Cohort Multiple randomized controlled trials open-label of immune modulatory drugs and other treatments in COVID-19 patients

CORIMUNO-19

INTERVENTIONAL RESEARCH PROTOCOL INVOLVING HUMAN PARTICIPANTS CONCERNING MULTIPLE IMMUNE REGULATORY MEDICATIONS FOR HUMAN USE

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1 SYNOPSIS

Title	CORIMUNO-COVIPLASM: EFFICACY OF CONVALESCENT PLASMA TO TREAT SARS-COV2 INFECTED PATIENTS , A NESTED TRIAL IN THE CORIMUNO-19 COHORT
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Additionnal sites	Other AP-HP hospitals according to needs
Sponsor of the study	Assistance Publique-Hôpitaux de Paris (AP-HP)
Partners of the study	AP-HP, EFS , IHU MI, REACTing Inserm
Study phase	Phase 2

CORIMUNO-COVIPLASM: EFFICACY OF CONVALESCENT PLASMA TO TREAT SARS-COV2 INFECTED PATIENTS , A NESTED TRIAL IN THE CORIMUNO-19 COHORT

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2 RATIONALE

2.1 COVID 19 disease

The coronavirus disease 2019 (COVID-19) viral pneumonia is now a worldwide pandemic caused by the Severe acute respiratory virus coronavirus 2 (SARS-CoV-2)[1]. The number of cases, and associated mortality has increased dramatically since the first cases in Wuhan, China in December 2019[2]. To date, no specific treatment has been proven to be effective for COVID-19[3]. Treatment is currently mainly supportive, with in particular mechanical ventilation for the critically ill patients (6.1% in a series of 1099 cases in China[ii]). Novel therapeutic approaches are in acute need. In this context, the therapeutic potential associated with convalescent plasma needs to be explored[4,5].

2.2 Convalescent plasma to treat viral diseases

Convalescent plasma treatment, i.e. passive polyclonal antibody (Ab) administration to provide immediate immunity, has been used to improve the survival rate of patients with severe acute respiratory syndromes of viral etiology[6]. Indeed, a number of studies, unfortunately all inadequately controlled for bias, have reported positive outcomes, including decreased mortality in the so-called Spanish Influenza A (H1N1) infections in 1915-1917[7], the more recent Influenza A (H1N1) infections in 2009/2010[8], and more importantly here, SARS-CoV infections in 2003[9]. A systematic review and exploratory meta-analysis performed in

2014 identified 32 studies of SARS coronavirus infection and severe influenza[7i] These studies involved 699 treated patients and 568 untreated "controls" (and 60 patients with unknown status). The review revealed evidence for a consistent reduction in mortality upon plasma therapy. Furthermore, exploratory *post hoc* meta-analysis showed a significant reduction in the pooled odds of mortality following treatment, compared with placebo or no therapy (odds ratio, 0.25; 95% CI:0.14–0.45; with limited heterogeneity: $I^2 = 0\%$)[7,10].

2.3 Convalescent plasma to treat SARS-CoV infected patients

In addition to being both highly pathogenic coronavirus with lung tropism, SARS-CoV-2 and SARS-CoV have been recently found to bind to the same entry receptor (ACE2) with similar affinity[11]. Furthermore, SARS-CoV polyclonal Ab inhibit SARS-CoV-2 spike glycoprotein (S) - mediated entry into cells.

SARS-CoV convalescent plasma has been shown to contain neutralizing Ab against the involved virus[12].Furthermore, neutralizing Ab elicited by primary infection of SARS-CoV can protect mice from re-infection[13]. Very recently, similar findings have been reported in monkeys regarding SARS-CoV-2[14]. Importantly, passive intra-peritoneal transfer of such SARS-CoV(1) Ab to naïve mice can prevent SARS-CoV replication in the respiratory tract[14].

