, the confidentiality of the data must be respected.

ANNEX

HEART FAILURE
NYHA SCALE (NEW YORK HEART ASSOCIATION)
FUNCTIONAL ASSESSMENT OF HEART FAILURE.

NYHA FUNCTIONAL CLASSIFICATION	
Class I	Without limitation of physical activity. Normal physical exercise does not cause fatigue, palpitations, or dyspnea.
Class II	Slight limitation of physical activity. No symptoms at rest. Ordinary activity causes fatigue, palpitations, or dyspnea.
Class III	Marked limitation of physical activity. No symptoms at rest. Less than ordinary physical activity causes fatigue, palpitations or dyspnea.
Class IV	Inability to carry out any physical activity; symptoms of heart failure are present even at rest and increase with any physical activity.

CIRRHOSIS (PORTAL BAVENO IV HYPERTENSION CONSENSUS)

CIRRHOSIS STAGES	
Stage 1	Absence of esophageal varices and ascites
Stage 2	Esophageal varices without a history of bleeding and without ascites.
Stage 3	Presence of ascites with or without esophageal varices.
Stage 4	Gastrointestinal bleeding due to portal hypertension, with or without ascites.

KIDNEY DISEASE CLASSIFCIATION KDIGO.

DEGREE	GLOMERULAR FILTRATION ML / MIN / 1.73 M2	DESCRIPTION
GRADE 1	> 90 G5	Normal or elevated
GRADE 2	60-89	Slightly diminished
GRADE 3	45-59	Slight to moderately decreased
GRADE 3b	30-44	Moderate to severely diminished
GRADE 4	15-29	Severely diminished
GRADE 5	<15	Kidney failure

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EVALUATION OF THE EFFICACY OF COVID-19 CONVALESCENT PLASMA ADMINISTRATION IN REDUCING THE PROGRESSION TO SEVERE DISEASE IN OLDER ADULTS WITH MILD SYMPTOMS DUE TO SARS-COV2

Hospital Central de San Isidro Principal Investigator: Dr. Ramiro Larrea
Dr. Carlos Bocalandro Hospital Principal Investigator: Dr. Aníbal Rondan
Principal Investigator Simply Evita Hospital: Dra. Valeria Fernández Viña
Evita Pueblo Hospital Principal Investigator: Dra. Sandra Azcárate
San Juan de Dios Hospital Principal Investigator: Dra. Ivonne Ritou
COVID- PAMI Centers Principal Investigator: Dr. Gonzalo Perez Marc
Principal Investigator of the Program: Dr. Fernando P. Polack (INFANT)

Co- Investigators: Dra. Romina Libster (INFANT / CONICET), Dr. Gonzalo Pérez Marc (HMC), Dr. Diego Wappner (SMG), Dr. Jorge Lantos (Los Arcos), Dr. Ricardo Valentini (CEMIC), Dr. Federico Etchenique (Ecco), Dr. Ma ximiliano De Zan (OSECAC), Dr. Gabriel Leberzstein (OSECAC) , Dr. Miguel González (Finochietto), Dr. Andrea Gamarnik (Leloir / CONICET), Dr. Jorge Geffner (UBA / CONICET), Bioq. Silvina Coviello (INFANT), Dr. Mauricio Caballero (INFANT / CONICET) , Dr. Damián Alvarez Paggi (INFANT / CONICET), Dr. Sebastián Esperante (INFANT / CONICET) , Dr. Federico Dimase (HMC), Dr. Susana Pastor Argüello (HMC) , Dr. Juan Molinos (Olivos Clinic), Dr. Pablo Cruz (Galician Center), Dra. María Dolores Silveyra (Anchorena Sanatorium), Dr. Alfonso Raggio (Antarctica Sanatorium), Dr. Juan Sebastián Riera (Ministry of Health of the Province of Buenos Aires), Dr. Enio García (Ministry of Health of the Province of Buenos Aires), Dr. Juan Canela (Ministry of Health of the Province of Buenos Aires), Dr. Mario Rovere (Ministry of Health of the Province of Buenos Aires) , Dr. Fernando Althabe (WHO), Dr. Eduardo Bergel (IECS),

Advisors: Dr. Daniel Stamboulian (FUNCEI)

1. INTRODUCTION

SARS-CoV2 is a new and particularly aggressive virus for elderly individuals, who represent between 73% and 90% of fatal cases in different regions of the world [28, 30, 40]. Mortality, the need for intensive care, mechanical ventilation, oxygen requirements, and hospitalizations for respiratory disease increase markedly with advancing age in patients [2, 3, 29, 32, 46]. In fact, the frequency of death from disease due to SARS-CoV2 (COVID-19) is 8% in patients between 70 and 80 years old, and increases to 14.8% in those over 80 [23]. Specifically in hospitalized patients older than 75 years, mortality is 29.4% [24], and in intensive care it amounts to an alarming 43.5% [25]. Several comorbidities associated with vascular and / or pulmonary disease worsen the prognosis of those infected even in patients younger than 70, including arterial hypertension, diabetes, obesity, and chronic obstructive pulmonary disease (COPD) [3,23,30,31]. To date, the virus has caused more than 290,000 deaths worldwide, more than 300 of them in Argentina which is contained through a transitional strategy quarantine quasi-universal [4]. There is no specific treatment available yet. The results of the efficacy trials for SARS-CoV2 vaccines will be known within a minimum of 10-14 months.

SARS-CoV2 is an enveloped virus that contains single stranded RNA in the positive sense bound to a nucleoprotein (protein N), within a capsid composed of matrix proteins (protein M). The envelope contains spine-shaped glycoproteins (protein S) that bind to the cellular receptor ACE2 in humans and generate neutralizing antibodies [13]. Primary SARS-CoV2 infection, like other respiratory diseases, generates an antibody response with early production of IgM followed by specific IgG against viral proteins [14]. Detection of virus neutralizing antibodies is common, reaching high levels of up to 1: 21,500 $PRNT_{50}$, mostly exceeding 1: 500 titers after 28 days of symptom onset in mild patients [41]. Approximately 5% of patients have neutralizing antibody levels <1:40, especially the younger ones [41]. A study of primary respiratory tract infection in rhesus macaques, using 10^6 pfu of SARS-CoV2 followed by a second intratracheal challenge using the same virus and doses 28 days later, demonstrated the absence of reinfection after an extensive evaluation by RT-PCR in tissues post-necropsy [42]. Neutralizing titers before the second inoculum ranged from 1:8-1:16 $PRNT_{50}$ [42]. **These findings - limited indeed, given the novelty of the problem - suggest that even low neutralizing antibody titers could prevent severe disease due to the virus.**

Protecting the populations most vulnerable to SARS-CoV2 is imperative, in the context of a highly infectious pathogen (R_0 estimated between 2 and 3.28) [27, 33, 34]. Its contagiousness rapidly overwhelms the health capacity of developed countries in different regions of the world [5] and threatens the health resources of developing countries [6]. Regions of Italy, Spain and the United States have been overwhelmed by the pandemic, which represents a serious threat to Argentina, coinciding with the beginning of the annual circulation of other lung pathogens, such as the common flu and respiratory syncytial virus [26]. Obviously, it would be

impossible to respond to an avalanche of critically ill patients [7], and any strategy aimed at reducing infections and the development of severe disease **is directly aligned with the medical objective of saving lives and with the health needs of the country in order to provide the best possible care for those patients who need it**.

Post-exposure prophylaxis to viruses and treatment in early stages of disease, through defenses obtained in convalescent plasma, is a widespread practice with successful antecedents in the history of medicine at a national and global level. As early as 1960, Brunell et al. managed to prevent clinical varicella in siblings with sick parents, using anti-varicella zoster immunoglobulins obtained from the plasma of previously infected patients [8]. Today, for example, enriched immunoglobulin for measles is used in unvaccinated people who were in contact with a patient for the previous 6 days with an efficacy close to 100% [9, 52]; a similar product enriched for varicella zoster virus is administered to unvaccinated pregnant women, newborns, and immunosuppressed patients in contact with infected persons within 96 hours, reducing the incidence of severe disease by 90% [10, 53, 54]; tetanus immunoglobulin supplements vaccination in soiled wound victims with incomplete primary immunization [43]; gamma globulin against hepatitis B is used as prevention for newborns of infected mothers with an efficacy of 75% [44, 55]; and rabies gamma globulin is ~ 100% effective in the prophylaxis of post-injury due to a rabid animal [11,56]. **Interventions using human immunity derived from convalescent plasma have been shown to be safe, have prevented countless cases of severe disease, and have preserved lives around the world.**

The main objective of our study is to evaluate the efficacy of convalescent plasma in reducing the progression to severe disease in people between 65-74 years with at least one comorbidity and in all those ≥75 years of age who present with mild symptoms of less than 48 hs of evolution at the time of screening and with an early diagnosis of COVID-19. *Our central hypothesis is that a single dose convalescent plasma compared against placebo (saline at 0.9%) administered up to 72 hours after the onset of symptoms by SARS-COV2, prevent progression to severe respiratory disease in subjects 65-74 years with at least one comorbidity and in ≥ 75 years irrespective of the presence of comorbidities.*

2. OBJECTIVES OF THE STUDY

2.1. Primary objective

To evaluate the efficacy of convalescent plasma, starting 12 hours after administration, in reducing the progression to severe respiratory disease in people between 65-74 years with at least one comorbidity and in all those ≥75 years with mild symptoms and a diagnosis of early COVID-19 until 15 days of administration of

treatment (16-18 days of disease considering the pre-symptomatic period before enrollment).

2.2. Secondary Objectives

The Secondary Objectives include determining if the administration of convalescent plasma up to 15 days or thereafter up to a maximum of *25 days of the administration of treatment in those still hospitalized*:

- Reduces the need for oxygen support with maximal oxygen therapy (O_2 reservoir mask) and/or use of non-invasive respiratory support (NIV support including CPAP) and/or admission to ICU and/or requirement of invasive mechanical ventilation due to SARS-CoV2 in patients between 65-74 years with at least one comorbidity and in all those ≥75 years.
- Reduces critical illness defined as (a) presence of acute respiratory failure (PaO2 / FiO2 ≤ 200 mm Hg.) and / or (b) shock (defined by need of vasoactive drugs to maintain MAP equal to or greater than 65 mm Hg) , and / or (c) multi-organ dysfunction syndrome (MODS): acute kidney injury (defined by a creatinine increase two or more times from baseline or a creatinine increase of 0.3 mg / dl) , elevated liver enzymes (transaminases) greater than three times the upper normal value , acute cardiomyopathy (defined by troponin elevation above the normal level and/or new electrocardiographic or echocardiographic changes of myocardial damage) in patients 65-74 years with at least one comorbidity and in all those ≥ 75 years due to COVID-19.
- Reduces mortality due to SARS-CoV2 in patients between 65-74 years with at least one comorbidity and in all those ≥ 75 years due to COVID-19.
- Decreases the length of oxygen support due to hypoxemia associated with COVID-19.
- Describe the safety of convalescent plasma administration in patients between 65-74 years with at least one comorbidity and in all those ≥75 years with COVID-19.
- Explore the concentration of IgG anti-S SARS COV2 in plasma of participants associated with the absence of severe respiratory disease obtained at 24 hours of infusion.

2.3. Exploratory Objectives

- Explore whether, rather than protect against the severe respiratory disease, administration of convalescent plasma delays the onset of the disease.
- Explore the effects of convalescent plasma on primary humoral immune response against infection by SARS COV2 at 90 days post-illness.

- Explore whether the effects on respiratory and cardiovascular disease and long-term mortality were affected by the intervention at 12 months of enrollment.
- Explore the correlation between viral load determined by RT-PCR at diagnosis and the response to plasma treatment.

3. EFFICACY ASSESSMENT CRITERIA

3.1.1. Primary Efficacy Assessment Criterion

Severe respiratory disease due to SARS-CoV2, confirmed by detection of viral RNA by RT-PCR, and defined by the presence of any of the following two variables in a non-exclusive way: (a) respiratory rate ≥30 per minute, (b) oxygen saturation in room air <93% [20,21]. The primary endpoint will be determined from 12 hours of the start of the infusion until 15 days since administering treatment.

3.1.2. Secondary Efficacy Assessment Criteria *(up to 15 days or, thereafter, up to a maximum of 2 5 days after the administration of treatment if continued hospitalization)*

- Need for oxygen support with maximum oxygen therapy (O_2 reservoir mask) and/or non-invasive respiratory support (NIV support including CPAP) and/or admission to ICU and/or requirement of invasive mechanical ventilation, due to SARS-CoV2.
- Critical illness defined as (a) presence of acute respiratory failure (PaO2 / FiO_2 ≤ 200 mmHg.) and/or (b) shock, and/or (c) multi-organ dysfunction syndrome (MODS) according to criteria detailed in section 2.2: acute kidney injury, elevated liver enzymes, acute cardiomyopathy, due to SARS- Cov2.
- Mortality due to COVID-19.
- Combination of the secondary efficacy endpoints # 1 (need for oxygen support with…) and / or # 2 (defined critical illness…) and / or # 3 (mortality from covid-19).
- Duration of oxygen requirement in patients with COVID-19 due to O_2 saturation in room air <93%.

