Undertaking by the Principle Investigator

Proposal for **"Efficacy of convalescent plasma therapy in patients with COVID-19: A randomized control trial"**

Name and code number of the project: **COPLA Trial-II/ILBS/2020 dated 24.05.2020**

1. Name, designation, and department of the Project Investigators:

Project Investigator I ILBS:
Dr. Meenu Bajpai, Add. Professor, Transfusion Medicine
Project Investigator II MAMC:
Dr. Suresh Kumar, Medical Director LNJP and HOD Medicine, MAMC
Project Investigator III RGSH:
Dr. Vikas Dogra, Asst. Prof. Pulmonology, RGSH, Delhi
Co-Project Investigators:

1. **Dr. Vandana Saluja, Associate Professor, Critical Care**
2. **Dr. Pratibha Kale, Associate Professor, Microbiology**
3. **Dr. Ashish Maheshwari, Asst. Professor, Transfusion Medicine**
4. **Dr. Amita Gupta, Blood Centre Officer, Transfusion Medicine**
5. **Dr. Ekta Gupta, Professor, Virology**
6. **Dr. Nirupama Trehanpati, Professor, Molecular and Cellular Medicine**
7. **Dr. Shiv Kumar Sarin, Professor, Hepatology**

2. Name and address of any other medical college, hospital, or Institution where parts of the study will be done: Delhi Govt. Hospitals which are designated COVID-19 treating Centres.
3. Number of ongoing project/clinical trials in which you are PI: **None**

a) I confirm that I will initiate the study after obtaining all regulatory clearance
b) I will not implement any deviation from the approved protocol without the prior consent of the sponsor and it will be intimated with the IEC at the earliest.
c) I confirm that the co-investigators and other members of the study team have been informed about their obligations and are qualified to meet them.
d) I will personally supervise the study and ensure that requirements of obtaining informed consent and other ethical requirements under ICMR and national regulatory guidelines are adhered to.
e) I will maintain accurate and complete records of all cases in accordance with GCP provisions and make them available for audit/inspection by IEC, regulatory authorities, sponsors, or their authorized representatives.
f) I confirm that all research/ study-related investigations/ procedures/ treatment/ any other activity will not be charged from the study participants it will be done at no additional charge to the study participant. Only the routine standard of care & treatment will be charged from the study subjects.
g) I will inform the IEC and the sponsors of any unexpected or serious adverse event at the earliest and definitely within seven days of its occurrence.
h) I will maintain the confidentiality of the identity of all participating subjects and assure the security and confidentiality of study data.
i) I and my colleagues will comply with statutory obligations, requirements, and guidelines applicable to such clinical studies.
j) I will inform IEC of the date of starting the study within 2 weeks of initiation of the trial and submit annual progress reports and final report to member secretary, IEC within 4 weeks of the due date.

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Submission of Project by the Project Investigator (PI) to Institute Ethics Committee (IEC)
Project Title: "Efficacy of convalescent plasma therapy in patients with COVID-19: A randomized control trial"

	Name, Designation & Qualifications	Address, Telephone, Fax and Email Id	Signature
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Section1: Project title

Section 2: Broad Subject
Transfusion Medicine and Pulmonary Medicine

Section 3: Duration
The estimated total duration of the project is 4months.

Section 4: Total Cost & FE Component: None

Section 5: Funding agency to which applying: None

Section 6: Project Category
Investigator-Initiated Randomized Controlled Trial

Section 7A: Collaborating Investigators/Institutions (Indian/International)
Institute of Liver and Biliary Sciences and
Lok Nayak Jai Prakash Hospital (LNJP)
Rajiv Gandhi Super-specialty Hospital (RGSH)