The above mentioned review identified 8 observational studies at moderate to high risk of bias that reported improved mortality after SARS-CoV – infected patients received various amount of convalescent plasma[7]. Notably, a small retrospective case-comparison study (19 vs 21 patients) showed a case fatality rate reduction after convalescent plasma treatment of 23% (95% CI: 6%-42%, p=0,049)[15]. Each patient received 200 to 400 ml of plasma. Also, a case series including 80 treated patients reported an overall mortality rate of 12,5% in severe deteriorating SARS-CoV (1) - infected patients while the overall SARS-related mortality rate in Hong-Kong was 17% during the SARS epidemic in 2003[10]. The mean volume of plasma infused was 279 + 127 ml (range 160-640 ml). Interestingly, a subgroup analysis found that those treated with a PCR positive but seronegative for SARS-CoV-1 has a significantly better outcome (i.e. discharge by day 22 vs after day 22 or death) than those who were seropositive at the time of plasma infusion (61% vs 21%, $p<0.001$). Similarly, those receiving convalescent plasma before (versus after) 14 days after onset of symptoms were found to have a better

outcome. In multivariate analysis, the time of convalescent plasma was reported to stay significant.

Overall, these findings favor an early administration during the infectious course, at a time where pathology may be driven mainly by viral replication. Lastly, and to the best of our knowledge, at least one study evaluating convalescent plasma to treat SARS-CoV-2 infected patients is underway in China[16]. In a recently reported uncontrolled case series of 5 critically ill patients with COVID-19 and acute respiratory distress syndrome (all on mechanical ventilation), administration of convalescent plasma containing neutralizing antibody was followed by an improvement in clinical status in all 5 patients [17].

In all cases, a close monitoring of treated patients with convalescent plasma to verify for any unintended side effects, in particular evidence of inflammatory flare-up, will be necessary.

2.4 Convalescent plasma mechanism of action

2.4.1 Ab-mediated immunopathology in CoV diseases

Although these last observations of TRALI appear isolated, the issue of potential toxicity associated with convalescent plasma needs to be addressed carefully. SARS-CoV-2 infected patients, as well as SARS-CoV (1) and MERS-CoV patients exhibit acute lung injury (ALI), that may evolve into acute respiratory disease syndrome (ARDS) and death. Such ALI is driven by acute inflammation through mechanisms that remain elusive.

Experimental studies as well as observations in humans suggest that at least initially in the course of SARS-CoV(1) - associated disease, the immune response, notably Ab-mediated, may aggravate ALI by skewing inflammation-resolving responses[18]. Such an Ab-dependent enhancement (ADE) has been suspected in a large variety of diseases[19]. However, with the notable exception of secondary dengue as well as dengue and respiratory syncytial virus (RSV) vaccinations, observations were made in the majority of cases *in vitro* or in animal models and limited evidence from epidemiological series or pathophysiology studies in humans have been reported so far. Heterotopic and/or non (i.e. insufficiently) - neutralizing Ab have been suggested to be contributive. The potential role of such Ab in elderly patients, previously exposed to a variety of coronavirus, is unknown but may contribute to the severity of COVID-19 in this population. Experimental MERS-CoV data in rabbits suggest that failing to develop

neutralizing Ab (or waning titers at distance of infection) may be a risk factor for severe lung disease upon re-exposure to MERS-CoV[20]. From a mechanistic perspective, non-neutralizing Ab may favor a more efficient viral uptake into the target cell in Fc-gamma or complement-mediated binding leading to enhanced replication and pathogenicity[21]. Furthermore, and as reported with inactivated RSV vaccination, a Th2-type immunopathologic responses upon rechallenge has been described in a mouse model following vaccination with an inactivated SARS-CoV(1) vaccine[22].

2.4.2 Early vs late Ab responses in CoV diseases

Peak in viral load in SARS patients has been reported to coincide with the first appearance of an Ab response[23]. *In vitro*, higher concentration of Ab collected from SARS-CoV(1) -infected patients (i.e. non-convalescent) facilitated SARS-CoV(1) infection and induced higher levels of virus-induced apoptosis[24]. Importantly, this phenomenon occurred via anti-spike (S) Ab that mediated ADE, but not via anti-nucleocapsid (N) Ab[xxi,25]. A possibly relevant observation is that temporal changes in S-specific and N-specific neutralizing Ab responses may differ significantly in patients who have either recovered from or succumbed to SARS-CoV(1) infection[26]. In comparison to patients who subsequently died, recovered patients had a delayed but sustained increase in (serum) neutralizing Ab titers with an increasing contribution of anti N Ab (not observed in patients that subsequently died). Increasing Ab affinity is most probably occurring as well. Long-term persistence of robust Ab (and cytotoxic T cell responses) has been reported in patients infected with SARS CoV-1 (1)[27]. Interestingly, very recent data in COVID-19 patients indicates seroconversion occurring after 6-12 days, but not followed by rapid decline in viral load[28]. This later finding is compatible with a suboptimal endogenous early Ab-response with regard to SARS-CoV-2 replication.