4. HYPOTHESIS AND JUSTIFICATION

4.1. Hypothesis

Our central hypothesis is that a convalescent plasma dose compared to placebo, and administered up to 72 hours from the onset of mild symptoms, will prevent progression to severe respiratory disease due to covid-19 in patients between 65-74 years with at

least one comorbidity and in all those ≥75 years who present with less than 48 hours of evolution and with mild symptoms.

4.2. Justification

The efficacy of an economically accessible therapeutic preparation against SARS-CoV2 analyzed by means of a randomized, double-blind study in vulnerable patients would allow its applicability to be immediately scaled up nationally and internationally through massive plasma donation campaigns in convalescent patients awaiting definitive solutions such as successful drugs, monoclonal antibodies, or vaccines [17]. Even if there is concentrated partial protection in the lower respiratory tract [18], *this same strategy could hypothetically allow immunization of subjects through controlled replication of the germ in the upper respiratory tract* (as in the case of passive administration of antibodies against respiratory syncytial virus in infants [19]).

5. STUDY DESIGN

A randomized, double-blind, placebo-controlled study to test the efficacy of convalescent plasma, administered up to 72 hours after the onset of symptoms, to prevent progression to severe respiratory disease. The study will be conducted in subjects aged 65-74 years at the least one comorbidity and all ≥ 75 years who presented with mild symptoms of less than 48 hours at the time of screening (as defined in section 5.1) and early diagnosis of COVID-19. Subjects will be followed for a minimum observation period of 15 days in which participants will remain under medical supervision daily to determine the primary endpoint. Monitoring will extend thereafter, up to 25 days if subjects remain symptomatic and hospitalized, to analyze secondary endpoints.

The study is projected to incorporate an estimated maximum of 210 patients (see 9.0 Sample size). Participants will be randomized in a 1:1 ratio.

Table 1. Treatment Assignments

Treatment Group	Range of subjects assigned by branch	Test Article	Intravenous Dosing Volume	Intervention Administration Day
A	105	Placebo (0.9% saline solution)	25 0 cc	Day 0
B	105	Convalescent plasma		

All participants will receive a single intravenous dose (EV) - according to the ADMINISTRATIVE AND TECHNICAL REGULATIONS RM 797/13 - 139/14 - 1507/15

Directorate of Blood and Blood Products Ministry of Health of the Nation (at http: // www. msal.gob.ar/disahe/images/stories/pdf/normas-hemoterapia.pdf) on Day 0 with the assigned test article, convalescent plasma or placebo (see Table 1). For each subject, participation in the study will last a minimum of 15 days or until the resolution of symptoms from the administration of the test article with a maximum of 25 days. Participating subjects will be monitored during and after administration of the test article to assess expected and unexpected safety events after plasma administration. A Data and Safety Monitoring Board will oversee the enrollment, efficacy, and safety of the participants throughout the study.

The study will be conducted at the San Juan de Dios Hospital, the Simply Evita Hospital, the Dr. Carlos Bocalandro Hospital , the Evita Pueblo Hospital, the San Isidro Central Hospital and the Antarctic Sanatorium of the Province of Buenos Aires in close coordination with health effectors of the provincial Ministry of Health and the Hospital Central Militar, the Sanatorio of Los Arcos, CEMIC, the Research Center OSECAC , the Sanatorio Finochietto , the Galician Center of Buenos Aires, the Sanatorio Anchorena and Olivos Clinic and will not interfere with the care and standards of patient care established for notification and management of this disease.

MOBILE-COVID TEAM. Given the context of the COVID-19 situation in the AMBA with the reduction in the availability of beds and the overload of hospital staff added to the exponential increase in severe cases, mildly symptomatic patients without oxygen requirements and from nursing homes find it extremely difficult (almost impossible) to be admitted to the hospitals. Therefore, to facilitate the incorporation of the main potential beneficiaries of this intervention to the study (that is, the most vulnerable elderly) and given the enormous existing public health need to provide therapeutic alternatives against this scourge, a COVID-Mobile unit will be added to monitor volunteers in COVID-PAMI centers where the administration of the investigational product (now clearly demonstrated as safe in publications in thousands of patients) are performed to the same standards and the same equipment as in all other research sites. The COVID-Mobile team will record the evolution of these participants who are under the care of doctors and health personnel from PAMI *on site*. Any transfer of these patients to centers of greater complexity due to the natural evolution of their disease will be the decision of the treating physicians of the PAMI, and the mobile research team will limit itself to continuing to collect data on their clinical progress in the same way as it does today when a patient is transferred or receives an early discharge from another institution.

5.1. Eligibility criteria

5.1.1 Inclusion Criteria:

A subject must meet the following criteria to be included in the study:

1. Age ≥ 75 years or age between 65-74 years with at least one of the following comorbidities:
    a. Diagnosis of arterial hypertension under pharmacological treatment.
    b. Known diagnosis of diabetes in treatment with one or more of the available drugs (Appendix I).
    c. Obesity (BMI -Body mass index- ≥ 30 kg / m2),
    d. Chronic obstructive pulmonary disease (COPD) treated with any of the available drugs (Appendix I).
    e. Cardiovascular disease defined as a) known diagnosis of coronary heart disease, b) history of ischemic stroke or hemorrhagic, or c) ICC (defined as FE < 40%).
    f. Chronic kidney disease (defined as a reduction in GFR below 60 ml/min/1.73 m^2).
2. Present <u>for less than 48 hs</u> : (A) axillary temperature ≥ 37,5°C or fever equivalence (defined as feeling cold and/or chills and/or unexplained sweating) , <u>combined with</u> (a) dry cough and / or (b) difficulty breathing and / or (c) odynophagia and / or (d) anosmia and/or (e) dysgeusia and / or (e) any of the following symptoms : fatigue, anorexia, myalgia or rhinorrhea .
3. SARS-CoV2 diagnosis confirmed by RT-PCR
4. Being able, according to medical judgment, to understand and comply with the study procedures and to consent or not to their participation.
5. Provide informed consent.
6. Patients with cognitive vulnerability with support in decision-making by their representative, can be included as detailed below. (see section 12)

5.1.2 Exclusion Criteria

A subject who meets <u>any</u> of the following criteria will be excluded from the study:

1. Present at the time of inclusion SEVERE RESPIRATORY DISEASE defined as (a) respiratory rate ≥30 per minute and / or (b) oxygen saturation in ambient air <93%.
2. HEART FAILURE in functional class III and IV (according to the functional classification of the New York Heart Association).
3. Known diagnosis of CHRONIC KIDNEY INSUFFICIENCY in filtration stages G4 and G5 (according to KDIGO classification).
4. Previous diagnosis of PRIMARY HYPOGAMMAGLOBULINEMIA (congenital and hereditary).
5. Previous diagnosis of MONOCLONAL GAMMOPATHIES (multiple myeloma, Waldenström macroglobulinemia, primary amyloidosis, heavy chain disease, among others).
6. Previous diagnosis of SELECTIVE DEFICIENCY OF IgA.
7. Previous diagnosis of MYELODYSPLASIC SYNDROMES. [WHO classification: refractory thrombocytopenia (TR), refractory anemia (RA), etc.]

8. Previous diagnosis of CHRONIC LYMPHOPROLIFERATIVE SYNDROMES. (WHO classification: peripheral B lymphocyte lymphomas, T lymphocyte and NK cell lymphomas, Hodgkin lymphoma).
9. KNOWN HYPERSENSITIVITY to the administration of immunoglobulins, plasma, monoclonal antibodies and / or vaccines.
10. Active cancer, defined as receiving or having received or receiving chemotherapy, radiotherapy, or new designer or monoclonal drug treatments in the last six months.
11. Known HIV, HBV, or HCV infection.
12. Chronic administration (defined as more than 14 calendar days) of immunosuppressants or other drugs that modify the immune system **at the time of enrollment** or within the 6 months prior to administration of study medication. An immunosuppressive dose of glucocorticoids will be defined as a systemic dose of ≥10mg of prednisone per day or its equivalent.
13. Solid organ transplant.
14. Known chronic liver disease diagnosed with stage II-III-IV cirrhosis.
15. Chronic lung disease with oxygen requirement.
16. Any other physical, psychiatric or social condition that may, at the discretion of the investigator, increase the risks of participation in the study for the participant or that may lead to the collection of incomplete or inaccurate safety data.
17. Patients who are receiving any type of anticoagulant therapy orally: family of dicoumarins (Warfarin such as Acenocoumarol) or direct acting anticoagulants (DOAC) (Rivaroxaban, Dabigatran, Apixaban) as well as those who are receiving heparin in any of its types for anticoagulant therapy purposes.

5.2. Study procedures (Table 2)

5.2.a. Participating population and identification process of potential subjects.

Subjects 65-74 years with at least one comorbidity and all ≥ 75 years who present for less than 48 hours the following symptoms: (**a**) temperature ≥ 37,5°C or fever equivalence (defined by feeling cold or chills or unexplained sweating) , <u>combined with</u> (**b**) dry cough and / or dyspnea and / or anosmia / dysgeusia and / or odynophagia and / or fatigue and / or anorexia and / or myalgias and / or rhinorrhea .

Those patients who meet the inclusion criteria and do not meet any of the aforementioned exclusion criteria will be invited to participate in the research phase of the study in which, if they accept (expressing their agreement by signing the informed consent - research ANNEX), a sample of respiratory secretions is obtained by swabbing the nasopharynx and oropharynx (according to the procedure and regulations of the Argentinean Ministry of Health) to assay for RNA of SARS-COV2 by reverse transcriptase-polymerase chain reaction (RT-PCR).

The sample will be processed and analyzed by the laboratory designated for participating institutions daily, using the same RT-PCR test to assess the presence of RNA of SARS-COV2. This determination will be made as soon as possible (within a

maximum of 24 hours) and under all the biosecurity standards indicated by the health authorities. The samples will be kept for later testing by RT-PCR for co-infections with influenza A and B, respiratory syncytial virus and other winter viral pathogens at the INFANT Foundation.

Patients who already have a positive result (+) considered valid by MOH standards will be invited to participate in the research phase of the study and will not be swabbed again .

5. 2 .b. Enrollment for participation in the study

If SARS-Co V 2 RNA is detected in the respiratory sample, the candidate will be informed about the details of the study and eligibility will be verified again. The candidates may decide not to participate in the investigation by their free will and without any consequence whatsoever. In the event that the subject is interested in participating in the study, and after their consent is attested with the signing of the informed consent for participation (ANNEX), a unique identification number will be assigned. Once its alphanumeric code has been assigned, vital signs will be obtained and a complete physical examination will be performed to obtain the following demographic and clinical information [1-3, 25, 47-51]:

- Sex
- Age
- Usual medications and those of the last 15 days.
- History of smoking
- Comorbidities of primary interest: arterial hypertension, diabetes, coronary heart disease, heart failure, history of stroke and AMI, COPD, chronic kidney disease, and obesity**.**
- Secondary comorbidities: asthma, history of cancer, liver diseases, and neurological diseases**.**

5.2.c. Random assignment

All participants with confirmed eligibility will be randomly assigned to a treatment group. The randomization of participating subjects will be conducted by the person in charge of randomizing the study using an electronic system. Once the patient is randomized, the person in charge of the allocation will communicate with a member of the Transfusion Medicine Central Team in the study who will remove the opaque bag treatment indicated in the freezer of the Central Laboratory. The Transfusion Medicine team will proceed to take the cold bag to the hospital. There, he/she will complete the preparation of the masked product and administer the indicated treatment to the participating patient, using a venous access previously obtained by a member of the hospital team for the infusion. Only the person responsible for randomization and the physician in the Transfusion Medicine Central Team administering treatment will know the product administered to each patient (unblind). Neither the patient nor the researchers will have knowledge of the

administered treatment, conducting a double-blind study. The unblind team will keep a record of the product assignments and their administrations that will be kept confidential. In the eventual need to open the blind, such records may be used.

5. 2 .d. Preparation and administration of the test article

The preparation and administration of the convalescent plasma or placebo (physiological solution) will be performed according to the ADMINISTRATIVE AND TECHNICAL REGULATIONS RM 797/13 - 139/14 - 1507/15 Directorate of Blood and Hemoderivatives Ministry of Health of the Nation. (http://www.msal.gob.ar/disahe/images/stories/pdf/normas-hemoterapia.pdf).

Once masked, the team of Transfusion Medicine will administered the product intravenously for 1.5 hours and up to 2 hours. After administration, local reactions at the injection site and systemic reactions will be monitored for 12 hours. *This is a minimal risk study, since the administration of plasma and saline (placebo in this study) are a daily habit in medical practice.* In the event of a medical emergency, when it is known that the treatment assignment may influence the medical care of the patient, the investigator or designee may request that the subject be unblinded for the emergency. However, prior to breaking the blind the investigator must make all reasonable efforts to discuss the decision to break the blind. The investigator is expected to provide a reason for the need to break the blind, based on a significant change in the participant's immediate or short-term medical care that will result from knowledge of the treatment assignment.

5. 2 .e. Taking a blood sample for titration of IgG anti-S SARS CoV2 in serum.

