Full title of trial	A Randomised Controlled Trial of plasma exchange with standard of care compared to standard of care alone in the treatment of severe COVID19 infection (COVIPLEX)
Short title	PEX in severe COVID19
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Sites(s)	[Single site]

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Protocol Version History

Version Number	Date	Protocol Update Finalised By (insert name of person):	Reasons for Update
1.1	18/06/2020	MScully	Ethics, HRA and MHRA changes

Signatures

The Chief Investigator and the JRO have discussed this protocol. The investigator agrees to perform the investigations and to abide by this protocol

The investigator agrees to conduct the trial in compliance with the approved protocol, EU GCP and UK Regulations for CTIMPs (SI 2004/1031; as amended), the UK Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the current Research Governance Framework, the GMO (Contained Use) Regulations 2000 (and subsequent amendments), the Sponsor's SOPs, and other regulatory requirements as amended.

Chief investigator

Professor Marie Scully

Signature Date

Sponsor

Dr Nick McNally
UCL

Signature Date

Contents

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List of abbreviations

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DI	Designated Individual
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
DVT	Deep vein thrombosis
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVigilance	European database for Pharmacovigilance
GAfREC	Governance Arrangements for NHS Research Ethics
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GMO	Genetically Modified Organisms
HTA	Human Tissue Authority
IB	Investigator Brochure
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised
MA	Marketing Authorisation

MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
NHS R&D	National Health Service Research & Development
PE	Pulmonary Embolism
PEX	Plasma exchange
PI	Principal Investigator
PIS	Participant Information Sheet
PL	Product License
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person (for release of trial drug)
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RSI	Reference Safety Information
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SDV	Source Document Verification
SOC	Standard of Care
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMA	Thrombotic Microangiopathy
TMG	Trial Management Group
TSC	Trial Steering Committee
TTP	Thrombotic Thrombocytopenic Purpura
VWF	Von Willebrand Factor

1 Trial personnel

See protocol cover page for Chief Investigator and Sponsor contact details.

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2 Summary

COVID19 is a viral pandemic associated with primarily respiratory pathology, in the form of microvascular and macrovascular thrombosis. In patients requiring hospital admission, there is severe disease, requiring respiratory support, from high dose oxygen therapy or ventilatory assistance, which may be invasive or non invasive. The pathology of COVID19 is poorly understood, but it is accepted there is an inflammatory-thrombotic basis. Despite current therapeutic platforms, there is no consensus on a specific therapy within a trial setting that has proven benefit in severe COVID 19.

Thrombotic microangiopathies, such as TTP, are a different disease, but have a comparable prothrombotic phenotype, and similar or higher inflammatory parameters, including D Dimers, ferritin, LDH and IL-6 at acute presentation and resolve with plasma exchange (PEX). The rationale in severe COVID19 infection is to undertake PEX to aid reduction of the hyperinflammation and reduce the morbidity and mortality to the lungs, but also systemically, such as the heart, kidneys and brain. A feasibility study of PEX therapy has been undertaken and confirmed a reduction in the inflammatory markers, no VTE/arterial events and normalisation of the renal function and cardiac function throughout the period of therapy. As plasma exchange is an intensive treatment modality, blocks of 5 daily PEX will be undertaken. Further blocks of PEX treatment can be initiated as dictated by the clinical and laboratory parameters. Unlike many therapeutic schedules, there is no immunosuppression associated with PEX; indeed, the resulting decrease in inflammatory markers were shown to be associated with an increase and sustained lymphocytes count. Therefore, as patients with COVID-19 have elevated procoagulant factors including VWF and factor VIII secondary to direct endothelial activation. This is associated with an exaggerated pro-inflammatory immune response and microvascular thrombosis; resulting in multi-organ dysfunction and eventually death. PEX will improve coagulopathy, as measured by VWF:ADAMTS 13 ratio and D Dimers, with an associated reduction in inflammation, organ-related microthrombosis, and ventilatory support.

Objectives:

Primary: To compare the reduction in inflammatory markers between Plasma Exchange (PEX) and the control group in patients with severe COVID

Secondary:
To compare rates of mechanical ventilation between Plasma Exchange (PEX) and control groups in patients with severe COVID requiring CPAP/ NIV at treatment onset

To compare rates of clinical thrombotic events either venous (deep vein thrombosis DVT or pulmonary embolism PE) or arterial thrombus (cardiac, neurological and peripheral vascular) between

	Plasma Exchange (PEX) and control groups in patients with severe COVID To compare reduction in the inflammatory-thrombotic response by monitoring von Willebrand factor VWFA antigen/ADAMTS 13 activity ratio between Plasma Exchange (PEX) and control groups in patients with severe COVID To compare the stability of cardiac function based on echocardiogram/troponin/BNP measurements cardiac function between Plasma Exchange (PEX) and control groups in patients with severe COVID To compare incidence of acute kidney injury as defined by KDIGO criteria between Plasma Exchange (PEX) and control groups in patients with severe COVID To compare mortality at day 28 between the PEX and control groups
Type of trial:	A Phase II, Parallel-group, unblinded, randomised controlled trial in COVID 19
Trial design and methods:	Patients will receive standard of care (SOC), or SOC and PEX. Single volume PEX capped at 3 litres if <100Kg and 4 litres if >100Kg. PEX will be given once a day for a minimum of 5 days. The course can be repeated at the discretion of the treating clinician, depending on patient's response based on a reassessment on D5-7, where there is clinical and biochemical improvement following initial 5-day block but persistent pro-thrombotic phenotype ie 5 days initial block plus reassess. Data collection includes routine laboratory parameters, FBC, renal function and liver function; inflammatory markers (D Dimers, LDH, CRP) and pre and post PEX samples to measure von Willebrand factor (VWF) and ADAMTS13 activity levels. The latter samples will be stored for further investigation related to COVID, for example, COVID19 viral analysis, cytokines. The control patients will have citrate and serum samples taken daily. Following the initial 5 day period. If patients have more than one 5 block of PEX, comparable daily samples will be taken. Thereafter, weekly to day 28.

Trial duration per participant:	From consent to 28 days
Estimated total trial duration:	From when first participant enrolled to last participant follow-up.
Planned trial sites:	Single-site
Total number of participants planned:	Minimum 20, maximum 40
Main inclusion/exclusion criteria:	Inclusion Criteria: • Age 18-70 • Proven COVID-19/high clinical suspicion of COVID-19 • Hypoxia/respiratory compromise defined as requiring respiratory support of >2L/min of oxygen by nasal cannulae to maintain SpO2≤96%. • Raised inflammatory parameters: at least 2 of the following: a. Raised LDH (> 2 x ULN) b. Raised D Dimers (> 2X ULN) c. Raised CRP (>2X ULN) • Females of childbearing potential have a negative pregnancy test within 7 days prior to being randomised. Participants are considered not of child bearing potential if they are surgically sterile (i.e. they have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are postmenopausal Exclusion Criteria: • Significant co-morbid illness with treatment escalation limited to CPAP • Active bleeding • PF ratio < 100 on mechanical ventilation OR noradrenaline requirement > 0.5mcg/kg/min to maintain MAP > 65mmHg (suggests futility) • Known allergies to Octaplas or excipients • Females who are pregnant
Statistical methodology and analysis:	The primary analysis will involve a comparison of the binary outcome '50% reduction in at least two inflammation markers' between the PEX+SOC and SOC trial arms using a chi-squared test. The risk difference (and ratio) will be estimated with a 95% confidence interval. All analyses will be performed on an intention to treat basis. Patient characteristics will be summarised by trial arm and inspected for balance. Patient flow throughout the trial will be summarised using a CONSORT diagram. Secondary outcomes will be summarised and compared using suitable statistical methods. For example, binary outcomes may be

compared using chi-squared tests and numerical outcomes may be compared using t-tests. P-values from tests of secondary outcomes may be adjusted to account for multiple testing. Appropriate regression methods will be used to perform adjusted analyses or to account for repeated measures.