Taken together, these findings suggest that the absence of reported serious adverse effects associated with convalescent plasma may be, at least in partly, in relation with a different quality of Ab in convalescent patients versus earlier during the acute phase of the disease. An appropriate assessment of the Ab response in convalescent patients with a requirement for the presence of an anti-SARS-Cov-2 neutralizing Ab titer at an adequate level in the collected plasma will be an important prerequisite.

We therefore hypothesize that early administration of convalescent plasma containing polyclonal neutralizing Abs may inhibit viral entry and replication (as recently suggested in vitro[xii]) and consequently blunt an early pro-inflammatory pathogenic endogenous Ab response.

3 INVESTIGATIONAL MEDICINAL PRODUCT: CONVALESCENT PLASMA

3.1 Convalescent plasma collection

Potential donors of **convalescent plasma** will be identified through various means, including hospitals taking care of such patient, practitioners treating outpatients or specific social messaging. Convalescent patients at least 14 to 28 days (per at date regulation regarding blood donation) after the symptoms resolution will be invited to undergo plasma apheresis, pending general eligibility such as an age between 18 and 65 years old and weight not less than 50 kg.

The convalescent donors will undergo standard pre-donation assessment to insure compliance with current regulations regarding plasma donation in France[29] including standard microbiological assessment, as well as anti-HLA Ab detection in women with children. Furthermore, and importantly, an appropriate anti-SARS-Cov-2 neutralizing Ab activity titer should be verified. Based on prior SARS-CoV (1) studies[xiii], a titer of ≥ 1/40 as assessed by cytopathic effect - based virus neutralizing tests (described in[30]) will be required. If found to be inadequate, the collected plasma may be oriented towards standard transfusion use, for example in trauma patients.

The apheresis procedure will to be performed per standard procedures. A mean of approximately 600 ml of plasma may undergo pathogen reduction treatment. At least two pathogen reduction technologies have has been found to adequately inactivate MERS-CoV in blood products[31,32]. Although formally untested as of now, one can reasonably assume approaching efficacy regarding SARS-CoV-2 in plasma. After an earlier report reporting a slight reduction in Ebola virus IgG and neutralizing activity in a convalescent plasma after Intercept pathogen reduction[33], a recently published larger study found that Intercept treatment did not significantly reduce Ebola virus IgG titers or neutralizing activity[34].

Presence of infectious viremia in convalescent patients is not expected, despite a recent report of positive RT-PCR recurrence on repeat throat swabs in in 4 asymptomatic patients 5 to 13 days after hospital discharge[35]. In addition to being an isolated observation as of now, establishing whether viral RNA detected by PCR in such a setting is associated with infectious virus remains to be established. Furthermore, current knowledge regarding viremia kinetics is not in favor of viremia occurring in convalescent, i.e. asymptomatic, patients. Lastly, previous studies with coronavirus or influenza infection convalescent plasma do not report adverse events suggestive of discernable "re"infection in patients acutely infected at time of transfusion. To verify these findings, the absence of SARS-CoV-2 RNA in the collected plasma will be checked before infusion (as per regulatory requirements for all infectious agents).

As mentioned earlier, convalescent donor's candidate for plasma donation should undergo eligibility screening just like any other donor, including eligibility criteria pertaining to prior COVID-19 disease. Such donors will therefore be eligible for standard blood donation. This consideration may result in questioning additional safety measures such as verifying the absence of viral RNA and/or pathogen reduction if not performed usually on blood products in the given jurisdiction. In France, plasma for transfusion currently undergoes pathogen reduction or quarantine for at least 2 months until a renewed microbiological assessment at time of subsequent plasma donation.

Current regulation authorizes a plasma donation up to every 2 weeks. Convalescent donors will be invited to undergo 3 donations at 2 week intervals. The protocol for convalescent plasma collection has received ANSM approval (18/3/20) and ethics approval (Comité de protection des personnes, Ile de France, 26/3/20). Once treated and qualified, plasma will be cryopreserved (in 200 to 250 ml units) and made available for clinical use.