Section 8: Project summary

Currently, no effective treatments are available for the COVID-19. Scientists and Researchers are working on many aspects of treatment options for the development of vaccination and medication to combat this life-threatening problem. Convalescent plasma from recovered COVID-19 patients contains antibodies against COVID-19 which may be beneficial to severely sick COVID-19 patients. We have recently concluded a pilot phase II open-label RCT on the efficacy of convalescent plasma in severe COVID 19 patients in which we have seen encouraging results. We plan to further study the efficacy and safety of convalescent plasma in COVID-19 severely sick patients through an RCT. We will collect up to 500 ml Convalescent Plasma from the COVID-19 recovered persons after 14 days of clinical recovery with two consecutive SARS CoV-2 negative tests by PCR at least 24 hours apart. This plasma will be tested and frozen and stored. On requisition it will be thawed and sent to the treating center. Two doses of 250 ml convalescent plasma each will be transfused on two consecutive days to patients who fit the eligibility criteria (Severely sick COVID-19 patients) and are randomized to the convalescent plasma group along with the standard of care and the other group will receive standard of care alone. Data will be collected to study the benefits and adverse events related to convalescent plasma transfusion.

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Section 9: Subject Keywords
COVID-19, COVID-19 Convalescent Plasma, Donor Plasmapheresis, ARDS, Immunoglobulins, Antibodies

Section 10: State of knowledge

The outbreak of severe acute respiratory syndrome due to COVID-19 (due to SARS-CoV-2 virus), which had originated in Wuhan, China, has become a pandemic involving more than 5million people across the globe. Currently, no specific drug therapy has been found useful with some benefits reported for remidisvir.

The virus causing COVID-19, SARS-CoV-2 is isolatable using VeroE6, Huh7, or human airway epithelial cells. Serological assays are needed for evaluation of the results of vaccine trials and the development of therapeutic antibodies. Among the four coronavirus structural proteins, the spike (S) and the nucleocapsid (N) are the main immunogens. Apart from antiviral treatment, virus-specific neutralizing antibody, which could accelerate virus clearance and prevent entry into target cells, serves as the main mechanism for the restriction and clearance of the viruses by the host. The convalescent plasma of the patients with these neutralizing antibodies can be used to treat patients with COVID-19. To date, no specific treatment has been proven to be effective for SARS-CoV-2 infection. The current evidence-based strategy relies on providing supportive care in mild cases and the need for mechanical ventilation and extracorporeal membrane oxygenation in severe cases. For over a century convalescent plasma has been used as prophylaxis or treatment of infectious diseases with variable success in different parts of the world

The experience of using convalescent plasma or immunoglobulins has been derived by its utility in improving the survival rate of patients with SARS wherein the patients who had no response to intravenous corticosteroids showed improvement. Lower mortality and shorter hospital stay were recorded for these patients. A study on 1775 patients by Cheng et al, the 80 patients who received convalescent plasma had a lower rate of mortality as compared to the overall mortality. They reported encouraging outcomes of the patients with the use of convalescent plasma in the 2003 SARS-CoV pandemic. In this study, they further found that 33 patients who received convalescent plasma transfusion within the two weeks of symptom presentation showed better outcomes. It has also been proven from previous studies that convalescent plasma can limit viral replication. Providing passive antibody therapy by convalescent plasma in COVID-19 could be one of the approaches towards disease mitigation in the absence of definitive therapy. Recovered donor convalescent plasma products demonstrate donor-related variations in antibody titers and specificities against specific infections.

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Convalescent plasma from recovered patients has shown improved survival in a recent study by Shen et al. on 5 critically ill patients with COVID-19. Improvements in Sequential Organ Failure Assessment (SOFA) Scores, PaO_2 /FiO_2, Acute Respiratory Distress Syndrome (ARDS) were seen along with a decrease in viral loads and an increase in protective antibody tires, although this intervention was not performed as a randomized clinical trial.

Dose: In recent reviews of studies on convalescent plasma therapy, the dose of CP has ranged from 200 ml to 600 ml in single or divided doses. This depends on the logistics of collection (The amount allowed in one donation as per the country's regulations). There is presently no consensus on the dose.