The level of missing data will be reported and sensitivity and/or adjusted analyses performed to account for missing data.

3 Background and Rationale

Mortality in COVID-19 is primarily associated with severe hypoxaemic respiratory failure and histological features of pulmonary thromboses. The proportion of all hospitalised patients requiring ICU admission varies from 7.3% to 32% [1-3], majority of who require respiratory support. Whilst the overall outcome of patients who are admitted to ICU is high, outcomes of patients who require mechanical ventilation are particularly poor; with 86% of ventilated patients dead by 28 days [3] or only a third of patients extubated by 14 days [4] (Table 1).

Author, Journal	Country	Cases admitted to ICU	% Mechanically ventilated	Mortality in mechanically ventilated group	Ove Mort
Xiaobo Yang **Lancet Resp** [3]	Jin Yin-tan hospital (Wuhan, China)	n=52	42% (n=22)	86.4% (19 of 22)	61. (n=
Dawei Wang **JAMA** [2]	Zhongnan Hospital (Wuhan, China)	n=36	47% (n=17)	(Not reported)	17 (n=
Huang Chaolin **Lancet** [1]	Jin Yintan Hospital (Wuhan, China)	n=13	15% (n=2)	(Not reported)	38 (n=
Arentz Matthew JAMA [5]	Evergreen Hospital (Washington, USA)	n=21	71% (n=15)	(Not reported)	67 (n=
Bhatraju Pavan NEJM [4]	Multi-Centre (9) Seattle area hospitals, USA	n=24	75% (n=18)	50% (n=9)	50 (n=
Grasselli Giacomo JAMA [6]	Multi-centre (72 hospitals, Lombardy), Italy	n=1591	88% (1150 of 1300 patients)	(Not reported)	26 (n=4

Table 1: Clinical features and outcomes of patients with COVID-19 admitted to intensive care units

Routine laboratory parameters of inflammation including ferritin, CRP, and D-dimers are elevated in these patients [7]. Levels of inflammatory markers are significantly higher in non-survivors compared to survivors [7], which may represent an exaggerated host immune response to the viral infection, leading to organ dysfunction and death. The proportion of coagulopathy is much greater among non-survivors compared to survivors, with an elevated D-dimer (1microg/ml) independently predicting mortality [7] (Table 2). Patients with COVID-19 have elevated levels of factor VIII and virtually all patients have detectable lupus anticoagulant [8].

	Non survivor (n=54)	Survivor (n=137)	p-value
Lymphocytes < $0.8x10^9$/L	41 (76%)	36 (26%)	<0.0001
Platelet count <$100x10^9$/L	10 (20%)	2 (1%)	<0.0001
LDH (IU)	521 (98%)	253 (54%)	<0.0001
Troponin I (> 28 pg/ml)	46%	1%	<0.0001
Prothrombin time (>16s)	13%	3%	-
Serum ferritin ug/L	1435 (96%)	503 (71%)	0.0008
IL-6 pg/ml	11 (7-14.5)	6.3 (5.0-7.9)	<0.0001
D Dimer >1 ug/ml	81%	24%	<0.0001

Table 2: Biochemical features of critically ill patients with COVID-19 (Adapted from (Zhou et al, Lancet March 28th 2020; 395:1054-62) [7])

Unlike 'typical' ARDS, patients with COVID-19 ARDS have good pulmonary compliance but are significantly hypoxemic early in the disease [9]. This suggests a significant shunt fraction which may be explained by impaired pulmonary microcirculation. Histological data suggests that this may be a result of microthrombi. In a series of 12 COVID-19 patients, autopsy revealed deep venous thrombosis in 7 of 12 patients (58%) in whom venous thromboembolism was not suspected before death; pulmonary embolism was the direct cause of death in 4 patients [10]. The primary cause of death was respiratory failure with exudative diffuse alveolar damage with massive capillary congestion often accompanied by microthrombi despite anticoagulation [11].

Consistent with histopathological data, the incidence of thromboembolic complications in critically ill patients with COVID-19 is high [12-14] (Table 3). The incidence of thromboembolic complications despite the use of thromboprophylaxis occurs in 17% to 31% of critically ill COVID-19 patients [12-14]. This is greater than matched patients with non- COVID-19 ARDS [13]. Similarly, the reported incidence of thromboembolic complications general ICU patients is also significantly lower, with a propensity for deep vein thrombosis (DVT) rather than pulmonary embolism (PE) [15].

The striking increased risk in thromboembolic complications in critically ill patients with COVID-19 is associated with pulmonary thromboembolic disease rather than deep vein thromboses [13]. This may relate to the underlying pathophysiology of COVID-19, which uses ACE2 receptor expressed by pneumocytes in the epithelial alveolar lining to infect the host, thereby causing lung injury [16]. Endothelial activation in patients with systemic inflammation is associated with activation and degranulation of endothelium in vascular beds leading to an increased plasma levels of VWF [17].

	Total population	Use of systemic thromboprophylaxis	All thrombotic complications	DVT alone	PE ± DVT	CVA
Helms J [13]	150 COVID-19 on ICU 233 Non- COVID-19 ARDS	n=150 (100%) Prophylaxis n=105 Therapeutic n=45 n=233 (100%) Prophylaxis n=188 Therapeutic n=45	n=27 (18%) n=14 (6%)	n=3 (2%) n=3 (1.3%)	n=25 (17%) n=3 (1.3%)	n= (1.3%) n=1 (0.4%)
Klok FA [14]	184 on ICU	184 (100%)	57 (31%)	n=3 (1.6%)	n=25 (13.6%)	n (1.6%)
Lodigiani C [12]	Ward: 326 (84%) ICU: 62 (16%)	75% of ward patients 100% of ICU patients	n=20 (6.4%) n=8 (16.7%)	n=4 (1.3%) n=1 (2.1%)	n=2 (4.2%) n=8 (2.5%)	n (1.9%) n (6.3%)
Zhang [15]	Non COVID-19	281 ICU patients	(9.6%)	n=24	n=1	

Table 3: Thromboembolic complications in patients with COVID-19

The UK already adopts a policy of thromboprophylaxis (after VTE risk assessment) in all hospital inpatients to prevent thrombosis. The risk of thrombosis is compounded in sick patients in HDU/ICU settings by immobility, co-morbidities, (arterial disease, diabetes) body weight, acute inflammatory response and associated therapies e.g. steroids.

UCLH has the largest international cohort of patients with thrombotic thrombocytopenic purpura (TTP) and other thrombotic microangiopathies. Their presentation is acute, associated with anaemia, thrombocytopenia and end organ damage, primarily, the heart, brain and kidney. The respiratory system is not affected in TTP. Other thrombotic microangiopathies (TMA) have variable organ involvement eg HUS does have pulmonary disease. The diagnosis of TMA is primarily clinical, but may be defined by histology. The mainstay of treatment is plasma exchange, using octaplas. The rationale for Octaplas is its safety profile and reduced high molecular weight forms of von Willebrand factor. The role of plasma exchange (PEX) is delivery of high volumes of plasma, replenishing deficient factors e.g. ADAMTS 13, natural anticoagulants/coagulation factors, and complement proteins, leading to normalization of routine laboratory parameters, in particular, FBC, renal function, and LDH. Furthermore PEX has been demonstrated to reduce inflammatory markers, which are extremely high at presentation in TMAs (comparable to levels seen in COVID19) and subsequently ameliorated following PEX. PEX is standard of care for thrombotic microangiopathies, which severe COVID-19 infection appears to mimic.

3.1 Hypothesis:

Patients with COVID-19 have elevated procoagulant factors including VWF and factor VIII secondary to direct endothelial activation. This is associated with an exaggerated pro-inflammatory immune response and microvascular thrombosis; resulting in multi-organ dysfunction and eventually death. PEX will improve coagulopathy, as measured by VWF:ADAMTS 13 ratio and D Dimers, with an associated reduction in inflammation, organ-related microthrombosis, and ventilatory support.