3.2 Safety of convalescent Plasma infusion

Convalescent plasma adverse events

None of the studies analyzed in the 2015 systematic review reported serious adverse events, although reporting of such events was most certainly not comprehensive. In a convalescent plasma trial for Ebola disease to which contributed the Etablissement Français du Sang (EFS)

in 2015, no serious adverse events were evidenced in 99 patients (minor adverse events were observed 8% of patients, mostly an increase in temperature (5%) and/or itching or skin rash (4%))[36]. Notably, 2 case reports of possible transfusion-related acute lung injury (TRALI) following convalescent plasma have been reported in a patient with Ebola disease[37] and patient with MERS-CoV[38]. In both cases, transfused plasma were found free of anti-HLA or anti-HNA Ab. In recent case series mentioned above, and although administered late in the course of the disease (10 to 22 days after onset), transfusion of 400 ml of ABO-compatible convalescent plasma was not associated with adverse events, including clinical or biological evidence for transfusion-associated inflammatory flare-up[16].

3.3 Justification of the schedule proposed for this nested trial

Two convalescent plasma units of 200 to 220 ml each will be transfused i.v. n,o later than 8 days after onset of clinical symptoms (see picture below) (±2 to account for availability of plasma). In the absence of acute unforeseen adverse events in the first 3 patients, an additional 2 plasma units of 200/220 ml will be transfused 24 hours after first 2 units, i.e a total of 4 units / patient. For the first 3 patients, and to verify the absence of any unanticipated acute or short-term serious adverse events, the 3rd and 4th plasma units will be infused 48 hours (vs 24 hours) after the first 2 units. Transfusion surveillance, treatment and reporting of adverse events will be performed per ANSM hemovigilance regulation regarding transfusion of labile blood products as well as through the specific clinical trial vigilance.

4 THE CORIMUNO-COVIPLASM PROTOCOL:

4.1 Description of the investigational medicinal product

The investigational medicinal product is a plasma unit provided by a COVID-19 convalescent pathogen-reduced (IA) plasma, fully compliant with ANSM regulation (ANSM authorisation, 11 mai 2007) as detailed in the investigator's brochure. This plasma unit will packaged and labelled per ANSM regulation regarding labile blood product. Upon receipt of a standard written prescription by the attending clinician, the EFS issuing department (service de délivrance de l'EFS), EFS personnel will select 2 ABO compatible plasma units in the

"convalescent plasma" inventory. These 2 plasma will follow standard ANSM approved procedures regarding thawing, issuing to the clinical ward and traceability.

Thawed plasma will be delivered to the clinical ward per standard ANSM approved procedures. Similarly, plasma transfusion (i. v. infusion 200 mL/h, 3,5 mL/mn), per- and post transfusion surveillance as well as traceability and hemovigilance will be fully compliant with current regulations.

Plasma administration: Two convalescent plasma units of 200 to 220 ml each will be transfused i.v. in hospitalized patients with mild disease (WHO grade 4 or 5, annexe 1) as soon as possible, and up to day 10 after initiation of clinical symptoms. In the absence of acute unforeseen adverse events in the first 3 patients, an additional 2 plasma units of 200/220 ml will be transfused 24 hours after first 2 units, i.e a total of 4 units / patient. For the first 3 patients, and to verify the absence of any unanticipated acute or short-term serious adverse events, the 3rd and 4th plasma units will be infused 48 hours (vs 24 hours) after the first 2 units.

Convalescent plasma collection and manufacturing: Potential donors of **convalescent plasma** will be identified through various means, including hospitals taking care of such patient, practitioners treating outpatients or specific social messaging. Convalescent patients at least 14 days after the symptoms resolution will be invited to undergo plasma apheresis, pending general eligibility such as an age between 18 and 65 years old and weight not less than 50 kg.

The convalescent donors will undergo standard pre-donation assessment to insure compliance with current regulations regarding plasma donation in France[39] including standard microbiological assessment, as well as anti-HLA Ab detection in women with children. Furthermore, and importantly, an appropriate anti-SARS-Cov-2 neutralizing Ab activity titer should be verified. Based on prior SARS-CoV (1) studies[13], a titer of >= 1/40 as assessed by cytopathic effect - based virus neutralizing tests (described in[40]) will be required. If found to be inadequate, the collected plasma may be oriented towards standard transfusion use, for example in trauma patients.