At 24 hours of completion of infusion of the treatment, a sample of 5 ml of venous blood will be obtained from all participants for titration of serum IgG anti-S SARS-COV2 and held at the Foundation INFANT. The assay will be performed by the ELISA method (COVIDAR IgG, Leloir / CONICET and Genetech IgG and sNT). Serum will be preserved to -20 °C and transferred by a shuttle authorized for sample handling system transport biological the Foundation.

Window for sample collection: +/- 4 hours. The sample may be taken within a minimum period of 20 hours and a maximum of 28 hours after the administration of the Research Product is complete.

5. 2. f. Daily clinical monitoring

We will perform one control daily from Day 0 and at least 15 days from the infusion and up to 25 days for those subjects who remain hospitalized with symptoms after day 15. Patients who are discharged prior to the day 15 will be monitored at home by a team of physicians trained for this purpose working in collaboration with the research centers. The following clinical information will be collected daily (using a questionnaire designed for this purpose) by study personnel and **without interfering with the patient's medical care or altering the standards recommended by the health care**

authorities for the management of patients with COVID-19 : (a) respiratory rate (looking at the chest excursion for 30 seconds) , (b) oxygen saturation, (c) temperature, (d) central heart rate , (e) cough and duration, (f) sore throat and duration , (g) feeling of fever / chills, (h) need for supplemental oxygen provision and duration, (i) need for intensive care and duration, (j) need for non-invasive or invasive respiratory support and duration, (k) evidence of SDMO : according to criteria for acute kidney injury , criteria for elevated liver enzymes and criteria for acute cardiomyopathy (detailed in section 2.2) , (l) survival.

Table 2. Schedule of study procedures.

Study Day	**-1 Research**	**0 Day 0**	**Daily follow up**
Informed consent for the evaluation of history, clinical condition and *SARS-COV2 diagnosis*	X		
Nasopharyngeal swab collection for confirmation of SARS-CoV2 by RT-PCR	X (1)		
Informed consent to participate in the study		X	
Medical history review		X	X
Vital signs		X	
Eligibility confirmation		X	
Concomitant medications		X	X
Random assignment of treatment		X	
Administration of the intervention		X	
Monitoring of transfusion		X	
Surveillance of adverse events		X *	(X)
Taking a blood sample after the infusion is complete			24 hours (+/- 4 hours)
Surveillance of respiratory symptoms		X	X

(1) This procedure will not be required if a result is available by a valid method at the time of patient screening.

We consider that the patient completes its participation when reaching day 15 (if the patient is already discharged), at the time of discharge between days 15 and 25, or at the expiration of day 25 if he/she continues hospitalized.

6. Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will monitor the safety of the subjects throughout the study. The DSMB includes at least experienced members in managing internal medicine, infectious diseases, and a biostatistician with specific experience in the design, analysis and safety of clinical trials. The DSMB will operate under an approved plan and will have the responsibility to monitor the outcomes/end points, adverse events (AE) and serious adverse events (SAE) , and recommend termination of the study if it appears at any point during the study that participants (or a subset of participants) are at undue risk as a result of their participation. The DSMB will meet (by teleconference) weekly to review the accumulated data on safety and efficacy and will conduct an interim analysis of the data. The DSMB will issue written recommendations based on its meetings regarding the continuity of the study. The minutes of each meeting will be recorded in documented minutes based on a pre-established work schedule. Any participant-specific protected health information reviewed by the DSMB will be kept completely confidential. Sessions will be closed without access to third parties.

7. Security Monitoring

The researcher at each institution and at a general level will supervise the safety of the study patient at his/her site(s) according to the requirements of this protocol and in accordance with current Good Clinical Practices (GCP). The investigator will monitor safety data at all study sites. Security monitoring will be carried out on an ongoing basis (for example, individual review of EA S, EAs and endpoints) and on a periodic cumulative basis.

Adverse event (AE)

An AE is any unfavorable medical event in a patient who was administered a study drug that may or may not have a causal relationship to the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease that is temporarily associated with the use of a study drug, regardless of whether it is considered related to the study drug.

An AE also includes any worsening (ie, any clinically significant change in frequency and / or intensity) of a pre-existing condition that is temporarily associated with the use of the investigational product.

Covid-19 progression will not be considered an AE if it is clearly consistent with the typical progression pattern of the disease

If there is any uncertainty that an AE is due to covid-19 progression only, it will be reported as an AE or SAE, as described in the appropriate protocol section.

Serious adverse event (SAE)

A SAE, by definition, is any unfavorable medical event that at any dose:

- Results in death: Includes all deaths, even those that appear to be unrelated to the study drug (for example, a car accident in which a patient is a passenger).
- It is life threatening: In the opinion of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE which, if it had occurred in a more severe form, could have caused death.
- Requires hospitalization or extension of existing hospitalization. Hospitalization is defined as admission to a hospital or emergency room for more than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than originally planned for the event, or prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant disability (substantial disruption of one's ability to carry out normal life functions).
- It is a major medical event - Major medical events may not immediately endanger life or result in death or hospitalization, but may endanger the patient or may require intervention to prevent one of the other serious outcomes listed above (for example, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias that do not result in hospitalization).

In the case specific of this study we will consider AE or SAE , according to the detailed description in section 11.2, those that are initiated within 12 hours after administration of the IP and clinical exacerbations and deaths associated with these events. We will not consider as AE and SAEs those events occurring after 12 hours of initiation of treatment, that are consistent with the clinical course in patients infected with SARS COV2.

Adverse Event Collection Period

The reporting period for AE/SAE begins when the participant was initially included in the study (date of signature of informed consent for participation) and receives the infusion and continues for events that occur in the next 12 hours (see section 11.2) . During the follow up period, after the initial 12 hours of IP administration subjects will be monitored for the clinical outcome associated with primary and secondary endpoints.

8. Leaving the Study Prematurely

Subjects may leave the study at any time if they wish, but we will make every effort to monitor them during the stipulated period to guarantee their safety .

9. Patient Replacement

Those patients who decide to drop out of the study prior to drug administration will be replaced, if necessary, to ensure an adequate number of evaluable patients.

10. Justification of the sample size and statistical analysis

There is significant uncertainty in the expected effect size of the intervention, and considering that the trial is expected to be completed in a relatively short period of time, the study is designed to have an interim analysis when the results of 50% of the subjects have been acquired.

Given the relative complexity of implementing this intervention, the minimally clinically important difference is established in a relative reduction of 40%, for an expected result rate of 50% in the control group that is reduced to 30% in the intervention group. A total sample size of 210 subjects (105 per test arm) will have 80% power, at a significance level (alpha) of 0.05 using a two-sided z-test with continuity correction. These results assume that 2 sequential tests are performed using the O'Brien-Fleming expenditure function to determine the limits of the test, as described in the table below.

Look	Time	Lower Bndry	Upper Bndry	Nominal Alpha	Power
1	0.50	-2.96259	2.96259	0.003	0.168
2	1.00	-1.96857	1.96857	0.049	0.806

Under the primary analysis strategy, we will use the Kaplan-Meier product cutoff distribution to compare treatment groups over time required to reach the primary outcome. An estimate of the relative risk and the 95% confidence interval will also be reported.

Based on a recommendation of the DSMB, we will also conduct an analysis stratified by age (65-74 years and ≥75 years) and adjust the statistical analysis by those significant risk factors whose distribution between groups can affect the outcome.

11. Test article and transfusion medicine

11.1. Voluntary donation of convalescent plasma

All procedures will be done in accordance with the STRATEGIC PLAN TO REGULATE THE USE OF PLASMA BY COVID-19 RECOVERED PATIENTS FOR THERAPEUTIC PURPOSES. (IF-2020-26315442-APN-SCS # MS)

https://www.boletinoficial.gob.ar/detalleAviso/primera/227976/20200418

Convalescent plasma will be obtained by inviting patients who experienced COVID-19 and have recovered satisfactorily in the Autonomous City and Province of Buenos Aires to participate as a voluntary donor, following the donation criteria established by the authorities. If the patient wishes to donate, they will voluntarily and altruistically sign the plasma donation consent (ANNEX).

Donors will be identified by the ministerial and institutional authorities (if it is a private body), contacted, and invited to donate in one of the five Blood Banks participating in this study:

a) Institute of Hemotherapy of the Province of La Plata
b) Central Military Hospital
c) Hemocentro Buenos Aires Foundation
d) Sarmiento Hematology Foundation
e) CEMIC

In order to donate plasma, the patient must comply with the conditions determined to date (https://www.boletinoficial.gob.ar/detalleAviso/primera/227976/20200418) or follow updates from the Ministry of Health.

Anti-SARS Cov2 antibody titration

After donating plasma by apheresis or hemodonation, in addition to the samples obtained for routine blood bank controls, a dry tube of 5 mL of whole blood will be obtained, labeled with the identification given to the donor, identification of the Blood Bank and label that identifies the purpose of the "PCC19" study to perform the antibody titer. These will be asaayed using the SARS CoV2 anti-protein S ELISA test, which in light of the existing data on protection against the virus allows an indirect extrapolation of the serum's neutralization capacity, optimized by the Leloir Institute in charge of Dr. Gamarnik, and currently used by health teams in Argentina to study immunity prevalence. Likewise, if possible, data will be correlated with the neutralizing antibody titer against a pseudovirus encoding protein S optimized by the same laboratory.

Tubes will be stored in a designated location within the Bank and shipped in an approved biological sample shipment to the INFANT Foundation (over 18 years of experience in testing) for assaying ELISAs and neutralizing antibodies.

The titers obtained by S ELISA will then be classified and those that are above 1: 1,000 selected to provide convalescent plasma for this study.

The additional high titer plasmas will also be stored to be sent to the Córdoba Blood Products Center (UNC), which will produce gammaglobulin enriched with anti-SARS-CoV2 antibodies.

Plasmapheresis (Institute of Hemotherapy of the Province in La Plata, Central Military Hospital, Hemocentro Buenos Aires Foundation, and Sarmiento Hematology Foundation)

Plasma donation will be conducted through an apheresis procedure with equipment and disposable supplies approved for this purpose, during which it is recommended to extract a volume no greater than 15% of the donor's blood volume. The anticoagulant to be used will be ACD-A or similar. In cases where volume replacement is not performed, plasma extraction should not exceed 600 ml per procedure.
The 48 hours interval must be respected between each procedure, not to exceed 2 donations in a week or 24 donations in a 12-month period.
The PCC19 units can be separated into 250ml aliquots, respecting the closed circuit and following the indications of the current standard operating procedure.

Hemodonation (CEMIC)

1-Plasma will be obatined with a Cobe Spectra equipment. 1.5 to 2 L of plasma will be extracted according to the donor's weight and tolerance to the procedure. In case of venous inaccessibility or opposition from the donor, between 400 and 500 ml of whole blood will be drawn (classic hemodonation)
2-The volume replacement will use NS and albumin solution.
3-During the procedure the plasma will be transferred to transfer bags of similar volume each (approximately 500ml).
4-The bags will be labeled as detailed below.
5-They will be frozen in the -56°C Righi vertical ultrafreezer (labeled Freezer # I, identified with COVID-19 convalescent plasma label in the Blood Bank) separated on shelves by bag type (1, 2 or 3).
6-The convalescent plasma will remain stored until its use or expiration (1 year), with appropriate safety criteria.
7-Disposal will be conducted under stipulated security regulations.
8- Stored aliquots of serum / plasma frozen for future determinations at -80°C in Eppendorf tubes.

Labelled
All units of PC COVID-19 must comply with the labeling required for fresh frozen plasma from each Blood Bank and must also have a clear identification, which must include:

- "Product Type: PC COVID-19"
- "Result of antibody titer for SARS-CoV-2" (if available)
- "CAUTION: product for research use only"
- "PROTOCOL: INFANT Foundation - Serum enriched with anti SARS-CoV2 antibodies"

Cold Chain of PCCOVID-19

1. The units are stored properly separated from the remaining plasma units and labelled for transfusional use in a place clearly identified for this purpose.

2. The PCC19 units will be stored at temperatures below -25°C, which allows a storage of 36 months and between -18°C and -25°C for 3 months of storage.

3. The units will be transported in a way to maintain the cold chain reliably.

4. Plasma units should be stored between 2 ºC and 6ºC until 24 hours after thawing. After then, they should be discarded.

Traceability

The Blood Bank and the Transfusion Service of the requesting Institution will implement a registry system that guarantees traceability between donors and recipients. In this special situation, they must also have a specific registry as this is a transfusion therapy administered in an experimental context.

11.2. Administration of the intervention

After assessing vital signs and verifying eligibility, the unblinded team from the Medical Transfusion Center will be notified of the result of the randomization process and drive to the assigned hospital with the masked treatment product cold. On arrival, they will proceed again to check the code assigned for treatment with a member of the laboratory of Transfusion Medicine of the hospital (see 5.2.c).

Placebo will be a 250 ml of normal saline (0.9%) sterile, masked and administered in the same way and speed as plasma. To avoid bias and maintain the study blinded, plasma and saline 0.9% will be masked using an opaque bag and tape that will not allow to differentiate both products. Members of the Medical Transfusion Central Team will conduct the intervention with a member of the local team. Thus, both members of the Transfusion Medicine Central Team and the respective member of Transfusion Medicine at the hospitals will not be blind, while the rest of the team with delegated functions in the studies in each Center and the patients will be blind to the intervention.