3.2 Pilot data

Levels of protein S, protein C, antithrombin, Factor VIII, vWf, platelet counts, and ADAMTS-13 activity were measured in patients admitted to the ICU for respiratory support. Levels of protein S, protein C, antithrombin, and ADAMTS-13 activity were within the normal range. In contrast, levels of factor VIII and VWF were significantly elevated among critically ill patients with COVID-19.

A total of 6 patients at UCLH with COVID-19 requiring advanced respiratory support with features of TMA were consented to undergo PEX. A total of 5 days single volume PEX was conducted, and patients clinical and biochemical data compared to matched controls. Matched controls included patients who were eligible for PEX but did not consent (n=1) or did not receive PEX due to limitations on staff resource (n=7).

There were no reported adverse events associated with PEX.

The pertinent findings were :

- no thrombotic events during the duration of PEX
- decrease in the VWF/ADAMTS 13 ratio throughout the period of treatment
- decrease in inflammatory markers, in particular, D Dimers, ferritin and LDH
- increase in lymphocyte count in all patients which was sustained after the PEX course was completed
- increase in median PaO_2:FiO_2 ratio from the beginning to the end of the PEX period
- No deterioration to acute kidney injury:
- Stable cardiac function as assessed by echocardiography

4 Assessment and management of risk

1.Central vascath insertion:

There is a risk of pain, infection and bleeding or thrombosis with central vascath insertion. All the central lines are put in by a defined trained group within the trust i.e. ICU/anaesthetics or interventional radiology. Patients with severe COVID-19 infection are likely to need central line access e.g. PICC/Central line. While these lines are not suitable for PEX, central venous access is common in COVID-19 patients in ICU. Patients will be monitored frequently for infections, bleeding or thrombosis

2: PEX

A. Reaction to plasma: There is a risk of infusional and allergic reactions and rarely anaphylaxis with the use of Octaplas. This is considerably reduced with the use of Octaplas compared to standard fresh frozen plasma (FFP) Reactions grade 1-3 are amenable to standard therapy including antihistamine, hydrocortisone and paracetamol. If a patient experiences symptoms of anaphylaxis, treatment would be stopped immediately.

B. Citrate reactions: Some patients treated with PEX present with features of hypocalcaemia (fatigue, paraesthesia, tremor, and hypocalcemia). This is treated with calcium boluses, but offset by a calcium infusion throughout PEX.

C. Risk of viral transmission: Standard measures to prevent infections resulting from the use of medical products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pool for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. When medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. However Octaplas LG undergoes a number of additional pathogen inactivation steps and is considered very safe.

The table below summarises the risks, frequencies and mitigations of the IMP(s) and NIMP(s) (delete NIMP if it is not applicable)

Name of IMP(s) / NIMP	Potential risk	Risk Frequency	Risk Management
Octaplas	-Reactions to plasma - -Pathogen transmission	-Severe reactions- grade 4- anaphylaxis <1% -Due to nanofiltration and S/D processing, this is the safest and most effective plasma available	-Any reactions treated with antihistamine, paracetamol and /or hydrocortisone -PEX would be stopped if any severe reaction/anaphylaxis -routine viruses are checked pre PEX.
PEX procedure	Citrate toxicity	10-20% of procedures	IV calcium is run during PEX and added boluses given if required

Vascath insertion	Infection, bleeding, thrombosis	Approx. 10%	Lines are changed weekly to reduce infection, intermediate LMWH given, reducing thrombosis. Bleeding rare as lines inserted by USS

Type A = No higher than the risk of standard medical care

5 Objectives

The rationale of this study is to compare outcomes of patients receiving PEX to those who do not. We hope to ascertain if PEX provides a clinical benefit to expand its use nationally and internationally, as there is currently no treatment which improves the morbidity and mortality of patients with severe COVID-19.

Primary objectives:
To compare reduction in inflammatory markers between Plasma Exchange (PEX) and control groups in patients with severe COVID

Secondary objectives:
To compare rates of mechanical ventilation between Plasma Exchange (PEX) and control groups in patients with severe COVID requiring CPAP/ NIV at treatment onset

To compare rates of clinical thrombotic events either venous (deep vein thrombosis DVT or pulmonary embolism PE) or arterial thrombus (cardiac, neurological and peripheral vascular) between Plasma Exchange (PEX) and control groups in patients with severe COVID

To compare reduction in the inflammatory-thrombotic response by monitoring von Willebrand factor VWF antigen/ADAMTS 13 activity ratio between Plasma Exchange (PEX) and control groups in patients with severe COVID

To compare the stability of cardiac function based on echocardiogram/troponin/BNP measurements between Plasma Exchange (PEX) and control groups in patients with severe COVID

To compare incidence of acute kidney injury as defined by KDIGO criteria between Plasma Exchange (PEX) and control groups in patients with severe COVID

To compare mortality at day 28 between the PEX and control groups

6 Trial design

6.1 Overall design

This a parallel-group randomised controlled trial, which will be unblinded to the investigators and patients .

Patients will be randomised in a 1:1 ratio to either PEX+SOC or SOC. PEX will be delivered in conjunction with standard of care in all patients as dictated by the treating clinicians.

PEX will be given for a minimum of 5 days, but the course can be repeated depending on patient's response, based on a reassessment on D5-7. The 5 day PEX will be repeated at the discretion of the treating clinician in patients showing clinical and biochemical improvement but a persistent pro-thrombotic phenotype following the initial 5-day block .

Patients will be followed up until 28 days post treatment.

1.2. **TRIAL SETTING**

The study will be undertaken within the COVID wards in hospital. Trial site feasibility will be undertaken to ensure that sites participating in the trial are able to undertake the plasma exchange procedure

7 Investigational Medicinal Products and Non-Investigational Medicinal Products

7.1 Name and description of IMP(s)

OctaplasLG solution for infusion

7.2 Source of IMP, Manufacture, Distribution and Storage

OctaplasLG solution for infusion is a UK licensed product. The MA holder is Octapharma Limited with PL 10673/0009. It is licensed for therapeutic plasma exchange

OctaplasLG will be sourced from hospital stock

(Appendix 1)

Drug storage and supply

Octaplas LG will be sourced via hospital pharmacy and stored at ≤ -18°C in the Blood Transfusion Laboratory).

Preparation and labelling of Investigational Medicinal Product

On request for Octaplas LG, an order is made via Blood transfusion. Either AB plasma or group specific product is made available for the patient and information for patients will be tagged to each unit, as per standard trust protocol for blood products. Each bag consists of 200mls of plasma. The label on the IMP bag will be as per requirements of Annex 13 (EudraLex Volume 4), and approved by relevant regulatory authority (MHRA).

Plasma is defrosted within blood bank as per standard SOP in a plasma thawer.

Octaplas LG will be couriered to the back up fridges.

Octaplas LG must be used within 24 hours or will be returned to the blood transfusion laboratory and destroyed. All blood products require a fate on the BT IT system.

7.3 Concomitant medication

Concomitant medications will be recorded in the Participant's medical records/CRF.

7.4 Post-trial IMP arrangements

No arrangements for IMP to be provided to trial participants post trial participation

8 Selection of Participants

Patients meeting the inclusion/exclusion criteria only will be approached and inclusion requires they meet these parameters.

Patients who have already consented to a COVID19 study involving an IMP or another research study relating to an IMP will not be eligible.

8.1 Eligibility of trial participants

8.1.1 *Trial participant inclusion criteria*

1. **Age > 18 years**
2. Proven COVID-19/high clinical suspicion of COVID-19*
3. Hypoxia/respiratory compromise defined as requiring respiratory support of >2L/min of oxygen by nasal cannulae to maintain SpO2≤96%.
4. Raised inflammatory parameters: at least 2 of the following:
   Raised LDH (> 2 x ULN)
   Raised D Dimers (> 2X ULN)
   Raised CRP (>2X ULN)
5. Females of childbearing potential have a negative pregnancy test within 7 days prior to being randomised. Participants are considered not of child bearing potential if they are

surgically sterile (i.e. they have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are postmenopausal

*In light of a 20% false negative rate with PCR swab tests, patients confirmed as having the clinical phenotype, in conjunction with raised inflammatory parameters and exclusion of any other precipitant, as judged by 2 consultants.