The apheresis procedure will to be performed per standard procedures. A mean of approximately 600 ml of plasma may undergo pathogen reduction treatment. At least two

pathogen reduction technologies have has been found to adequately inactivate MERS-CoV in blood products[41,42]. Although formally untested as of now, one can reasonably assume approaching efficacy regarding SARS-CoV-2 in plasma. After an earlier report reporting a slight reduction in Ebola virus IgG and neutralizing activity in a convalescent plasma after Intercept pathogen reduction[43], a recently published larger study found that Intercept treatment did not significantly reduce Ebola virus IgG titers or neutralizing activity[44].

Presence of infectious viremia in convalescent patients is not expected, despite a recent report of positive RT-PCR recurrence on repeat throat swabs in in 4 asymptomatic patients 5 to 13 days after hospital discharge[45]. In addition to being an isolated observation as of now, establishing whether viral RNA detected by PCR in such a setting is associated with infectious virus remains to be established. Furthermore, current knowledge regarding viremia kinetics is not in favor of viremia occurring in convalescent, i.e. asymptomatic, patients. Lastly, previous studies with coronavirus or influenza infection convalescent plasma do not report adverse events suggestive of discernable “re”infection in patients acutely infected at time of transfusion. To verify these findings, the absence of SARS-CoV-2 RNA in the collected plasma will be checked before infusion.

As mentioned earlier, convalescent donor’s candidate for plasma donation should undergo eligibility screening just like any other donor, including eligibility criteria pertaining to prior COVID-19 disease. Such donors will therefore be eligible for standard blood donation. This consideration may result in questioning additional safety measures such as verifying the absence of viral RNA and/or pathogen reduction if not performed usually on blood products in the given jurisdiction. In France, plasma for transfusion currently undergoes pathogen reduction or quarantine for at least 2 months until a renewed microbiological assessment at time of subsequent plasma donation.

Current regulation authorizes a plasma donation up to every 2 weeks. Convalescent donors will be invited to undergo 3 donations at 2 week intervals. The protocol for convalescent plasma collection has received ANSM approval (18/3/20) and ethics approval (Comité de protection des personnes, Ile de France, 26/3/20) . Once treated and qualified, plasma will be cryopreserved (in 200 to 250 ml units) and made available for clinical use.

4.2 Authorised and prohibited treatments (medicinal, non-medicinal, surgical), including rescue medications

The medical staff is expected to monitor patients and administer any drug required for the treatment and/or prevention of all the usual complications that can develop in this setting.

As mentioned earlier, transfusion surveillance, treatment and reporting of adverse events will be performed per ANSM hemovigilance regulation regarding transfusion of labile blood products.

Transfusion will be at a slow rate and under close monitoring, notably to identify and treat circulatory overload occurrence or other transfusion-related immediate side effects. Close monitoring will obviously be maintained after transfusion to detect any further unintended side effects, in particular evidence of increased inflammatory in the lungs or systemically.

4.3 PLASMA supply of the investigational centers

Convalescent plasma will be issued by the local EFS blood issuing center as all other blood products issued for patients in the given hospital, and in compliance with ANSM hemovigilance regulation.

4.4 Traceability in investigational centers

In accordance with the rules of Good Practices and to track the treatment given to each patient, all the information related to the treatment will be collected on a traceability sheet (Issuing, date of administration, time of administration, blood product identification number, and expiry date, and dose administered). Furthermore, transfusion traceability as per ANSM hemovigilance regulation will be undertaken as well.

4.5 Methods for monitoring compliance with the treatment

To track the treatment given to each patient, all the information related to the treatment will be collected on a traceability sheet. This sheet will be prospectively and exhaustively monitored by clinical research assistants during the study. In case of deviations from the protocol there will be reminders to the centers and regular checks.

4.6 Control

Control patients will receive the best standard of care.

5 DESIGN AND DATA COLLECTION

5.1 Design

This is a nested randomized trial within the CORIMUNO-19 platform trial (see protocol synopsis of CORIMUNO-19 in annex 2).

An average of 120 participants will be expected (60 participants in each arm) (see statistical section);

Availability of ABO compatible plasma will be checked by investigator when a CORIMUNO-19 patients is eligible. If so, randomization will be undertaken and patient will be offered to participate in this nested trial if he is allocated to the experimental arm.

Information and written consent collection will be done by the investigator

5.2 Specificity of the convalescent plasma treatment arm and associated controls

Eligible randomized patients may not be able to receive the intended plasma treatment because of ABO-compatible blood product unavailability. This may occur especially early-on, at a time when eligible (i.e. more than 14 to 28 days after disease resolution) convalescent plasma donors will be in limited numbers. As mentioned above, and to ensure proper randomization, availability of ABO compatible plasma will be verified with EFS for all eligible patients subjected to subsequent randomisation. This may be important, considering a potential association between recipient blood group and COVID-19 occurrence[46] or severity (not reported as of 28/3/20).