To prepare the plasma, 250 ml bags will be thawed at 37 ° C, according to the operating procedures of the Department of Transfusion Medicine at the Hospital. Plasma will be infused slowly (at least 1.5 hours and up to 2 hours) according to the hemodynamics of the patient and monitored for 12 hours and adverse effects early and late attributable to transfusion recorded.

Night window for the passage of the research product: between 8:00 p.m. and 8:00 a.m., a window of +8 hours will be tolerated for the passage of the research product. A maximum of 80 hours (72 + 8) from onset of symptoms will be allowed in these cases before starting the infusion. This exception will only be allowed in this night time.

Monitoring of adverse events associated with plasma transfusion

Transfusion-associated circulatory overload (TACO)

Transfusion-associated circulatory overload (TACO) is the most common pulmonary complication and is an independent risk factor for hospital morbidity and mortality, with a higher incidence in critically ill patients [58]. The estimated frequency of TACO varies

from 1% to 5% depending on the hemovigilance system [59], up to 8% in advanced post-surgical patients, and 11% in critically ill patients [60 61 62]. Risk factors include heart, lung, or kidney disease, age ≥70 years, and a positive, pre-transfusion fluid balance [63-64]. Most cases of TACO are prevented by slowing the transfusion rate and establishing the usual measures for fluid overload in susceptible populations. Overload constitutes a requested AE, but if it does not improve within 120 minutes after the infusion or requires - in the opinion of the responsible professionals - transfer of the patient to intensive care due to poor clinical progression, should be reported immediately as a SAE.

Diagnostic criteria for TACO [19]
During or up to 12 hours after the transfusion, TACO is characterized by the presence of a total of 3 or more of these criteria:
A. Acute or worsening respiratory compromise
B. Evidence of acute or worsening pulmonary edema based on clinical and / or chest radiographic images and / or other noninvasive assessment of cardiac function (echocardiogram)
C. Evidence of cardiovascular changes not explained by the patient's underlying medical condition, including: tachycardia, hypertension, widened pulse pressure, jugular venous distention, enlarged cardiac silhouette, and/or peripheral edema.
D. Evidence of fluid overload, including any of the following: a positive fluid balance; response to diuretic therapy, or dialysis combined with clinical improvement; and variation of the patient's weight.
E. Increased level of B-type natriuretic peptide (eg, BNP or NT-pro BNP) above the age-specific reference range and greater than 1.5 times the pre-transfusion value.

Transfusion Associated Acute Pulmonary Injury (TRALI)
This is an acute respiratory distress syndrome, it will be considered a SAE and it occurs during or within six hours after the administration of the transfusion. Prospective studies of TRALI reported very low incidence rates (0.0008% to 0.001% of transfused patients) [19] after the implementation of strategies to prevent the transfusion of blood components obtained from multiparous female donors. In our study, multiparous women will not be invited to donate plasma.
Treatment of a patient with TRALI involves immediate interruption of the transfusion.

TRALI diagnostic criteria: [28]
TRALI Type I: patients who do not have risk factors for ARDS and meet the following criteria:
A. i. Acute onset
ii. Hypoxemia ($Pa\ O_2$/ $Fi\ O_2$ ≤ 300 or SpO_2 <90% in room air).
iii. Pulmonary edema with clear evidence of bilateral images (CXR, CT or ultrasound)
iv. There is no evidence of left ventricular hypertrophy or, if present, it is not the main contributor to hypoxemia.
B. Initiation during or within 6 hours of transfusion.
C. Temporarily unrelated to an alternative risk factor for ARDS.

TRALI Type II: patients who have risk factors for ARDS (but have not been diagnosed with ARDS) or who have existing mild ARDS (Pa / Fi 200-300), but whose respiratory status is deteriorating and is considered to be due to a transfusion based on:
a. The results described in categories a and b of TRALI Type I, and
b. Stable respiratory status within 12 hours prior to transfusion

Allergic - Anaphylactic Reactions
Allergic reactions generally occur during or within 4 hours of transfusion and are most frequently associated with platelet transfusions (302 per 100,000 platelet units) [29]. Symptoms are caused by mediators such as histamine, released in mast cell and basophil activation [30]. Frequently, the clinical presentation is mild (rash, pruritus, urticaria, and angioedema are localized) and they are a solicited AE. Mild allergic transfusion reactions generally resolve with the administration of the usual treatment for allergic reactions, being able to restart the infusion of the unit. The transfusion should be stopped if symptoms reappear. The incidence of anaphylactic reactions is 8 / 100,000 units of transfused platelets. The most severe reactions generally present with bronchospasm, respiratory distress, and hypotension and constitute a SAE and should be reported as such immediately [31-35].

Acute hemolytic transfusion reactions
Acute hemolytic transfusion reactions (ATRs) can occur when incompatible red blood cells are transfused or, less frequently, large amounts of plasma incompatible with the patient's ABO are transfused. The central pathophysiological mechanism is intravascular hemolysis and is considered a SAE. It presents with sudden fever and chills, retroperitoneal pain and dyspnea, hemoglobinuria and even disseminated intravascular coagulation, acute renal failure, and shock. Since fever and chills may be the only early signs, it is important to monitor the patient during the transfusion and stop the transfusion immediately if there is any change in vital signs or unexpected symptoms appear. Treatment is based on supportive measures to alleviate symptoms. Proper patient identification and adherence to all procedures related to handling pretransfusion specimens and administration of transfusions are essential to prevent ATRs [36].

Transfusion Communicable Infections [39]
The risk of transmission of infectious diseases through transfusions has been dramatically reduced, secondary to the great advances in unit testing, and pathogen inactivation for plasma units and their components [51] and the implementation of rigorous donor selection methods. In our environment, the samples are tested for HBV, HCV, HIV, HTLV and *Trypanosoma cruzi* [52]. In the United States, the risk of acquiring HBV and HIV by transfusion is 1:280,000 and 1:1,467,000, respectively [53 54]. Due to freezing of plasma samples, contamination by bacterial pathogens and CMV is extremely rare. There are only a dozen cases among the millions of transfusions reported in Germany and Canada of bacterial transmission. It is estimated that the potential source of this contamination would have been the water baths used to defrost the units. This is easily avoidable with proper cleaning and sterilization of defrosters [39].

12. Ethical considerations

Statement of Good Clinical Practice

This study will be conducted in accordance with the protocol and with the following considerations:

- the ethical principles that have their origin in the Declaration of Helsinki,
- the current Good Clinical Practice (GCP) guidelines from the International Council of Harmonization (ICH),
- current laws and regulations.

The protocol, the Informed Consent forms (ICF) and other relevant documents have been reviewed and approved by INFANT Foundation, the participating authorities and sent to the Ethics Committee (EC) for evaluation.

Ethics Committee (EC):

A properly constituted EC, as outlined in the ICH guidelines for GCP, must review and approve:

- The protocol, ICF and any other materials that are provided to the participants before any subject can enter the study
- Any amendment or modification to the study protocol or to the CRF prior to implementation, unless the change is necessary to eliminate an immediate danger to patients, in which case the EC should be informed as soon as possible

In addition, they must be informed of any event that may affect the safety of patients or the continued conduct of the clinical study.

INFANT should receive a copy of the approval letter from the EC before sending drug supplies to the investigator at each hospital. The approval letter should include the title of the study, the documents reviewed, and the date of the review.

The investigator must keep on file the records of the EC review and approval of all study documents

Informed Consent Process

The ICF used by the researcher will be approved by the corresponding EC.

It is the responsibility of the investigator or delegated professional to obtain the written informed consent from each subject prior to their participation in the study and after the objectives, procedures, and potential risks of the study have been fully explained in language that the subject can understand. The ICF must be signed and dated by the researcher or delegated personnel who performed the consenting process.

The investigator or delegated staff will explain the nature of the study to the participant and answer all questions about the study. He/she will inform them that their participation is voluntary. The participant must sign the informed consent form (ICF) before any specific study activity takes place.

Participants who can understand but cannot write and / or read will have the IC read to them in the presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was obtained.

Two copies will be signed. The investigator should keep one copy as part of the patient's study record, and the other signed copy should be given to the participant.

- Patients with cognitive vulnerability:
  They may be included after obtaining informed consent from their legal representative as appropriate:
  to. Patients who have a statement of disability: duty of who has been designated as curator whenever there is such a statement.
  b. Patients who can decide for themselves prior assistance of a "support" person according to provisions of the Law: usually the patient can designate who can help him/her decide.
  c. Patients without a judicial declaration of incapacity and who have not appointed a support or representative either: the patients' rights law will apply.
  The means to prove the representation can consist of any document that proves the appointment as curator (if applicable) or any advance directive of the patient where it establishes who represents him in health matters, or documents that prove the relationship according to Law 26529.

13. Confidentiality and Protection of Personal Data

The investigator will take all appropriate measures to ensure that the anonymity of each study subject is maintained in research records transmitted outside the health center. The original and essential documents of the study must be kept in strict confidence at each research center by the study team.

The personal data of the participants will be stored in the study center in a password-protected print and/or electronic format or in a locked room, to guarantee the exclusive access of authorized study personnel.

To protect the rights and freedoms of natural persons in relation to the processing of personal data, a unique and specific alphanumeric code will be assigned to the participants. The records or data sets of the participants that are transferred will contain the alphanumeric code; the names of the participants will not be transferred. All other identifiable data transferred between researchers will be identified by this unique, participant-specific code. The study center will maintain a confidential list of participants who participated in the study under strict security (password protected or in a locked room), linking the alphanumeric code of each participant with their real identity.

14. Study Documentation

Records and documents, including signed FCIs, regarding the conduct of this study will be retained by the investigator for 15 years after study completion, unless local regulations or institutional policies require a longer retention period.
The investigator from each participating institution should consult with INFANT before discarding or destroying any essential study documents after study completion or interruption. If approved, records must be destroyed in a way that ensures confidentiality.

15. Study monitoring

15.1. Monitoring of study sites

The study monitor will visit each site prior to enrolling the first patient and periodically during the study in accordance with the Approved Study Monitoring Plan.

The monitor receives weekly reports from each of the centers with the number of patients in a period of research and enrolled.

Monitoring visits and centralized monitoring activities will be carried out in accordance with all applicable regulatory requirements and standards in force in Argentina. It is understood that the monitor will contact each researcher and
their responsible team regularly and will be allowed to verify the generation of the different study records.

It will be the monitor's responsibility to inspect the data capture systems at regular intervals throughout the study to verify compliance with the protocol and the integrity, precision and consistency of the data; and adherence to the ICH GCP and local regulations on conducting clinical research. The monitor should have access to laboratory reports, study medication, records associated with it, and other medical records necessary to verify the entries in the EDC.

An unblinded **monitor** will be assigned whose role will be limited to auditing
the logistic data, management and study treatment registration according to the approved protocol and treatment instructions:

- reception and storage conditions
- randomization and administration
- return or destruction / final reconciliation

15.2. Source document requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents).

The researcher must keep all the source documents in the file of the data submitted to the study form (CRF). Some data generated from the study may be entered directly into the EDC system (direct data capture), after approval of the process by the Ethics Committees involved. Case report forms and source documents must be available at all times.

15.3. Case Report Form Requirements

Study data obtained in the course of the study will be recorded in case report forms (CRF) and sent to INFANT in scan format. Once received, they will be archived and processed by entering the EDC system by trained INFANT personnel. All required CRFs must be completed for each patient enrolled in the study. The investigator should retain a copy of each patient's CRF case book as part of the study record and should be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

16. Audits and inspections

This study may be subject to a quality assurance audit or inspection. If this occurs, the investigator is responsible for:

- Provide access to all facilities, study data and documents necessary for inspection or audit.
- Communicate any information arising from the inspection of the regulatory authorities to INFANT immediately.
- Take all appropriate measures requested by INFANT to resolve the problems found during the audit or inspection.

Documents subject to audit or inspection include, but are not limited to, all source documents, CRF, medical records, correspondence, FCI, CE files, supporting laboratory quality control and certification documentation, and relevant records for the study being conducted. they maintain pharmacy facilities. The storage conditions of study material are also subject to inspection. Additionally, sponsor representatives may observe the conduct of any aspect of the clinical trial or its support activities both within and outside of the investigator's institution.

In all cases, the confidentiality of the data must be respected.

ANNEX

HEART FAILURE
NYHA SCALE (NEW YORK HEART ASSOCIATION)
FUNCTIONAL ASSESSMENT OF HEART FAILURE.

NYHA FUNCTIONAL CLASSIFICATION	
Class I	Without limitation of physical activity. Normal physical exercise does not cause fatigue, palpitations, or dyspnea.
Class II	Slight limitation of physical activity. No symptoms at rest. Ordinary activity causes fatigue, palpitations, or dyspnea.
Class III	Marked limitation of physical activity. No symptoms at rest. Less than ordinary physical activity causes fatigue, palpitations or dyspnea.
Class IV	Inability to carry out any physical activity; symptoms of heart failure are present even at rest and increase with any physical activity.