8.1.2 *Trial participant exclusion criteria*

1. Significant co-morbid illness with treatment escalation limited to CPAP **such as, but not limited to, active cancer, severe cardiac or renal disease, history of organ transplantation, active inflammatory disease**
2. Active bleeding
3. PF ratio < 100 on mechanical ventilation OR noradrenaline requirement > 0.5mcg/kg/min to maintain MAP > 65mmHg (suggests futility)
4. Known allergies to Octaplas or excipients
5. Females who are pregnant **or breastfeeding**

8.2 Recruitment

Participant recruitment at a site will only commence when the trial has

1. Been initiated by the Sponsor (or its delegated representative), and
2. Issued with the 'Open to Recruitment' letter.

Patients will be recruited following admission to hospital for supportive care relating to presumed or confirmed COVID19. Those deemed appropriate for inclusion, meeting the above criteria, will be discussed by 2 senior clinicians and approached about the study. In conjunction, this will be discussed with the next of kin. Currently a pathway exists for COVID patients between ED/AMU, ICU and dedicated areas within the hospital.

8.3 Informed consent procedure

The Principal Investigator (PI) has overall responsibility for the informed consent of participants at their site and will ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained, and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP), and Declaration of Helsinki. If delegation of consent occurs then details will be provided in the site delegation log.

The right of a participant to refuse participation without giving reasons will be respected. The participant will remain free to withdraw at any time from the study without giving reasons and

without prejudicing his / her further treatment, and will be provided with a contact point where he / she may obtain further information about the study.

Participants will be severely ill at the time of eligibility (non-invasive ventilation or intubated on mechanical ventilation and sedation), such that the Medicines for Human Use (Clinical Trials) Regulations provides guidance. Those who are not sedated and intubated will have been through a psychologically anxiety provoking event and will often be extremely distressed due to severe difficulty breathing and hypoxia. As such they may be unable to fully comprehend an important consideration when the intervention under investigation is time sensitive. The PI is responsible for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence.

A legal representative can be asked to give consent on behalf of an adult lacking capacity to do so themselves.

Those who are able to act as a legal representative in Clinical Trials of Investigational Medicinal Products (CTIMPs), in England and Wales are:

- Personal legal representative i.e. a person not connected with the conduct of the trial who is suitable to act as the legal representative by virtue of their relationship with the adult, and is available and willing to do so. If one is not available:
- Professional legal representative i.e. a doctor responsible for the medical treatment of the adult if they are independent of the study, or a person nominated by the healthcare provider.

Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies:

All data and samples collected as part of this trial will be available for COVID19 related research, to improve the understanding of the condition. This may be within the team/trust or in collaboration with external researchers. All data/samples in the latter situation will be anonymised.

Patients with COVID19, provided, or high clinical suspicion, on HDU/ICU, will have their information reviewed by the trial team. If they forfill the inclusion criteria, as confirmed by 2 members of the trial team, they will be offered the opportunity to participate in the study. This will be discussed with their primary admitting clinician. The study will be discussed with the patient and they will be given an opportunity to read the PIS. Once permission is sort, the patients NOK will be contacted to explain the study and ensure they are happy for inclusion. Patients will be given 24 hours to confirm their participation and consent.

In patients who unable to consent, but for whom would fit the inclusion criteria, their NOK will be contacted. Consent would be required within 24 hours. This can be signing the form by email. If this is not possible, email confirmation they understand the study and confirm consent on behalf of the patient.

Finally, in patients who are eligible, but there is no NOK a legal representative can be contacted on behalf of the patient and give consent.

Limitation to recruitment will be the number of patients already receiving PEX. Therefore, all patients admitted with COVID19 may not be approached.

9 Trial procedures

9.1 Pre-treatment Assessments

All cases screened for the study will be captured and reason for not being recruited documented.

The following trial specific procedures will be carried out after consent:

1.Demographics recorded including gender, age, height, weight, race

2. Medical History recorded to exclude underlying pre morbid conditions, VTE history, Smoking history

3. General physical examination

4. Concomitant Medication recorded: Primarily antibiotics, noradrenaline use

5. Blood tests

-Serum pregnancy test (for women of child bearing potential) in last 7 days

-Baseline inflammatory parameters and routine bloods (FBC, renal, liver function and coagulation screen with fibrinogen, LDH, CRP, D dimer, ferritin)

-Hepatitis A, B, C and HIV pre PEX (result does not need to be available before PEX)

-Troponin T/BNP (result does not need to be available before PEX)

-C3/4 (result does not need to be available before PEX)

-Autoimmune screen (ANA, ENA) (result does not need to be available before PEX)

-Factor VIII, VWF, ADAMTS-13 activity (result does not need to be available pre PEX

-IgG and IgM to COVID-19 (result does not need to be available before PEX)

-PCR result for COVID-19 (result does not need to be available before PEX, see inclusion criteria for definition of probable COVID))

6. Respiratory parameters: SaO2,RR

-PaO2, FiO2

-Method of assisted ventilation eg HDNOHFNO, CPAP

-P:F ratio

CXR/ CT/HRCT : if undertaken as part of routine clinical care

7.Cardiac investigations

- ECG (result does not need to be available before PEX)

- Echocardiography (if available within 48 hours of enrolment to study)

The results from the following routine procedures may be used:

Blood test results within 48 hours of enrolment

PCR result for COVID-19 within past 14 days (result does not need to be available before PEX, see inclusion criteria for definition of probable COVID)

Pregnancy test within 7 days

Where routine results are not available, the procedure(s) will be carried out at screening after consent.

All pre-treatment procedures will be carried out as specified in the schedule of assessments **(appendix 2).**

9.2 Registration / Randomisation Procedures

Participant randomisation will be undertaken remotely at sites using central randomisation system developed by Sealed Envelope.

Following participant consent, and confirmation of eligibility (see section 8.1 for pre-treatment assessments) the registration/randomisation procedure described below will be carried out.

Participants are considered to be enrolled into the trial following: consent, pre-treatment assessments (see section 8.1), confirmation of eligibility, completion of the registration/randomisation process, allocation of the participant trial number and treatment by the central coordinating team/remote system.

Patients will be randomized to either PEX+SOC or SOC in a 1:1 ratio using block randomization with varying blocks sizes.

Randomisation will be carried out by the online randomisation system provided by commercial company Sealed Envelope . This will be accessed by a designated member of staff who will communicate the treatment allocation to the clinical team.

9.3 Treatment Schedule

IMP = OctaplasLG, Octapharma, Limited UK: 40mls/Kg intravenously via plasmapheresis

Licensed for therapeutic plasma exchange

OctaplasLG via plasmapheresis

Intravenous infusion of Octaplas to the nearest litre (which in the majority of patients will be 3 litres) through a Cobe Spectra apheresis machine over 2-3 hour, with removal of a comparable volume of plasma once daily for 5 days.

Single volume PEX capped at 3 litres if <100Kg and 4 litres if >100Kg.

PEX will be given for a minimum of once a day for 5 days, but the course can be repeated depending on patient's response, based on a reassessment on D5 to D7. The 5 day PEX will be repeated in patients showing clinical and biochemical improvement but persistent pro-thrombotic phenotype following the initial 5-day block

The Cobe Spectra is the preferred technology for plasma exchange, but plasma exchange may be performed on haemofilters.