5.3 Inclusion Criteria:

- Patients included in the CORIMUNO-19 cohort
- Mild severity (grade 4 or 5 as described in the WHO scale, see annexe 1) occurring up to day 10 after initiation of clinical symptoms.

5.4 Exclusion Criteria:

- Pregnancy
- Current documented and uncontrolled bacterial infection.
- Prior severe (grade 3) allergic reactions to plasma transfusion

6 ENPOINTS FOR THE COVIPLASM TRIAL

6.1 Efficacy endpoints

Primary endpoints:

1. Survival without needs of ventilator utilization (including non- invasive ventilation, NIV) at day 14 of randomization (WHO score < 6) or additional immunomodulatory treatment (such as steroids or IL-6R Ab). Thus, events considered are the need of ventilator use (including non invasive ventilation, NIV), or death.
2. Early end point : WHO progression scale ≥7 (see annex 1) at day 4 of randomization

Secondary end-points:

1. WHO progression scale (annex 1) at 4, 7 and 14 days after randomization, overall survival at 14 and 28 after randomization, time to discharge, time to oxygen supply independency.
2. Biological parameters (as per the CORIMUNO-19 biological follow-up) improvement at day 4, 7 and 14 after randomization.

6.2 Safety endpoints

Occurrence of severe adverse events known to be associated with plasma transfusion such as transfusion associated circulatory overload (TACO), transfusion related acute lung injury (TRALI), and severe allergy will be reported.

Occurrence of systemic and/or local (lungs) inflammation associated with convalescent plasma transfusion will also be reported.

6.3 Specific data to be collected for this trial

Standard surveillance of plasma transfusion and reporting of adverse events per ANSM hemovigilance

7 EXPECTED BENEFITS AND RISKS

The clinical benefit is globally to prevent death in all patient groups.

Other benefits are to:

- blunt not only the pneumopathy-induced damage but also other COVID-19-associated injuries such as acute kidney injury (AKI), myocarditis, secondary bacterial infections.
- shorten the duration of hospital stay with minimization of physical (hospital acquired pressure ulcers, increased morbidity and mortality associated with nosocomial infections), psychological and economic complications related with prolonged stay.
- Shortening the hospital stay fosters not only individual clinical benefit but also collective clinical benefit through facilitation of collective access to caregivers.

The expected risk are:

In France all transfusion-related adverse events are reported to the ANSM through the hemovigilance system. In 2018, with 280 000 plasma transfused, incidence of TACO, TRALI and allergy (all imputability) were 2.1, 1.0 and 103.7 / 100 000 plasma transfused, respectively. Among allergies with a reasonable imputability (imputability grade 2 and 3), incidence of severe allergy (severity grade 3) was 29/ 100 000 plasma transfusion[47].

8 STATISTICAL METHODS

8.1 Principles of cohort multiple randomized controlled trials

The key features of the cohort multiple Randomized Controlled Trials (cmRCT) design are:

(I) Recruitment of a large observational cohort of patients with the condition of interest

(II) Regular measurement of outcomes for the whole cohort

(III) Capacity for multiple randomised controlled trials over time

Patients enrolled in the cohort agree to allow their longitudinal data to be used in the aggregate. They also allow their data to be used to identify them to be invited to participate in research interventions or for comparison purposes for intervention trials that may be conducted with other patients while they are participating in the cohort.

In the cmRCT design, only eligible patients randomly selected to be offered an intervention, are contacted and offered treatment. Eligible patients not selected to be offered an intervention are not notified about this trial and will be in the control group. Consent for specific trials will be obtained from those eligible patients who are invited and accepted the offer to participate. In the cmRCT design, as described to patients when they consent to participate in the cohort, only eligible patients randomly selected to be offered an intervention, but not eligible non-selected patients, are contacted and offered treatment. Eligible patients not selected are not notified about the trial. Consent for specific trials will be obtained from those eligible patients who are invited and accept the offer to participate. Post-intervention outcomes among eligible patients who accept the offer to receive the intervention will be compared with outcomes among patients from the cohort who were identified as eligible for the intervention, but were not randomly selected to be offered the intervention and not contacted about the intervention.