CIRRHOSIS (PORTAL BAVENO IV HYPERTENSION CONSENSUS)

CIRRHOSIS STAGES	
Stage 1	Absence of esophageal varices and ascites
Stage 2	Esophageal varices without a history of bleeding and without ascites.
Stage 3	Presence of ascites with or without esophageal varices.
Stage 4	Gastrointestinal bleeding due to portal hypertension, with or without ascites.

KIDNEY DISEASE CLASSIFCIATION KDIGO.

DEGREE	GLOMERULAR FILTRATION ML / MIN / 1.73 M2	DESCRIPTION
GRADE 1	> 90 G5	Normal or elevated
GRADE 2	60-89	Slightly diminished
GRADE 3	45-59	Slight to moderately decreased
GRADE 3b	30-44	Moderate to severely diminished
GRADE 4	15-29	Severely diminished
GRADE 5	<15	Kidney failure

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Protocol versions

Protocol version	Date	Modifications
2.0	12-may-20	Originally submitted.
3.0	23-jun-20	Eligibility criteria were updated to include elderly subjects with cognitive impairment as represent a vulnerable population for COVID-19 disease severity.
4.0	22-jul-20	Secondary endpoint definition update: a) Inclusion of a combined analysis of the three secondary endpoints and, b) Inclusion of an additional secondary endpoint for duration of the oxygen supplementation in patients with oxygen saturation <93% at room air.
5.0	27-jul-20	Inclusion of geriatric institutions transformed by the health system into low-complexity units were as study centers.
6.0	02-nov-20	As recommended by the DSMB the analysis plan was updated to include a stratified analysis by age (65-74 years and ≥75 years)

EFFICACY EVALUATION OF COVID-19 CONVALESCENT PLASMA ADMINISTRATION IN THE DECREASE OF PROGRESSION TO SEVERE DISEASE IN ELDERLY ADULTS WITH MILD SYMPTOMS OF SARS-COV2

Interim Analysis Plan

September 11th 2020

Report to:
Main Researcher: Fernando Polack

Written by:
L. Gibbons, E. Bergel, M. Berrueta, F. Althabe

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OBJETIVES

To evaluate the efficacy of convalescent plasma, from 12 hours of administration, in reducing progression to severe respiratory disease in subjects between 65-74 years of age with at least one comorbidity or ≥75 years old, with mild symptomatology and with early COVID-19 diagnosis up to 15 days of treatment administration (16-18 days of disease considering the symptomatic period previous enrollment) in an interim analysis.

Secondary outcomes include determining if convalescent plasma administration up to 15 days, or from there up to a maximum of 25 days since treatment administration if the patient remains in hospital, achieve to:

- To reduce the need of respiratory support with maximum oxygen therapy (oxygen reservoir mask) and/or the use of non-invasive respiratory support (NIV support, including CPAP) and/or admission to the intensive care unit (ICU) and/or invasive mechanical ventilation assistance because of SARS-CoV2 in patients between 65-74 years of age with at least one comorbidity or in patients ≥75 years old with COVID-19.
- To reduce critical systemic illness defined as (a) presence of acute respiratory failure (PaO2/FiO2 ≤ 200 mm Hg.) and/ or (b) shock (defined by the need of support with vasoactive drugs to maintain the mean arterial pressure ≥ 65 mm Hg.) and/or (c) multiorganic shock syndrome: acute renal injury (defined by creatinine increase two or more times from baseline or creatinine increase of 0.3 mg/dl), increase of hepatic enzymes (transaminase) in three or more times the normal range, acute cardiomyopathy (define by the increase of troponin above normal range and/ or new electrocardiographic or echocardiographic abnormalities due to myocardial damage) due to SARS-Cov2 in patients between 65-74 years of age with at least one comorbidity or in patients ≥75 years old with COVID-19.
- To reduce the mortality due to SARS-Cov2 in patients between 65-74 years of age with at least one comorbidity or in all patients ≥75 years old with COVID-19.
- To describe the safety of convalescent plasma administration in patients between 65-74 years of age with at least one comorbidity or in all patients ≥75 years old with COVID-19.
- To explore the concentration of anti-SARS-CoV2 in the plasma of the participants associated with the absence of severe respiratory disease obtained 24 hours after infusion.

EFFECTIVENESS ASSESSMENT CRITERIA

Primary criteria of effectiveness evaluation

Severe respiratory disease due to SARS-CoV2, confirmed by viral ARN detection with RT-PCR, and defined by the presence of any of the following two variables in a non-exclusive way: (a) respiratory rate (RR) ≥30 per minute (b) O2 sat<93% at room air. The primary endpoint will be determined from 12 hours from the start of the infusion until 15 days since the administration of the treatment (12h – 15 d).

Secondary criteria of effectiveness evaluation

(Up to 15 days or from there up to a maximum of 25 days since treatment administration if the patient remains in hospital).

- Need of respiratory support with maximum oxygen therapy (oxygen reservoir mask) and/or the use of non-invasive respiratory support (NIV support including CPAP) and/or admission to the intensive care unit (ICU) and/or invasive mechanical ventilation assistance due to SARS-CoV2.
- Critical systemic illness defined as: (a) presence of acute respiratory failure (PaO2/FiO2 ≤ 200 mm Hg.) and/ or (b) shock and/or (c) multiorganic shock syndrome, acute renal injury, increase of hepatic enzymes and acute cardiomyopathy due of SARS-Cov2.
- Mortality due to SARS-Cov2.
- Combination of secondary criteria of effectiveness evaluation, #1 (Need of respiratory support…) and/ or #2 (Severe disease define as...) and/or #3 (Mortality due to SARS-Cov2).
- Duration of oxygen support requirement in patients with COVID-19 due to O2 sat<93% at room air.

STATISTICAL ANALYSIS

The socio-demographic characteristics, vital signs and comorbidities of primary and secondary interest of the participants will be described. For both primary and secondary outcomes the proportion by treatment group and the relative risk with its 95% confidence interval will be reported.

The analysis will be made over two populations:

1) Intention-to-treat (ITT). All the randomized patients with follow-up until 15 days from transfusion beginning date (or since randomization if they had not received treatment) will be included.
2) Modified intention-to-treat (mITT). All the randomized patients with follow-up until 15 days from transfusion beginning date will be included, with the exception of patients with the following conditions:

a. Has not received the treatment
b. Has lost eligibility criteria between randomization and treatment administration, regardless if they had received the treatment. (I.e., those patients who, in advance or at the time of starting treatment, had already developed severe disease, primary outcome of the study).

Note: The inclusion of this result in this interim analysis is subject to EC confirmation.

SAMPLE SIZE AND DETENTION RULES ACCORDING THE PROTOCOL.

- Given the relative complexity of implementing this intervention, the minimally clinically important difference was set at a 40% relative reduction for an expected outcome rate of 50% in the control group reduced to 30% in the intervention group.
- A total sample size of 210 subjects (105 per trial arm) was estimated to have 80% power at a significance level (alpha) of 0.05 using a two-sided z-test with continuity correction.
- The study protocol contemplates the execution of an interim analysis when a 50% of the projected sample sized is achieved.
- There is significant uncertainty in the expected effect size of the intervention, and considering that the trial is expected to be completed in a relatively short period of time, the study is designed to have an interim analysis when the results of 50% of the subjects have been acquired.
- These results assume that 2 sequential tests are performed using the O'Brien Fleming expense function to determine the test limits, as described in the table below:

Look	Time	Lower Boundary	Upper Boundary	Nominal Alpha	Power
1	0.50	-2.96259	2.96259	0.003	0.168
2	1.00	-1.96857	1.96857	0.049	0.806

VARIABLES DEFINITION

Table 1: Primary outcomes definition.

N	Variable names	Definition	Variables in the CRF
(1)	Severe respiratory disease due to SARS-CoV2	Presence of respiratory rate ≥30 per minute or O2 sat<93% at room air from 12 hours from the start of the infusion until 15 days since the administration of the treatment (12h – 15 d). - Yes (At least one day had some of the two events) - No (None of the two events in the 15 days)	Variables definition in (2) and (3)
(2)	Respiratory rate (RR) ≥30 per minute	Presence of respiratory rate ≥30 per minute from 12 hours from the start of the infusion until 15 days since the administration of the treatment (12h – 15 d). - Yes (At least one day had some of the two events) - No (None of the two events in the 15 days)	Respiratory rate ≥30 per minute (**Form 7, variable 4**). 12 hours from the start of the infusion until 15 days since the administration of the treatment (12h – 15 d). (**Form 5, Variable 2 y 5**)
(3)	Oxygen saturation <93% at room air	Presence O2 sat<93% at room air from 12 hours from the start of the infusion until 15 days since the administration of the treatment (12h – 15 d). - Yes (At least one day had some of the two events) - No (None of the two events in the 15 days)	Oxygen saturation <93% at room air between (**Form 7, variable 5**). 12 hours from the start of the infusion until 15 days since the administration of the treatment (12h – 15 d). (**Form 5, Variable 2 y 5**)

Table 2: Secondary outcomes definition.

N	Variable names	Definition	Variables in the CRF
(4)	Oxygen support and/or non-invasive respiratory support and/or admission to ICU and/or invasive mechanical ventilation assistance.	Oxygen support and/or non-invasive respiratory support and/or admission to ICU and/or invasive mechanical ventilation assistance from 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. - Yes (At least one of the four events was registered in the 15/25 days) - No (None of the four events in the 15/25 days)	Variables definition in (5), (6), (7) y (8)
(5)	Oxygen support	Need of oxygen support from 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. - Yes (the event was registered in the 15/25 days) - No (The event was not registered in the 15/25 days)	Oxygen support (**Form 7, Variable 14**) 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. (**Form 5, Variable 2 y 5**)
(6)	Non-invasive respiratory support	Need of non-invasive respiratory support from 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. - Yes (the event was registered in the 15/25 days) - No (The event was not registered in the 15/25 days)	Non-invasive respiratory support (**Form 7, variable 16**) 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. (**Form 5, Variable 2 y 5**)
(7)	UCI admission	Admission to the intensive care unit (ICU) from 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. - Yes (the event was registered in the 15/25 days) - No (The event was not registered in the 15/25 days)	UCI admission (**Form 7, variable 15**) 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. (**Form 5, Variable 2 y 5**)
(8)	Invasive mechanical ventilation assistance requirement	Invasive mechanical ventilation assistance requirement from 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. - Yes (the event was registered in the 15/25 days) - No (The event was not registered in the 15/25 days)	Invasive mechanical ventilation assistance requirement (**Form 7, variable 17**) 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. (**Form 5, Variable 2 y 5**).
(9)	Critical systemic illness	Presence of acute respiratory failure, shock or multiorganic shock syndrome from 12 hours from the start of the	Variables definition (10), (11) y (12)

		infusion until 15/25 days if the patient remains in hospital. - Yes (At least one of the three events was registered in the 15/25 days) - No (None of the three events in the 15/25 days)	
(10)	Acute respiratory failure	Presence of acute respiratory failure: PaO2/FiO2 ≤ 200 mmHg from 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. - Yes (the event was registered in the 15/25 days) - No (The event was not registered in the 15/25 days)	Acute respiratory failure (**Form 7, variable 18**) 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. (**Form 5, Variable 2 y 5**).
(11)	Shock	Need of support with vasoactive drugs to maintain the mean arterial pressure ≥ 65 mm Hg from 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. - Yes (the event was registered in the 15/25 days) - No (The event was not registered in the 15/25 days)	Shock (**Form 7, variable 20**). 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. (**Form 5, Variable 2 y 5**).

Table 2: Secondary outcomes definition (cont.)