The following drugs are considered to be non-investigational medicinal products (NIMPs) in this Trial:

Medications used during plasma exchange (NIMPs)

The following drugs are standard adjunctive treatment during plasma exchange which may be given during PEX

- Calcium replacement either oral or iv
- Hydrocortisone 100mg intravenously
- Chlorpheniramine 10mg intravenously (or 4mg orally)
- Paracetamol 1g orally.

All medications need to be documented on the CRF and source document.

These are NIMPS as they are not treating the disease but are used to potentially reduce any infusional side effects of plasma exchange.

Intermediate dose LMWH for all patients within the study: <100Kg 40mg BD enoxaparin (or equivalent LMWH), > 100Kg, 60mg BD Enoxaparin

9.3.1 *Dose Modifications*

3 litre PEX if ≤100Kg and 4 litre PEX if >100Kg

.

9.4 Subsequent assessments and procedures

9.4.1 *Visit schedule and assessments*

A schedule of all trial assessments and procedures is set-out in **Appendix 3.**

Day 1- 5

- eligibility check pre PEX if randomised to PEX
- Vitals pre and post PEX (temperature, blood pressure, pulse, respiratory rate and oxygen saturation level) or once daily
- Plasma exchange if randomised to PEX
- assessment of compliance with PEX
- general physical examination
- recording of relevant concomitant medications eg start stop dates of antibiotics, noradrenaline
- Daily routine bloods (FBC, renal, liver function and coagulation screen with fibrinogen)
- Inflammatory markers on D1,D3 &D5 (LDH, CRP, D dimer, ferritin)
- Citrated plasma and serum samples pre and post PEX, or daily for those randomised to SOC to save for VWD screen, ADAMTS13 activity, COVID-19 serology, and multiplex inflammatory markers related to ILs cytokines, interferons, and vascular markers of endothelial injury. Spare samples can be used for COVID-19 related research as authorised by the trial team
- Respiratory parameters: Oxygen requirement, respiratory rate, type of ventilator support- as pat of standard of care assessment
- Echocardiogram on D1
- Troponin and BNP on D1
- adverse event collection
- Reactions to Plasma exchange: graded 1-4
- Complications related to central vascath
- Need for antibiotics
- Deterioration requiring ventilation
- Arterial or venous thrombotic event

Reassessment (Day 5-7)

Review of clinical and laboratory parameters by trial team. Consideration of further 5 day block of PEX if clinical and biochemical improvement following initial 5-day block but persistent pro-thrombotic phenotype

*If a patient has a second 5 days of PEX started-follow instructions for day 1-5 above

Follow up Day 6 - 28*

- Vitals (temperature, blood pressure, pulse, respiratory rate)
- general physical examination-weekly
- recording of concomitant medications-related to antibiotics, new cardiac medication, but not all the routine medicines re SOC and not including PRN medications.
- Daily routine bloods (FBC, renal, liver function and coagulation screen with fibrinogen)
- Inflammatory markers, at least 3 x/week (LDH, CRP, D dimer, ferritin)
- Citrated plasma and serum samples taken at least weekly to 28 days to save for VWD screen, ADAMTS 13 activity, COVID-19 serology, and multiplex inflammatory markers related to ILs cytokines, interferons, and vascular markers of endothelial injury. Spare samples can be used for COVID-19 related research as authorised by the trial team
- Respiratory parameters
- Echocardiography D7
- Troponin/BNP weekly D7, D14, D21, D28
- Adverse event collection
- Need for antibiotics
- Deterioration requiring ventilation
- Arterial or venous thrombotic event

End of study Day 28

- 28 day mortality and outcomes
- Echocardiogram, if available, D28

9.5 *Laboratory Assessments and Procedures*

Local laboratories

The following tests will be carried out at Local Laboratories:

Laboratory test	Parameters
BLOOD	
Haematology	leukocytes, erythrocytes, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), platelets, neutrophils, eosinophils, basophils, lymphocytes, monocytes;

Serum chemistry	alanine transaminase (ALT), alkaline phosphatase, total bilirubin, creatinine, urea, potassium, sodium, albumin
Clotting screen	Prothrombin time, activated partial thromboplastin time, clauss fibrinogen,
Inflammatory markers	C reactive protein (CRP), lactate dehydrogenase (LDH), D dimer, ferritin
Pregnancy test	Serum bhCG
Virology test	Covid 19 PCR, Covid 19 IgM and IgG, Hepatitis-B-virus surface antigen (HBsAg), anti-hepatitis C virus (anti-HCV) antibodies, immunodeficiency virus 1 and 2 (anti-HIV1/2) antibodies,
Cardiac markers	Troponin, BNP
Procoagulant markers	Factor VIII, VWF, ADAMTS-13 activity
Autoimmune screen	C3/C4 ANA ENA
Multiplex inflammatory markers	cytokines including interleukins, interferons, and vascular markers of endothelial injury 'cytokine storm'

Central laboratories

No central laboratory

Translational Research Samples

Citrated plasma and serum samples can be used for COVID-19 related translational research as authorised by the trial team. All data and samples will be available for COVID19 related research, to improve the understanding of the condition. This may be within the team/trust or in collaboration with external researchers. All data/samples in the latter situation will be anonymised.

The samples will be spun and stored in Special Coagulation Laboratory, 60 Whitfield street, London W1T4EU

Any analysis of samples needs a formal risk assessment re aerosol risk when spinning or as part of analysis and will only be undertaken following health and safety sign off within HSL/UCLH/UCL.

9.7 Assessment of IMP/NIMP compliance

PEX and NIMP will be administered as an inpatient IMP by trained apheresis staff as per Trust protocol so there will be no compliance issues.

9.*8. Discontinuation/withdrawal of participants*

Discontinuation of Trial Treatment for clinical reasons

A participant may be withdrawn from trial treatment whenever continued participation is no longer in the participant's best interests, but the reasons for doing so must be recorded. Reasons for discontinuing treatment may include

disease progression whilst on therapy

unacceptable toxicity: **anaphylaxis to plasma**

intercurrent illness which prevents further treatment

patients withdrawing consent to further trial treatment

Any alterations in the participant's condition which justifies the discontinuation of treatment in the site investigator's opinion

Persistent non-compliance to protocol requirements

The decision to withdraw a participant from treatment must be recorded in the CRF and medical notes, and the sponsor when required should be notified in writing.

In these cases participants remain within the trial for the purposes of follow-up for safety and or data analysis according to the treatment option to which they have been allocated

Participant withdrawal from trial treatment

If a participant expresses their wish to withdraw from trial treatment, sites should explain the importance of remaining on trial follow-up and seek permission to allow use of routine follow-up data to be used for trial purposes. The importance of safety follow-up should be emphasised to the participant in the Participant Information Sheet.

The decision of the participant to withdraw from treatment must be recorded in the CRF and medical notes.

The participant may withhold their reason for withdrawal however, if the participant gives a reason for their withdrawal, this should be recorded.

Withdrawal of Consent to Data Collection

If a participant explicitly states they do not wish to contribute further data to the trial their decision must be respected and recorded in the CRF and medical notes.

Loss to follow-up

If a participant moves from the area, every effort should be made for the participant to be followed up at another participating trial site and for this new site to take over the responsibility for the participant.

9.8 Replacements

Withdrawn participants would not be replaced

9.9 Stopping rules

The trial may be stopped before completion for the following reasons:

Anaphylaxis to plasma during PEX

On the recommendation of the TMG

On the recommendation of the sponsor and CI

9.10 Definition of End of Trial

The end of trial is day 28 of the last participant.

10 Recording and reporting of adverse events and reactions

Collection, recording and reporting of adverse events (including serious and non-serious events and reactions) to the sponsor will be completed according to the sponsor's SOP (INV/S05).