In the context of the COVID crisis, the advantage of the cmRCT design to conduct multiple trials that draw participants from the same patient cohort is important given the imperative that we have to answer multiple research questions (some identified and others not yet identified) in a very short time (a few weeks).

8.2 Planned statistical methods, including the timetable for any planned interim analyses

For the CORIMUNO-19-COVIPLASM trial, individuals in the cohort eligible in the participating centers are randomized 1:1 until a predefined sample size is reached. **An interim analysis is performed at mid-trial, but inclusions are not frozen to wait for the interim analysis.**

Baseline characteristics will be described with summary statistics, namely frequencies and percentages, or medians and interquartile ranges (IQR). We will use a group sequential design, based on a modified intention to treat (mITT), to avoid prolonging the trial after either efficacy or futility had been established. An interim analysis will be done every time an additional 60 patients reached the primary outcome (30 patients per arm). The analysis of the

primary outcome will be performed using a proc seqdesign (SAS software, version 9.4 or later). The secondary safety outcomes will be analyzed using Poisson regression method, accounting for all adverse events and not only the first one. All the analyses will be described in a statistical analysis plan (SAP) that will be written and signed before freezing of the database.

8.3 Statistical criteria for termination of the study

We will use a frequentist approach (i.e. non-Bayesian) for this specific trial. The O'Brien-Fleming α-spending function will be used to determine the lower and upper efficacy boundaries. It is not expected that the properties of the boundaries would be significantly different when using O'Brien Fleming boundaries in the frequentist trials compared to the use of the posterior distribution of hazard ratio with the Bayesian approaches applied in the CORIMUNO cohort. At each interim analysis, if the z-statistic is less than the lower efficacy boundary value, the trial could be stopped for futility upon decision of the DSMB (indicative and not binding futility boundary). If the z-statistic is higher than the upper efficacy boundary value, then the trial may be stopped for efficacy (again this boundary is not binding and the DSMB may propose to continue the accrual based on other information, such as secondary outcomes or safety). When no stopping for futility or efficacy is decided, 60 additional patients (30 per am) will be recruited.

8.4 Number of participants and justification

The predetermined sample size, controlling for the α risk and power given, is 120 participants, based on an expected survival rate without needs of ventilator utilization of 50% in the control group and 80% in the experimental group. With sample sizes of at least 60 in the control group and 60 in the experimental group, we will have a 95% power to detect a treatment difference of 30% between the two groups using a two-sided z-test with 5% significance level assuming that the variances are unpooled and that a continuity correction was not used. These results assume that the group sequential design has 1 interim sequential tests (2 total looks including final analysis). The O'Brien-Fleming spending function is used to determine the efficacy test

boundary. The sample size calculation was made using the statistical software package nQuery Advanced version 8.5.2.0, using the group sequential test (GST) for two proportion.
GST Boundaries (Z scale):

- Lower Efficacy Bounds: -2.963, -1.969
- Upper Efficacy Bounds: 2.963, 1.969

8.5 Anticipated level of statistical significance

The current decision boundaries allow to control for a frequentist type I error rate of 0.049.

8.6 Subject replacement strategy

No subject replacement is planned.

8.7 Method for taking into account missing, unused or invalid

We do not expect missing data for the primary outcome. However, were data to be missing, they will be imputed as failures for the trial monitoring. No imputation will be used for secondary efficacy and safety outcomes.

8.8 Management of modifications made to the analysis plan for the initial strategy

All the analyses will be described in a statistical analysis plan (SAP) that will be written and signed before freezing of the database), in order to accommodate any event or protocol modification that may have occurred and that would affect the way the analysis should be conducted. We do not expect modifications of the initial analysis strategy. However, should such modifications occur after the SAP has been validated, a modified SAP would be issued. The original SAP as well as the modified SAP will be kept in the study files, with the justification for any modification.

8.9 Choice of individuals to be included in the analyses

The primary endpoints analyses will be performed in the modified Intention to treat (mITT) basis. All randomized participants will be included in the mITT population except those who have not accepted the intervention and those who are unable to receive planned plasma therapy due to the unavailability of ABO compatible blood products.

9 RECORDING AND REPORTING ADVERSE EVENTS

The sponsor, represented by its safety Department, shall continuously assess the safety of each investigational medicinal product throughout the trial.