N	Variable names	Definition	Variables in the CRF
(12)	Multiorganic shock syndrome	Presence of some of the following events from 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. - Acute renal injury: increase in two or more times from baseline or creatinine increase of 0.3 mg/dl. - Increase of hepatic enzymes (transaminase) in three or more times the normal range. - Acute cardiomyopathy: increase of troponin above normal range and/ or new electrocardiographic or echocardiographic abnormalities due to myocardial damage. - Yes (At least one of the three events was registered in the 15/25 days) - No (None of the three events in the 15/25 days)	Acute renal injury (**Form 7, variable 19.a**) Increase of hepatic enzymes (**Form 7, variable 19.b**) Acute cardiomyopathy (**Form 7, variable 19.c**) 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital (**Form 5, Variable 2 y 5**).
(13)	Mortality due to covid-19	Mortality due to covid-19 from 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. - Yes (the event was registered in the 15/25 days) - No (The event was not registered in the 15/25 days)	Patient death (**Form 7, variable 21**). 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital (**Form 5, Variable 2 y 5**).
(14)	Combination of secondary criteria of effectiveness evaluation- (4) or (9) or (13)	Need of respiratory support with oxygen and/or the use of non-invasive respiratory support and/or admission to the ICU and/or critical systemic illness or mortality due to COVID-19 from 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. - Yes (At least one of the six events was registered in the 15/25 days) - No (None of the six events in the 15/25 days)	Variables definition in (4), (9) y (13)
(15)	Duration of oxygen support requirement in patients with COVID-19 due to O2 sat<93% at room air.	Number of days that oxygen support was required	Oxygen support (**Form 7, variable 14**)

Table 3: Adverse events definition

N	Variable names	Definition	Variables in the CRF
(16)	Cardiac volume overload associated with the transfusion	Presence of cardiac volume overload associated with the transfusion during the infusion and between 12 hours after. - Yes (the event was registered) - No (The event was not registered)	**Form 6, variable 3**
(17)	Allergic or anaphylactic reaction	Presence of allergic or anaphylactic reaction during the infusion and between 12 hours after. - Yes (the event was registered) - No (The event was not registered)	**Form 6, variable 4**
(18)	Thrombophlebitis	Presence of thrombophlebitis during the infusion and between 12 hours after. - Yes (the event was registered) - No (The event was not registered)	**Form 6, variable 5**
(19)	Vasovagal syndrome	Presence of vasovagal syndrome during the infusion and between 12 hours after. - Yes (the event was registered) - No (The event was not registered)	**Form 6, variable 6**
(20)	Hematoma at site	Presence of hematoma at site during the infusion and between 12 hours after. - Yes (the event was registered) - No (The event was not registered)	**Form 6, variable 7**
(21)	Nervous injury	Presence of nervous injury at site during the infusion and between 12 hours after. - Yes (the event was registered) - No (The event was not registered)	**Form 6, variable 8**
(22)	Tetany (hyperventilation)	Presence of tetany (hyperventilation) during the infusion and between 12 hours after. - Yes (the event was registered) - No (The event was not registered)	**Form 6, variable 9**
(23)	Total events	Total number of events	**Sum of (16), (17), (18), (19), (20), (21), (22)**

RESULT TABLES

Figure 1: Consort

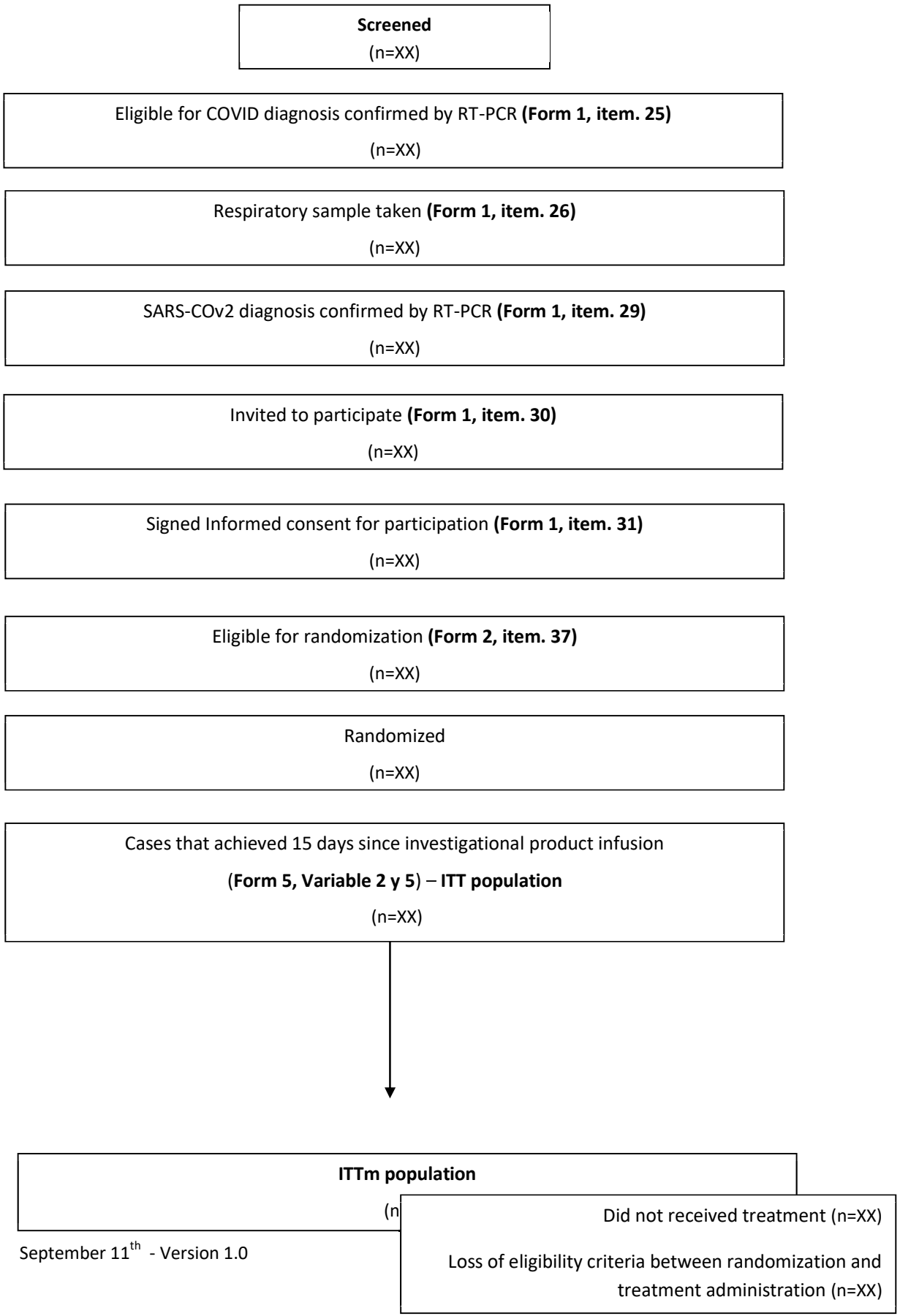

Table 4: Socio-demographic characteristics, vital signs and primary and secondary comorbidities

Variables	Plasma		Placebo	
Socio-demographic characteristics	**n/N**	**%**	**n/N**	**%**
Age in years*				
Age by categories				
• 65-74 years				
• ≥75 years				
Sex				
• Female				
• Male				
Vital signs				
Axillary temperature*				
Heart Rate*				
Systolic blood pressure*				
Diastolic blood pressure*				
Respiratory rate*				
Oxygen saturation at room air*				
Hours from initiation of symptoms*				
Respiratory rate (≥30 RPM)				
Oxygen saturation < 93%				
Primary Comorbidities				
Hypertension under treatment				
Diabetes under treatment				
Obesity				
COPD under treatment				
Cardiovascular disease**				
Chronic renal failure				
Secondary comorbidities				
Asthma or other respiratory disease				
Non-cirrhotic liver disease				
Cancer (not active)				
Neurologic disease				
History of smoking				
Receives medications regularly				
Received medications in last 15 days				

* Media and Standard deviation

** Define as Known diagnosis of coronary disease, stroke history, congenital heart failure (EF < 40%).

Table 5: Primary Endpoint. Proportion of cases – ITT analysis

	Plasma		Placebo		Relative Risk	P value
	n/N	%	n/N	%	(95% CI)	
Severe Respiratory Disease						
• Respiratory Rate ≥30 por minuto						
• Oxygen satiration at room air <93%						

Table 6: Primary Endpoint. Proportion of cases – ITTm analysis

	Plasma		Placebo		Relative Risk	P value
	n/N	%	n/N	%	(95% CI)	
Severe Respiratory Disease						
• Respiratory Rate ≥30 por minuto						
• Oxygen satiration at room air <93%						

Table 7: Secondary outcomes: Case proportions –ITT

	Plasma		Placebo		Relative Risk	P value
	n/N	%	n/N	%	(95% CI)	
Oxygen support and/ or non-invasive respiratory support and/or admission to UCI and/or invasive mechanical ventilation assistance requirement						
• Oxygen support					-	
• Non-invasive respiratory support					-	
• Admission to UCI					-	
• Mechanical ventilation					-	
Critical systemic Illness						
• Acute respiratory failure					-	

• Shock	-
• Multiorganic shock syndrome	-
Mortality due to SARS-CoV2	
Support with maximum oxygen therapy and/ or non-invasive respiratory support and/or admission to UCI and/or invasive mechanical ventilation assistance requirement and/or severe disease and/or mortality	
Duration in days of the oxygen support requirement *Ω	
Duration in days of the oxygen support requirement *B	

* Median and quartiles (quartile 1 – quartile 3)

Ω Only those who oxygen required were considered (n=in Group A y n=in Group B)

B Only those who oxygen required and survived were considered (n=in Group A y n=in Group B)

Table 8: Secondary outcomes: Time to event – ITTm analysis

	Plasma		Placebo		P value
	Median	**(Q1-Q3)**	**Median**	**(Q1-Q3)**	
Respiratory rate ≥30 x m					
Oxygen saturation <93%					
Support with maximum oxygen therapy and/ or non-invasive respiratory support and/or admission to UCI and/or invasive mechanical ventilation assistance requirement					
• 100% oxygen support					-
• Non-invasive respiratory support					-
• Admission to UCI					-
• Mechanical ventilation					-
Critical systemic Illness					
• Acute respiratory failure					-
• Shock					-
• Multiorganic shock syndrome					-
Mortality due to SARS-CoV2					
Support with maximum oxygen therapy and/ or non-invasive respiratory support and/or admission to UCI and/or invasive mechanical ventilation assistance requirement and/or severe disease and/or mortality					
Duration in days of the oxygen support requirement *Ω					
Duration in days of the oxygen support requirement *B					

* Median and quartiles (quartile 1 – quartile 3)

Ω Only those who oxygen required were considered (n=in Group A y n=in Group B)

B Only those who oxygen required and survived were considered (n=in Group A y n=in Group B)

Table 9: Solicited adverse events – ITT analysis

	Serious				Non- serious			
	Plasma		Placebo		Plasma		Placebo	
	n/N	%	n/N	%	n/N	%	n/N	%
Cardiac volume overload associated with the transfusion								
Allergic or anaphylactic reaction								
Thrombophlebitis								
Vasovagal syndrome								
Hematoma at site								
Nerve injury								
Tetany (hyperventilation)								
Total events*								

* Median and quartiles (quartile 1 – quartile 3)

Table 10: Solicited adverse events – ITTm analysis

	Serious				Non- serious			
	Plasma		Placebo		Plasma		Placebo	
	n/N	%	n/N	%	n/N	%	n/N	%
Cardiac volume overload associated with the transfusion								
Allergic or anaphylactic reaction								
Thrombophlebitis								
Vasovagal syndrome								
Hematoma at site								
Nerve injury								
Tetany (hyperventilation)								
Total events*								

* Median and quartiles (quartile 1 – quartile 3)

EFFICACY EVALUATION OF COVID-19 CONVALESCENT PLASMA ADMINISTRATION IN THE DECREASE OF PROGRESSION TO SEVERE DISEASE IN ELDERLY ADULTS WITH MILD SYMPTOMS OF SARS-COV2

Final Analysis Plan

November 6th 2020

Report to:
Main Researcher: Fernando Polack

Written by:
Biostatistics: L. Gibbons

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OBJETIVES

To evaluate the efficacy of convalescent plasma, from 12 hours of administration, in reducing progression to severe respiratory disease in subjects between 65-74 years of age with at least one comorbidity or ≥75 years old, with mild symptomatology and with early COVID-19 diagnosis up to 15 days of treatment administration (16-18 days of disease considering the symptomatic period previous enrollment).

Secondary outcomes include determining if convalescent plasma administration up to 15 days, or from there up to a maximum of 25 days since treatment administration if the patient remains in hospital, achieve to:

- To reduce the need of respiratory support with maximum oxygen therapy (oxygen reservoir mask) and/or the use of non-invasive respiratory support (NIV support, including CPAP) and/or admission to the intensive care unit (ICU) and/or invasive mechanical ventilation assistance because of SARS-CoV2 in patients between 65-74 years of age with at least one comorbidity or in patients ≥75 years old with COVID-19.
- To reduce critical systemic illness defined as (a) presence of acute respiratory failure (PaO2/FiO2 ≤ 200 mm Hg.) and/ or (b) shock (defined by the need of support with vasoactive drugs to maintain the mean arterial pressure ≥ 65 mm Hg.) and/or (c) multiorganic shock syndrome: acute renal injury (defined by creatinine increase two or more times from baseline or creatinine increase of 0.3 mg/dl), increase of hepatic enzymes (transaminase) in three or more times the normal range, acute cardiomyopathy (define by the increase of troponin above normal range and/ or new electrocardiographic or echocardiographic abnormalities due to myocardial damage) due to SARS-Cov2 in patients between 65-74 years of age with at least one comorbidity or in patients ≥75 years old with COVID-19.
- To reduce the mortality due to SARS-Cov2 in patients between 65-74 years of age with at least one comorbidity or in all patients ≥75 years old with COVID-19.
- To describe the safety of convalescent plasma administration in patients between 65-74 years of age with at least one comorbidity or in all patients ≥75 years old with COVID-19.
- To explore the concentration of anti-SARS-CoV2 in the plasma of the participants associated with the absence of severe respiratory disease obtained 24 hours after infusion.

EFFECTIVENESS ASSESSMENT CRITERIA

Primary criteria of effectiveness evaluation

Severe respiratory disease due to SARS-CoV2, confirmed by viral ARN detection with RT-PCR, and defined by the presence of any of the following two variables in a non-exclusive way: (a) respiratory rate (RR) ≥30 per minute (b) O2 sat<93% at room air. The primary endpoint will be

determined from 12 hours from the start of the infusion until 15 days since the administration of the treatment (12h – 15 d).