10.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. *Therefore an AE can be any unfavourable or unintended change in the structure (signs), function (symptoms) or chemistry (laboratory data) in a participant to whom an IMP or procedural intervention has been administered, including occurrences which are not necessarily caused by or related to that product.*
Adverse Reaction (AR)	Any untoward and unintended response in a participant to an investigational medicinal product which **is related** to any dose administered to that participant. *This includes medication errors, uses outside of protocol (including misuse and abuse of product)*
Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction	Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that: • results in death, • is life-threatening*, • requires hospitalisation or prolongation of existing hospitalisation**,

	• results in persistent or significant disability or incapacity, or • consists of a congenital anomaly or birth defect *A life- threatening event, this refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. ** Hospitalisation is defined as an in-patient admission, regardless of length of stay. Hospitalisation for pre-existing conditions, including elective procedures do not constitute an SAE. Some medical events may jeopardise the subject or may require an intervention to prevent one of the above characteristics/consequences. Such **important medical events** should also be considered as serious. The term "**severe**" is often used to describe the intensity of an event or reaction (mild, moderate or severe) and should not be confused or interchanged with the term "**serious**".
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature, severity or outcome of which is not consistent with the Reference Safety Information.
Reference Safety Information (RSI)	A list of medical events that defines which reactions are expected for the IMP being administered to clinical trial subjects, and so do not require expedited reporting to the Competent Authority. It is contained in a specific section in the Summary of product characteristics (SmPC) or the Investigator Brochure (IB).

10.2 Recording adverse events

All adverse events will be recorded in the medical records in the first instance. All adverse events will be recorded from consent to the end of trial.

All adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate.

Non-serious Adverse Events (AEs) and Serious Adverse Events (SAEs) associated with COVID-19 infection will not be collected in the CRFs or reported to Sponsor for this trial. Refer to 'Serious Adverse Events which do not require immediate reporting' section for further details.

10.3 Assessments of Adverse Events

Each adverse event will be assessed for severity, causality, seriousness and expectedness as described below.

10.3.1 *Severity*

Category	Definition
Mild	The adverse event does not interfere with the participant's daily routine, and does not require intervention; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the participant's routine, or requires intervention, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health

10.3.2 *Causality*

The assessment of relationship of adverse events to the administration of IMP is a clinical decision based on all available information at the time of the completion of the case report form.

The causality assessments will be captured in the trial specific CRF, SAE Log or SAE Reporting Form.

The following categories will be used to define the causality of the adverse event:

Category	Definition
Related	A causal relationship between an IMP/investigational treatment and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.
Not related	There is no reasonable possibility of a causal relationship between an IMP/investigational treatment and an adverse event.

10.3.3 *Expectedness*

Category	Definition
Expected	An adverse event which is consistent with the information about the IMP listed in the current approved Reference Safety Information (RSI) for the trial.

Unexpected	An adverse event which is <u>not consistent</u> with the information about the IMP listed in the current approved Reference Safety Information (RSI) for the trial.

* this includes listed events that are more frequently reported or more severe than previously reported

The RSI to be used to assess expectedness is section 4.8 of the SmPC for octaplasLG (human plasma proteins).

10.3.4 *Seriousness*

All events are assessed for seriousness as defined for an SAE in section 10.1.

10.4 Procedures for recording and reporting Serious Adverse Events

All serious adverse events (SAEs/SARs/SUSARs) will be recorded in the medical records in the first instance. Serious Adverse Events (SAEs) related to COVID-19 will not be collected in the CRFs or reported to Sponsor for this trial. Refer to 'Serious Adverse Events which do not require immediate reporting' section for further details.

All other SAEs will be recorded in the CRF, the Sponsor's SAE Recording Log and SAE Reporting Form.

All SAEs will be recorded from randomisation until the end of the trial (i.e. 28 days after enrolment).

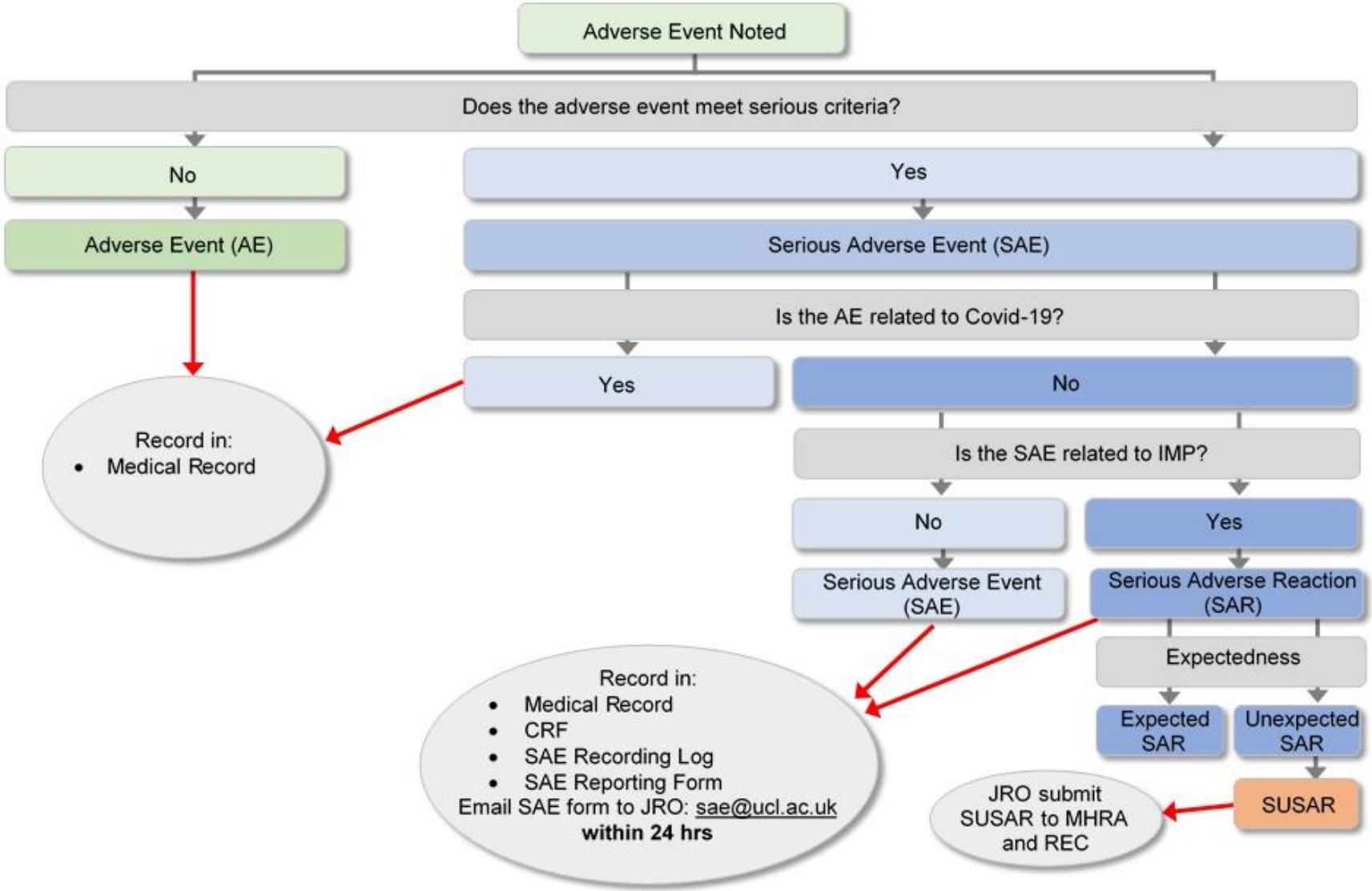
All SAEs (except COVID-19 related SAEs) must be recorded on a SAE Reporting Form. The CI/PI or designated individual will complete the sponsor's SAE form email to the Sponsor at SAE@ucl.ac.uk, within 24 h of his / her becoming aware of the event. The Chief or Principal Investigator will respond to any SAE queries raised by the sponsor as soon as possible.