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1 ANNEX

Annex 1: WHO progression scale

OMS Progression scale	Descriptor	Score
Uninfected	Uninfected; non viral RNA detected	0
Ambulatory	Asymptomatic; viral RNA detected	1
Ambulatory	Symptomatic; Independent	2
Ambulatory	Symptomatic; Assistance needed	3
Hospitalized : mild disease	Hospitalized; No oxygen therapy	4
Hospitalized : mild disease	Hospitalized; oxygen by mask or nasal prongs	5
Hospitalized : severe disease	Hospitalized; oxygen by NIV or High flow	6
Hospitalized : severe disease	Intubation and Mechanical ventilation, pO2/FIO2>=150 OR SpO2/FIO2>=200	7
Hospitalized : severe disease	Mechanical ventilation, (pO2/FIO2<150 OR pO2/FIO2<200) OR vasopressors (norepinephrine >0.3 microg/kg/min)	8
Hospitalized : severe disease	Mechanical ventilation, pO2/FIO2<150 AND vasopressors (norepinephrine >0.3 microg/kg/min), OR Dialysis OR ECMO	9
Death	Dead	10

ANNEX 2 : BRIEF SYNOPSIS OF THE COVIMMUNO-19 PLATFORM TRIAL AND STATISTICAL CONSIDERATIONS

Summary :

The CORRIMUNO-19 cohort is specifically designed to conduct trials within cohorts.

These trials are randomized, controlled adaptive trials, with frequent interim monitoring to facilitate the following: dropping of poorly performing arms, introduction of new candidate therapies and modification of current optimized standard-of-care (oSOC).

In its simplest iteration, the study can be viewed as a series of 2-arm comparisons whereby the superior treatment, if identified, from each pairwise comparison becomes the basis of the new supportive care backbone (hence the term “optimized SOC”, or oSOC, to describe this potentially evolving backbone) common to each future arm of the study and against which additional investigational interventions may then be added to the protocol, tested and compared: Arm A: optimized SOC alone Arm B: Investigational treatment X + optimized SOC.

- If this pairwise comparison shows the superiority of Arm B over Arm A, then investigational treatment X featured in Arm B will be incorporated into the new SOC common to each future arm of the study (assuming adequate drug supply exists to permit this).
- Conversely, if a given pairwise comparison of Arm A versus Arm B fails to yield a clear statistical winner in terms of the primary endpoint, then subsequent pairwise comparisons will not incorporate the “failed” intervention featured in current Arm B into the new oSOC backbone.

1.1 Adding new trials in the cohort :

The choice of which experimental treatments may be studied in trials nested in the cohort and the order in which they are to be studied will be made by the scientific committee of the cohort, which is composed of a panel of physicians with expertise in the care and management of patients with Covid-19 infection.

1.2 Clinical trial process

- Trials with no overlap of the targeted population i.e. with inclusion and exclusion criteria leading to distinct groups will be driven in parallel. Thus, patients of the cohort will be randomized in the trial corresponding to their characteristics.

- Trials with overlap of the targeted population will be driven sequentially. A first set of patients will be included in the first trial (A). After inclusion of the predefined number of patients in the i^{th} set, the set $(i+1)^{th}$ set of patients will be included in one (B) of the other trials with the overlapped targeted population. This allows to run the interim analyses of trial A on the *i*-th set and to continue to include patients in trials B. After the results of the interim analysis it will be decided to continue or not the trial A and potentially to come back to trial A or not for the $(i+2)^{th}$ set of patients

  The sample of the sets will depend of each trial.

- Inclusions of new sets will stop when statistical analyses conclude on futility or efficacy or by DSMB decision.

1.3 Methodological elements of trials nested in the cohort :

- Trials nested in the cohorts may involve:
  - All patients of the cohort
  - OR a subpopulation of patients with specific eligibility criteria (e.g., patients in ICU, patients with a specific biomarker, etc.)
- Endpoints of the trials may involve:
  - The endpoints regularly collected in the cohort (see section 4.4)
  - OR specific endpoints collected for the given trial
- Interventions may be of any type (e.g., medications, non pharmacological treatments, organisation of care…). According to the cmRCT design, a random sample of patients is selected among all patients eligible for the trial and is proposed the intervention. Their outcome is compared to patients who did not receive the intervention.
- All elements of trials will be defined in specific dedicated protocols.
- Patients who will be proposed for the intervention will provide a new consent, specific for the trial. Patients who serve as controls will not provide a new consent, according to the cmRCT design.