Secondary criteria of effectiveness evaluation

(Up to 15 days or from there up to a maximum of 25 days since treatment administration if the patient remains in hospital).

- Need of respiratory support with maximum oxygen therapy (oxygen reservoir mask) and/or the use of non-invasive respiratory support (NIV support including CPAP) and/or admission to the intensive care unit (ICU) and/or invasive mechanical ventilation assistance due to SARS-CoV2.
- Critical systemic illness defined as: (a) presence of acute respiratory failure (PaO2/FiO2 ≤ 200 mm Hg.) and/ or (b) shock and/or (c) multiorganic shock syndrome, acute renal injury, increase of hepatic enzymes and acute cardiomyopathy due of SARS-Cov2.
- Mortality due to SARS-Cov2.
- Combination of secondary criteria of effectiveness evaluation, #1 (Need of respiratory support…) and/ or #2 (Severe disease define as...) and/or #3 (Mortality due to SARS-Cov2).
- Duration of oxygen support requirement in patients with COVID-19 due to O2 sat<93% at room air.
- Comparison of IgG antibodies titer.

STATISTICAL ANALYSIS

The socio-demographic characteristics, vital signs and comorbidities of primary and secondary interest of the participants will be described. For both primary and secondary outcomes the proportion by treatment group and the relative risk with its 95% confidence interval will be reported. A logistic regression model will be used in case it is necessary to adjust for covariates. Time to event will be evaluated using Kaplan- Meier survival analysis comparing the groups with Log-Rank test. When necessary Cox regression model will be used to make adjustments. The analysis of the primary outcome will be done stratifying by age groups.

The analysis will be made over two populations:

1) Intention-to-treat (ITT). All the randomized patients with follow-up until 15 days from transfusion beginning date (or since randomization if they had not received treatment) will be included.
2) Modified intention-to-treat (mITT). All the randomized patients with follow-up until 15 days from transfusion beginning date will be included, with the exception of patients with the following conditions:
    a. Has not received the treatment
    b. Has lost eligibility criteria between randomization and treatment administration, regardless if they had received the treatment. (I.e., those patients who, in advance or at the time of starting treatment, had already developed severe disease, primary outcome of the study).

In addition, serious and non-serious adverse events according to treatment group will be reported

Main conclusions will be based on the mITT population analysis.

SAMPLE SIZE AND DETENTION RULES ACCORDING THE PROTOCOL.

- Given the relative complexity of implementing this intervention, the minimally clinically important difference was set at a 40% relative reduction for an expected outcome rate of 50% in the control group reduced to 30% in the intervention group.
- A total sample size of 210 subjects (105 per trial arm) was estimated to have 80% power at a significance level (alpha) of 0.05 using a two-sided z-test with continuity correction.

VARIABLES DEFINITION

Table 1: Primary outcomes definition.

N	Variable names	Definition	Variables in the CRF
(1)	Severe respiratory disease due to SARS-CoV2	Presence of respiratory rate ≥30 per minute or O2 sat<93% at room air from 12 hours from the start of the infusion until 15 days since the administration of the treatment (12h – 15 d). - Yes (At least one day had some of the two events) - No (None of the two events in the 15 days)	Variables definition in (2) and (3)
(2)	Respiratory rate (RR) ≥30 per minute	Presence of respiratory rate ≥30 per minute from 12 hours from the start of the infusion until 15 days since the administration of the treatment (12h – 15 d). - Yes (At least one day had some of the two events) - No (None of the two events in the 15 days)	Respiratory rate ≥30 per minute (**Form 7, variable 4**). 12 hours from the start of the infusion until 15 days since the administration of the treatment (12h – 15 d). (**Form 5, Variable 2 y 5**)
(3)	Oxygen saturation <93% at room air	Presence O2 sat<93% at room air from 12 hours from the start of the infusion until 15 days since the administration of the treatment (12h – 15 d). - Yes (At least one day had some of the two events) - No (None of the two events in the 15 days)	Oxygen saturation <93% at room air between (**Form 7, variable 5**). 12 hours from the start of the infusion until 15 days since the administration of the treatment (12h – 15 d). (**Form 5, Variable 2 y 5**)

Table 2: Secondary outcomes definition.

N	Variable names	Definition	Variables in the CRF
(4)	Oxygen support and/or non-invasive respiratory support and/or admission to ICU and/or invasive mechanical ventilation assistance.	Oxygen support and/or non-invasive respiratory support and/or admission to ICU and/or invasive mechanical ventilation assistance from 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. - Yes (At least one of the four events was registered in the 15/25 days) - No (None of the four events in the 15/25 days)	Variables definition in (5), (6), (7) y (8)
(5)	Respiratory support with maximum oxygen therapy (oxygen reservoir mask)	Need of oxygen 100% support from 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. - Yes (the event was registered in the 15/25 days) - No (The event was not registered in the 15/25 days)	Oxygen support (**Form 7, Variable 14**) + (**Form 7, variable 14b**) 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. (**Form 5, Variable 2 y 5**)
(6)	Non-invasive respiratory support	Need of non-invasive respiratory support from 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. - Yes (the event was registered in the 15/25 days) - No (The event was not registered in the 15/25 days)	Non-invasive respiratory support (**Form 7, variable 16**) 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. (**Form 5, Variable 2 y 5**)
(7)	UCI admission	Admission to the intensive care unit (ICU) from 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. - Yes (the event was registered in the 15/25 days) - No (The event was not registered in the 15/25 days)	UCI admission (**Form 7, variable 15**) 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. (**Form 5, Variable 2 y 5**)
(8)	Invasive mechanical ventilation assistance requirement	Invasive mechanical ventilation assistance requirement from 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. - Yes (the event was registered in the 15/25 days) - No (The event was not registered in the 15/25 days)	Invasive mechanical ventilation assistance requirement (**Form 7, variable 17**) 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. (**Form 5, Variable 2 y 5**).
(9)	Critical systemic illness	Presence of acute respiratory failure, shock or multiorganic shock syndrome	Variables definition (10), (11) y (12)

		from 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. - Yes (At least one of the three events was registered in the 15/25 days) - No (None of the three events in the 15/25 days)	
(10)	Acute respiratory failure	Presence of acute respiratory failure: PaO2/FiO2 ≤ 200 mmHg from 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. - Yes (the event was registered in the 15/25 days) - No (The event was not registered in the 15/25 days)	Acute respiratory failure (**Form 7, variable 18**) 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. (**Form 5, Variable 2 y 5**).
(11)	Shock	Need of support with vasoactive drugs to maintain the mean arterial pressure ≥ 65 mm Hg from 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. - Yes (the event was registered in the 15/25 days) - No (The event was not registered in the 15/25 days)	Shock (**Form 7, variable 20**). 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. (**Form 5, Variable 2 y 5**).

Table 2: Secondary outcomes definition (cont.)

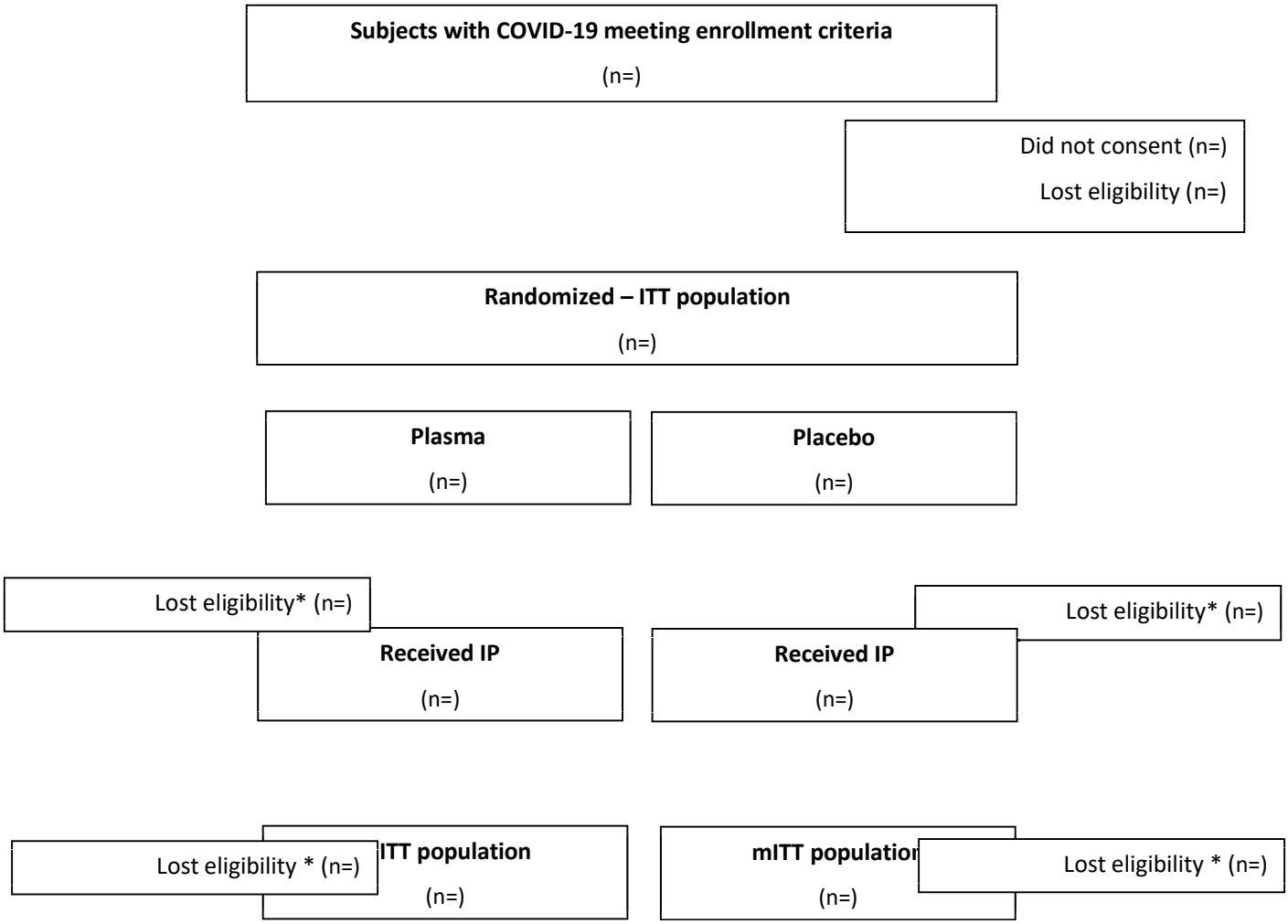
N	Variable names	Definition	Variables in the CRF
(12)	Multiorganic shock syndrome	Presence of some of the following events from 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. - Acute renal injury: increase in two or more times from baseline or creatinine increase of 0.3 mg/dl. - Increase of hepatic enzymes (transaminase) in three or more times the normal range. - Acute cardiomyopathy: increase of troponin above normal range and/ or new electrocardiographic or echocardiographic abnormalities due to myocardial damage. - Yes (At least one of the three events was registered in the 15/25 days) - No (None of the three events in the 15/25 days)	Acute renal injury (**Form 7, variable 19.a**) Increase of hepatic enzymes (**Form 7, variable 19.b**) Acute cardiomyopathy (**Form 7, variable 19.c**) 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital (**Form 5, Variable 2 y 5**).
(13)	Mortality due to covid-19	Mortality due to covid-19 rom 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. - Yes (the event was registered in the 15/25 days) - No (The event was not registered in the 15/25 days)	Patient death (**Form 7, variable 21**). 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital (**Form 5, Variable 2 y 5**).
(14)	Combination of secondary criteria of effectiveness evaluation- (4) or (9) or (13)	Need of respiratory support with oxygen and/or the use of non-invasive respiratory support and/or admission to the ICU and/or critical systemic illness or mortality due to COVID-19 from 12 hours from the start of the infusion until 15/25 days if the patient remains in hospital. - Yes (At least one of the six events was registered in the 15/25 days) - No (None of the six events in the 15/25 days)	Variables definition in (4), (9) y (13)
(15)	Duration of oxygen support requirement in patients with COVID-19 due to O2 sat<93% at room air.	Number of days that oxygen support was required	Oxygen support (**Form 7, variable 14**)

Table 3: Adverse events definition

N	Variable names	Definition	Variables in the CRF
(16)	Cardiac volume overload associated with the transfusion	Presence of cardiac volume overload associated with the transfusion during the infusion and between 12 hours after. - Yes (the event was registered) - No (The event was not registered)	**Form 6, variable 3**
(17)	Allergic or anaphylactic reaction	Presence of allergic or anaphylactic reaction during the infusion and between 12 hours after. - Yes (the event was registered) - No (The event was not registered)	**Form 6, variable 4**
(18)	Thrombophlebitis	Presence of thrombophlebitis during the infusion and between 12 hours after. - Yes (the event was registered) - No (The event was not registered)	**Form 6, variable 5**
(19)	Vasovagal syndrome	Presence of vasovagal syndrome during the infusion and between 12 hours after. - Yes (the event was registered) - No (The event was not registered)	**Form 6, variable 6**
(20)	Hematoma at site	Presence of hematoma at site during the infusion and between 12 hours after. - Yes (the event was registered) - No (The event was not registered)	**Form 6, variable 7**
(21)	Nervous injury	Presence of nervous injury at site during the infusion and between 12 hours after. - Yes (the event was registered) - No (The event was not registered)	**Form 6, variable 8**
(22)	Tetany (hyperventilation)	Presence of tetany (hyperventilation) during the infusion and between 12 hours after. - Yes (the event was registered) - No (The event was not registered)	**Form 6, variable 9**
(23)	Total events	Total number of events	**Sum of (16), (17), (18), (19), (20), (21), (22)**