Completed SAE forms must be sent within 24 hours of becoming aware of the event to the Sponsor
Email forms to SAE@ucl.ac.uk

Managing serious adverse events in a multi-site trial

- SAEs from all sites must be reported to Sponsor as detailed above. The SAE Reporting Forms should be emailed to the CI at the same time as forwarding to the Sponsor. The CI will perform an assessment of the SAE in collaboration with the Sponsor. It should be noted that the CI cannot overrule the causality assessment provided by the PI.
- SAE Recording Logs should be sent to UCLH data manager as per the data management plan, and to the Sponsor upon request.

Flow Chart for SAE Reporting



10.5 Serious Adverse Events which do not require immediate reporting

SAEs associated with COVID-19 disease do not require recording in the CRF, SAE Recording Log or SAE Reporting Form. However, if the relationship between the IMP and an SAE cannot be ruled out the SAE must be recorded and reported to Sponsor as detailed above.

There is high rate of expected deterioration in this group of patients. Anticipated adverse events/interventions associated with COVID-19 infection which are not required to be captured as an SAE/AE include:

-abnormal pathology results from presentation (including inflammatory markers related to a hyperinflammatory response)

-secondary infection

-renal failure

-cardiac disease e.g. arrythmias, right heart failure

-intubation and ventilation

-VTE/arterial thrombosis

-end organ damage developing either biochemical e.g. AKI, liver impairment or clinical e.g. Intubation, thrombosis (either venous or arterial such as stroke)

-death from COVID19

This will be captured within the medical notes. These represent SAEs but are anticipated based on the natural history of the COVID-19 disease and so do not require immediate reporting. Mortality will be captured as an endpoint.

10.6 Notification of Deaths

Deaths related to COVID-19 disease is an endpoint of the trial and will be captured in the CRF. All other SAEs should be reported to Sponsor as described in the Procedures for recording and reporting Serious Adverse Events section above.

10.7 Reporting SUSARs

The sponsor will notify the main REC and MHRA of all SUSARs. SUSARs that are fatal or life-threatening must be notified to the MHRA and REC within 7 days after the sponsor has learned

of them. Other SUSARs must be reported to the REC and MHRA within 15 days after the sponsor has learned of them.

10.8 Development Safety Update Reports

The sponsor will provide the main REC and the MHRA with Development Safety Update Reports (DSUR) which will be written in conjunction with the trial team and the Sponsor's office. The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

10.9 Pregnancy

Pregnancy is considered to be highly unlikely during the study as participants are hospitalised for the duration of the trial.

In the unlikely event that a female participant or the female partner of a male participant becomes pregnant at any point during the trial, a completed trial specific Pregnancy Reporting Form will be emailed to the Sponsor SAE@ucl.ac.uk, within 24 hours of his / her becoming aware of the event in line with the Sponsors SOP (JRO/INV/S05). The Chief or Principal Investigator will respond to any queries raised by the sponsor as soon as possible.

Completed Pregnancy Reporting Forms must be sent within **24 hours** of becoming aware of the event to the Sponsor
Email forms to SAE@ucl.ac.uk

The Sponsor must be kept informed of any new developments involving the pregnancy through the completion of a follow-up Pregnancy Reporting Form. Any pregnancy that occurs in a female trial subject during a clinical trial should be followed to termination or to term.
Consent to report information regarding the pregnancy must be obtained from the pregnant participant. A trial-specific pregnancy monitoring information sheet and informed consent form for trial participants and the partners of trial participants must be used for this purpose.

With consent additional information regarding the pregnancy will be collected and reported to the Sponsor, the Sponsor will advise on the length of follow up of the pregnancy/ child on a case by case basis,

10.10 Reporting Urgent Safety Measures and other safety events

If any urgent safety measures are taken the CI/ PI shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA, the relevant REC and Sponsor of the measures taken and the circumstances giving rise to those measures.

10.11 Notification of Serious Breaches to GCP and/or the protocol (SPON/S15)

A "serious breach" is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

The sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of –

(a) the conditions and principles of GCP in connection with that trial; or (b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. The sponsor's SOP on the 'Notification of violations, urgent safety measures and serious breaches' will be followed.

10.12 Reporting incidents involving a medical device(s)

Any adverse incident involving a medical device should be reported to the manufacturer of the device.

This is especially important where the incident has led to or, was it to occur again could lead to an event classified as serious (see section 9.2 for definition of SAE). Other minor safety or quality problems should be reported along with incidents that appear to be caused by human error.

Local trust reporting procedures may also need to be followed. It is the responsibility of the PI and trial site team to ensure they are aware of any specific local requirements for reporting device incidents.

Sites to report to the manufacturer and an incident form forwarded to the central trial coordinator.

Adverse incidents related to a medical device can be reported directly to the MHRA via the online system (www.mhra.gov.uk). Alternative contact details: Medicines & Healthcare products Regulatory Agency Adverse Incident Centre (Tel: 020 7084 3080; Fax 020 7084 3109).

11 Data management and quality assurance

11.1 Confidentiality

All data will be handled in accordance with the UK Data Protection Act 1998.

Case Report Forms (CRFs) for sites will not bear the participant's name or other personal identifiable data. The participant's initials, date of birth and trial identification number, will be used for identification and this will be clearly explained to the patient in the Patient information sheet. Patient consent for this will be sought.

11.2 Data collection tools and source document identification

At UCLH, All data will be available on hospital IT clinical system (EPIC) as source documentation and captured on Sealedenvelopes.com. As there may be a number of datapoints re observations in a 24 hour period, only those captured within the daily trial update, eg as a median will be recorded.

Data will be collected from sites on Trial specific case report forms (CRFs)

Source data are contained in source documents and must be accurately transcribed on to the CRF. Examples of source documents are medical records which include laboratory and other clinical reports etc.

A source document list will be implemented prior to the start of the trial to identify:

which data is to be recorded directly onto the CRF;

which data is recorded firstly into source documents, such as medical notes, and then transcribed into the CRF

It is the responsibility of the investigator to ensure the accuracy of all data entered in the CRFs. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

11.3 Completing Case Report Forms

CRFs from sites must be completed and signed by staff that are listed on the site staff delegation log and authorised by the CI/ PI to perform this duty. The CI/ PI is responsible for the accuracy of all data reported in the CRF.

Once completed the original CRFs must be sent to HRU, UCLH and a copy kept at site. The CRFs must be returned at least weekly of the participant visit. Source data verification of a CRF page should be completed and all data queries answered prior to submission where possible.

11.4 Data handling and analysis

All data will be added to an external validated database hosted by Sealed Envelope.

Data will be reviewed by two independent members of the trial team and presented to the TMG

12 Statistical Considerations

12.1 Outcomes

12.1.1 *Primary outcomes*

The (binary) primary outcome is whether a 50% reduction (from baseline) has been observed in at least two inflammatory markers (based on CRP, LDH and D dimer) throughout the period of PEX or SOC over a comparable time, following initiation of study.

12.1.2 *Secondary outcomes*

1. Number of patients requiring mechanical ventilation who required only supplemental O2/CPAP at study entry. This will be captured throughout the period of the study, by review of the oxygen requirements and ventilatory support required throughout the study (O2 requirement or PaO2:FiO2 (P:F ratio) sequentially)
2. 50% decrease in VWFAg/ADAMTS 13 activity ratio from baseline to end of PEX.
3. Prevent deterioration in myocardial function on ECHO/ cardiac parameters -monitoring of cardiac function through echocardiogram and/ or BNP and Troponin levels throughout studty period
4. Clinical thrombotic events documented by imaging either venous DVT/PE, or arterial thrombus (cardiac, neurological and peripheral vascular) throughout the study period
5. Incidence of acute kidney injury as defined by KDIGO criteria throughout study period
6. Mortality at 28 days

12.2 Sample size and recruitment

12.2.1 *Sample size calculation*

Mortality of patients on intensive care with COVID-19 has been reported to range from 48% of patients no longer on ITU (ICNARC report on COVID-19 in critical care, 27 Mar 2020) to 86% of patients who required invasive mechanical ventilation (Yang, Lancet Respiratory Medicine, Feb 2020).