RESULT TABLES

Figure 1: Consort



*Subjects that received the intervention but lost eligibility before being transfused (presence of primary outcome before transfusion)

Table 4: Characteristics of ITT population

Variables	Plasma		Placebo	
Socio-demographic characteristics	**n/N**	**%**	**n/N**	**%**
Age in years*				
Age by categories				
• 65-74 years				
• ≥75 years				
Sex				
• Female				
• Male				
Vital signs				
Axillary temperature*				
Heart Rate*				
Systolic blood pressure*				
Diastolic blood pressure*				
Respiratory rate*				
Oxygen saturation at room air*				
Hours from initiation of symptoms*				
Respiratory rate (≥30 RPM)				
Oxygen saturation < 93%				
Comorbidities				
Hypertension under treatment				
Diabetes under treatment				
Obesity				
COPD under treatment				
Cardiovascular disease**				
Chronic renal failure				
Secondary comorbidities				
Asthma or other respiratory disease				
Non-cirrhotic liver disease				
Cancer (not active)				
Neurologic disease				
History of smoking				
Receives medications regularly				
Received medications in last 15 days				

* Media and Standard deviation

** Define as Known diagnosis of coronary disease, stroke history, congenital heart failure (EF < 40%).

Table 5: Characteristics of ITTm population

Variables	Plasma		Placebo	
Características socio-demográficas	**n/N**	**%**	**n/N**	**%**
Variables				
Socio-demographic characteristics				
• Age in years*				
• Age by categories				
65-74 years				
• ≥75 years				
• Sex				
Female				
Male				
Vital signs				
Axillary temperature*				
Heart Rate*				
Systolic blood pressure*				
Diastolic blood pressure*				
Respiratory rate*				
Oxygen saturation at room air*				
Hours from initiation of symptoms*				
Respiratory rate (≥30 RPM)				
Oxygen saturation < 93%				
Comorbidities				
Hypertension under treatment				
Diabetes under treatment				
Obesity				
COPD under treatment				
Cardiovascular disease**				
Chronic renal failure				
Secondary comorbidities				
Asthma or other respiratory disease				
Non-cirrhotic liver disease				
Cancer (not active)				
Neurologic disease				
History of smoking				

* Media and Standard deviation

** Define as Known diagnosis of coronary disease, stroke history, congenital heart failure (EF < 40%).

Table 6: Primary Endpoint. Proportion of cases - ITT

	Plasma		Placebo		Relative Risk	P value
	n/N	%	n/N	%	(95% CI)	
Severe Respiratory Disease						

Table 7: Primary Endpoint: Time to event - ITT

	Plasma		Placebo		P value*
	Median	(Q1-Q3)	Median	(Q1-Q3)	
Severe Respiratory Disease					

*Log Rank Test

Figure 2: Kaplan-Meier survival curve of severe respiratory disease due to SARS-CoV2 by treatment group – ITT Analysis

Table 8: Primary outcome: Proportion of primary endpoint cases by age group - ITT

	Plasma		Placebo		Relative Risk	P value
	n/N	%	n/N	%	(95% CI)	
Severe Respiratory Disease						
• 65-74 years						
• ≥75 years						

Table 9: Primary outcome. Time to event by group age - ITT

	Plasma		Placebo		P value
	Median	(Q1-Q3)	Median	(Q1-Q3)	
Severe Respiratory Disease					
• 65-74 years					
• ≥75 years					

*Log Rank Test

Figure 3: Kaplan-Meier survival curve of severe respiratory disease due SARS-CoV2 in 65-74 years old by treatment group – ITT Analysis

Figure 4: Kaplan-Meier survival curve of severe respiratory disease due SARS-CoV2 in ≥75 years old by treatment group – ITT Analysis

Table 10: Secondary outcomes: Case proportions –ITT

	Plasma		Placebo		Relative Risk	P value
	n/N	%	n/N	%	(95% CI)	
Respiratory rate ≥30 x m						
Oxygen saturation <93%						
Support with maximum oxygen therapy and/ or non-invasive respiratory support and/or admission to UCI and/or invasive mechanical ventilation assistance requirement						
• 100% oxygen support					-	
• Non-invasive respiratory support					-	
• Admission to UCI					-	
• Mechanical ventilation					-	
Critical systemic Illness						
• Acute respiratory failure					-	
• Shock					-	
• Multiorganic shock syndrome					-	
Mortality due to SARS-CoV2						
Support with maximum oxygen therapy and/ or non-invasive respiratory support and/or admission to UCI and/or invasive mechanical ventilation assistance requirement and/or severe disease and/or mortality						
Duration in days of the oxygen support requirement *Ω						
Duration in days of the oxygen support requirement *B						

* Median and quartiles (quartile 1 – quartile 3)

Ω Only those who oxygen required were considered (n=in Group A y n=in Group B)

B Only those who oxygen required and survived were considered (n=in Group A y n=in Group B)

Table 11: Secondary outcomes: Time to event – ITT analysis

	Plasma		Placebo		P value
	Median	(Q1-Q3)	Median	(Q1-Q3)	
Respiratory rate ≥30 x m					
Oxygen saturation <93%					
Support with maximum oxygen therapy and/ or non-invasive respiratory support and/or admission to UCI and/or invasive mechanical ventilation assistance requirement					
• 100% oxygen support					-
• Non-invasive respiratory support					-
• Admission to UCI					-
• Mechanical ventilation					-
Critical systemic Illness					
• Acute respiratory failure					-
• Shock					-
• Multiorganic shock syndrome					-
Mortality due to SARS-CoV2					
Support with maximum oxygen therapy and/ or non-invasive respiratory support and/or admission to UCI and/or invasive mechanical ventilation assistance requirement and/or severe disease and/or mortality					
Duration in days of the oxygen support requirement *Ω					
Duration in days of the oxygen support requirement *B					

* Median and quartiles (quartile 1 – quartile 3)

Ω Only those who oxygen required were considered (n=in Group A y n=in Group B)

B Only those who oxygen required and survived were considered (n=in Group A y n=in Group B)

Figure 5: Kaplan- Meier survival curve. Time to support with maximum oxygen therapy and/ or non-invasive respiratory support and/or admission to UCI and/or invasive mechanical ventilation assistance requirement by treatment group- ITT analysis

Figure 6: Kaplan- Meier survival curve. Time to critical systemic Illness by treatment group- ITT analysis

Figure 7: Kaplan- Meier survival curve. Time to mortality due to COVID-19 by treatment group- ITT analysis

Figure 8: Kaplan- Meier survival curve. Time to Support with maximum oxygen therapy and/ or non-invasive respiratory support and/or admission to UCI and/or invasive mechanical ventilation assistance requirement and/or critical systemic Illness and/or mortality – ITT analysis

Table 12: Requested adverse events – ITT analysis

	Serious				Non- serious			
	Plasma		Placebo		Plasma		Placebo	
	n/N	%	n/N	%	n/N	%	n/N	%
Volume overload								
Allergic reaction								
Trombophlebitis								
Vasovagal syndrome								
Hematoma at site								
Nerve injury								
Tetany (hyperventilation)								
Total events*								

* Median and quartiles (quartile 1 – quartile 3)

Table 13: Primary Endpoint. Proportion of cases - ITTm

	Plasma		Placebo		Relative Risk	P value
	n/N	%	n/N	%	(95% CI)	
Severe Respiratory Disease						

Table 14: Primary Endpoint: Time to event - ITTm

	Plasma		Placebo		P value*
	Median	(Q1-Q3)	Median	(Q1-Q3)	
Severe Respiratory Disease					

*Log Rank Test

Figure 9: Kaplan-Meier survival curve of severe respiratory disease due to SARS-CoV2 by treatment group – ITTm Analysis

	Plasma		Placebo		P value
	Median	(Q1-Q3)	Median	(Q1-Q3)	
Severe Respiratory Disease					
• 65-74 years					
• ≥75 years					

Table 15: Primary outcome: Proportion of primary endpoint cases by age group - ITTm

Table 16: Primary outcome. Time to event by age group - ITTm

	Plasma		Placebo		P value
	Median	(Q1-Q3)	Median	(Q1-Q3)	
Severe Respiratory Disease					
• 65-74 years					
• ≥75 years					

*Log Rank Test

Figure 10: Kaplan-Meier survival curve of severe respiratory disease due SARS-CoV2 in 65-74 years old by treatment group – ITTm analysis

Figure 11: Kaplan-Meier survival curve of severe respiratory disease due SARS-CoV2 in ≥75 years old by treatment group – ITTm analysis

Table 17: Secondary Outcomes: Case proportions – ITTm analysis

	Plasma		Placebo		Relative Risk	P value
	n/N	%	n/N	%	(95% CI)	
Respiratory rate ≥30 x m						
Oxygen saturation <93%						
Support with maximum oxygen therapy and/ or non-invasive respiratory support and/or admission to UCI and/or invasive mechanical ventilation assistance requirement						
• 100% oxygen support					-	
• Non-invasive respiratory support					-	
• Admission to UCI					-	
• Mechanical ventilation					-	
Critical systemic Illness						
• Acute respiratory failure					-	
• Shock					-	
• Multiorganic shock syndrome					-	
Mortality due to SARS-CoV2						
Support with maximum oxygen therapy and/ or non-invasive respiratory support and/or admission to UCI and/or invasive mechanical ventilation assistance requirement and/or severe disease and/or mortality						
Duration in days of the oxygen support requirement *Ω						
Duration in days of the oxygen support requirement *B						

* Median and quartiles (quartile 1 – quartile 3)

Ω Only those who oxygen required were considered (n=in Group A y n=in Group B)

B Only those who oxygen required and survived were considered (n=in Group A y n=in Group B)

Table 18: Secondary outcomes: Time to event – ITTm analysis

	Plasma		Placebo		P value
	Median	**(Q1-Q3)**	**Median**	**(Q1-Q3)**	
Respiratory rate ≥30 x m					
Oxygen saturation <93%					
Support with maximum oxygen therapy and/ or non-invasive respiratory support and/or admission to UCI and/or invasive mechanical ventilation assistance requirement					
• 100% oxygen support					-
• Non-invasive respiratory support					-
• Admission to UCI					-
• Mechanical ventilation					-
Critical systemic Illness					
• Acute respiratory failure					-
• Shock					-
• Multiorganic shock syndrome					-
Mortality due to SARS-CoV2					
Support with maximum oxygen therapy and/ or non-invasive respiratory support and/or admission to UCI and/or invasive mechanical ventilation assistance requirement and/or severe disease and/or mortality					
Duration in days of the oxygen support requirement *Ω					
Duration in days of the oxygen support requirement *B					

* Median and quartiles (quartile 1 – quartile 3)

Ω Only those who oxygen required were considered (n=in Group A y n=in Group B)

B Only those who oxygen required and survived were considered (n=in Group A y n=in Group B)

Figure 12: Kaplan- Meier survival curve. Time to support with maximum oxygen therapy and/ or non-invasive respiratory support and/or admission to UCI and/or invasive mechanical ventilation assistance requirement by treatment group – ITTm analysis

Figure 13: Kaplan- Meier survival curve. Time to critical systemic Illness by treatment group – ITTm Analysis

Figura 14: Kaplan- Meier survival curve. Time to mortality due to COVID-19 by treatment group- ITT analysis – ITTm Analysis

Figura 15: Kaplan- Meier survival curve. Time to Support with maximum oxygen therapy and/ or non-invasive respiratory support and/or admission to UCI and/or invasive mechanical ventilation assistance requirement and/or critical systemic Illness and/or mortality – ITTm analysis

Table 19: Requested adverse events – ITTm analysis

	Serious				**Non- serious**			
	Plasma		**Placebo**		**Plasma**		**Placebo**	
	n/N	**%**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
Cardiac volume overload associated with the transfusion								
Allergic or anaphylactic reaction								
Thrombophlebitis								
Vasovagal syndrome								
Hematoma at site								
Nerve injury								
Tetany (hyperventilation)								
Total events*								

* Median and quartiles (quartile 1 – quartile 3)

Analysis plan versions

Analysis plan version	Date	Modifications
1.0	11-Sep-20	Original analysis plan in Spanish developed for the interim analysis and submitted to the Data Safety Monitoring Board.
2.0	06-nov-20	Final analysis plan, translated to English. As recommended by the DSMB the analysis plan was updated to include a stratified analysis by age (65-74 years and ≥75 years). The final analysis plan was also expanded to be in line with the analysis plan section of the protocol that included a time to event analysis of the primary outcome.