We aim to recruit up to 40 patients in total (20 per arm). We will have 80% power to detect a statistically significant difference between the treatment groups at the 5% level assuming that PEX+SOC will reduce inflammation markers in 80% of patients compared to just 20% for SOC if we recruit 20 patients. The power is increased to 99% if 40 patients are recruited. Alternatively, if the effect is lower, e.g. PEX+SOC reduces markers in 65% of patients, then the power will be 85% based on 40 patients.

12.2.2 *Planned recruitment rate*

Subjects will be recruited throughout the COVID19 pandemic

12.3 Randomisation methods

Patients will be randomized to either PEX+SOC or SOC in a 1:1 ratio using block randomization with varying blocks sizes.

Randomisation will be carried out by the commercial company Sealed Envelope which provides online randomisation. This will be accessed by a designated member of staff who will communicate the treatment allocation to the clinical team.

12.4 Statistical analysis plan

12.4.1 *Summary of baseline data and flow of participants*

Patient characteristics will be summarised by trial arm and inspected for balance. Patient flow throughout the trial will be summarised using a CONSORT diagram. **(APPENDIX 4)**

12.4.2 *Primary outcome analysis*

The primary analysis will involve a comparison of the binary outcome '50% reduction in at least two inflammation markers' between the PEX+SOC and SOC trial arms using a chi-squared test. The risk difference (and ratio) will be estimated with a 95% confidence interval. All analyses will be performed on an intention to treat basis.

12.4.3 *Secondary outcome analysis*

Secondary outcomes will be summarised and compared using suitable statistical methods. For example, binary outcomes may be compared using chi-squared tests and numerical outcomes may be compared using t-tests. P-values from tests of secondary outcomes may be adjusted to account for multiple testing. Appropriate regression methods will be used to perform adjusted analyses or to account for repeated measures.

12.4.4 *Sensitivity and other planned analyses*

The level of missing data will be reported and sensitivity and/or adjusted analyses performed to account for missing data.

12.5 Interim analysis

No planned interim analysis

13 Record keeping and archiving

At the end of the trial, all essential documentation will be archived securely by the CI and trial sites for a minimum of 25 years from the declaration of end of trial.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of Good Clinical Practice and all applicable regulatory requirements.

The sponsor will notify sites when trial documentation can be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

14 Oversight Committees

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14.1 Trial Management Group (TMG)

The TMG will include the Chief Investigator and trial staff. The TMG will be responsible for overseeing the trial. The group will meet regularly monthly and will send updates to PIs.

The TMG will review recruitment figures, SAEs and substantial amendments to the protocol prior to submission to the REC and/or MHRA. All PIs will be kept informed of substantial amendments through their nominated responsible individuals.

15 Direct Access to Source Data/Documents

The investigator(s)/ institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

16 Ethics and regulatory requirements

The sponsor will ensure that the trial protocol, participant information sheet, consent form, submitted supporting documents have been approved by the appropriate regulatory body (MHRA in UK) and an appropriate research ethics committee, prior to any participant recruitment. The protocol, all other supporting documents including and agreed amendments, will be documented and submitted for ethical and regulatory approval as required. Amendments will not be implemented prior to receipt of the required approval(s).

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The chief investigator will prepare the APR.

Within 90 days after the end of the trial, the CI/Sponsor will ensure that the main REC and the MHRA are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply the Sponsor with a report of the clinical trial which complies with the format as defined by the EMA. This will then be uploaded to EudraCT for availability to the MHRA and a copy of the report will be submitted to the main REC, within 1 year after the end of the trial.

The study will be reviewed and authorised to proceed through urgent regulatory review by UCLH COVID19 Clinical trial group

17 Monitoring requirement for the trial

The sponsor will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

The degree of monitoring will be proportionate to the objective, purpose, phase, design, size, complexity, blinding, endpoints and risks associated with the trial.

18 Finance

No financial interests by CI, PIs or trial management members.

18.1 Insurance

University College London holds insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

Arrangements must be in place, with the manufacturer, to cover the malfunction and breakdown of the apheresis platform.

19 Publication policy

Access to the final trial dataset

- All individuals involved in the trial will have access to the full dataset

Dissemination policy

- the data arising from the trial will be available to all medical investigators
- that on completion of the trial, the data will be analysed and tabulated and a Final Trial Report prepared
- presentation of results at national/international meetings in the future and submission for peer reviewed publication

20 References

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395(10223):497-506.
2. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA.* 2020.
3. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med.* 2020.
4. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. *N Engl J Med.* 2020.
5. Arentz M, Yim E, Klaff L, et al. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. *JAMA.* 2020.
6. Grasselli G, Zangrillo A, Zanella A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA.* 2020.
7. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020;395(10229):1054-1062.
8. Bowles L, Platton S, Yartey N, et al. Lupus Anticoagulant and Abnormal Coagulation Tests in Patients with Covid-19. *N Engl J Med.* 2020.
9. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. Covid-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med.* 2020.
10. Wichmann D, Sperhake JP, Lutgehetmann M, et al. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. *Ann Intern Med.* 2020.
11. Menter T, Haslbauer JD, Nienhold R, et al. Post-mortem examination of COVID19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings of lungs and other organs suggesting vascular dysfunction. *Histopathology.* 2020.
12. Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res.* 2020;191:9-14.
13. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med.* 2020.
14. Klok FA, Kruip M, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res.* 2020.
15. Zhang C, Zhang Z, Mi J, et al. The cumulative venous thromboembolism incidence and risk factors in intensive care patients receiving the guideline-recommended thromboprophylaxis. *Medicine (Baltimore).* 2019;98(23):e15833.
16. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet.* 2020;395(10234):1417-1418.
17. McGill SN, Ahmed NA, Christou NV. Increased plasma von Willebrand factor in the systemic inflammatory response syndrome is derived from generalized endothelial cell activation. *Crit Care Med.* 1998;26(2):296-300.

Appendix 2: Pre study assessments

	Screening (Pre-treatment assessment)	**Treatment Phase**				
Day	Day – 2 to Day -1	Day 1	Day 7	Day 14	Day 21	Day 28
Window of flexibility for timing of visits:			e.g. +/- 2 days	e.g.+/- 2 days	E.g..+/- 3 days	e.g.+/- 3 days
Informed Consent	X					
Medical History	X					
Physical Examination						
Vital Signs	X	X	X	X	X	X
Eligibility confirmation	X	X				
Add ALL Protocol Assessments including bloods/urine, ECGs, scans, c as applicable both trial specific and routine (include separate row for each assessment)	X	X	X	X	X	X
Randomisation	X					
IMP administration		X	X	X	X	X
Adverse Events review	X	X	X	X	X	X
Concomitant Medication review	X	X	X	X	X	X

Appendix 3- Schedule of assessments

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 14	Day 21	Day 28
FBC	X	x	X	x	x	x	x	x	x	x
Biochemistry	x	x	X	x	x	x	x	x	x	x
Coagulation screen including fibrinogen	x		X		x		x	x	x	x
Inflammatory markers (D Dimer, ferritin, LDH, CRP)	x		X		x		x	x	x	x
Virology testing (Hepatitis A, B,C HIV)	x									
COVID19 Testing	x									

Pregnancy test: serum bHCG	x									
Autoimmune screen: ANA, ENA	x									
Cardiac testing: Troponin/BNP	x				x		x	x	x	x
Procoagulant samples: Pre and post PEX. Daily in non PEX group/following PEX. Including cytokine storm analysis	x	x	X	x	x	x	x	x	x	x
ECG/Echocardiagram	x						x			x
Concomitant mediations eg antibiotics, Noradrenaline	x	x	X	x	x	x	x	x	x	x

Change in respiratory support eg HD oxygen/CPAP/Intubation	x	x	X	x	x	x	x	x	x	x
haemofiltration	x	x	X	x	x	x	x	x	x	x