Titer: Neutralizing titre is difficult to perform as it requires a live virus culture and a BSL 3 facility. IgG/IgM titers can be done on ELISA (Most studies doing this method). Few studies have shown that IgG titre closely follows the neutralizing titre. The minimum titers vary from study to study (see Table 1)

Minimum Titre Requirements for Convalescent Plasma (ref-22-25)

Author	Country	Neutralizing antibody titer
Duan et al	China	>1:640
FDA recommendations	USA	>1:160 (1:80 acceptable)
ISBT Working party recommendations for convalescent plasma for LIC and MIC	-	1:160 (1:80 acceptable)
Shen et al	China	>1:40
Zhang et al	China	Not determined before transfusion
Joyner et al	USA	Not mentioned

The International Society of Blood Transfusion (ISBT) as well as the US FDA recommends a minimum titer of 80 (> 160 is preferable).

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Risks

Recipient Safety (ref:21)

In a recent report from Mayo Clinic, USA on 5000 convalescent plasma transfusions (CPT) in COVID-19 patients, 36 Serious Adverse Events (SAEs) were reported(< 1% of all transfusions). Of the 15 deaths reported (0.3% of all transfusions) four were judged to be related (possible: 3, definitely: 1) CPT. There were 21 non-death SAEs (see Table 2)

Table 2: Serious Adverse Event (SAE) associated with convalescent plasma transfusion (n=5,000)

Four hour mortality reports	Reported(n=36)	Related(n-25)	Estimated(95% CI)
Mortality	15	4	0.08% (0.03%, 0.21%)
Transfusion associated circulatory overload(TACO)	7	7	0.14% (0.07%, 0.29%)
Transfusion related acute lung injury(TRALI)	11	11	0.22% (0.12%, 0.39%)
Severe allergic transfusion reaction	3	3	0.06% (0.02%, 0.18%)
Seven Day reports	**Reported**		**Estimated(95% CI)**
Mortality	602		14.9% (13.8%, 16.0%)

Donor Safety: The convalescent plasma donation by Plasmapheresis was found to be a safe procedure in the RCT done at ILBS-MAMC. No adverse events were noted during 16 procedures done under this trial. No other studies reported any SAEs during donor plasmapheresis

Section 11: Importance of the proposed project/ Justification for subject area:

COVID-19 is a major pandemic that has spread across all countries with a case-fatality rate varying from 1.2-10% or higher. Currently, there is no definitive therapy recommended for the management, and the results of convalescent plasma transfusion as a supportive therapy appear encouraging. The data from our pilot RCT is encouraging and therefore there is a need for a wider randomized controlled trial that could address the safety and efficacy of CP in the management of patients with severe COVID-19 using a larger sample size.

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If patients are counseled on recovery to donate convalescent plasma and this is frozen and sent to treatment centers, it may be used to transfuse severely sick patients and may improve outcomes.

Section 12: **Review of facilities and expertise** available in the institution

The study will be carried out jointly at ILBS which has a fully functional Transfusion Medicine Department and facilities for collection of convalescent plasma and Delhi Govt. hospitals which are designated as COVID-19 treatment centers and are equipped with modern facilities for patient care and have the infrastructure for carrying out this study.

Section 13: **Study Design**

Aim and Objectives

Primary Objective: To study the efficacy of convalescent plasma in severe COVID 19 patients in time to clinical improvement (Clinical improvement: Reduction of two points in ordinal scale or live discharge from the intensive care unit, whichever is earlier)

The six-point scale is as follows:

1. *death=6;*
2. *hospital admission for extracorporeal membrane oxygenation or mechanical ventilation=5;*
3. *hospital admission for non-invasive ventilation or high-flow oxygen therapy=4;*
4. *hospital admission for oxygen therapy (but not requiring high-flow or non-invasive ventilation)=3;*
5. *hospital admission but not requiring oxygen therapy=2;*
6. *discharged or having reached discharge criteria (defined as clinical recovery—ie, normalization of pyrexia, respiratory rate 94% on room air, and relief of cough, all maintained for at least 72 h)=1.*

Secondary Objectives:

1. The proportion of patients in each category according to the ordinal scale at 48 hours and day 7, 14, and 28 after randomization
2. Duration of oxygen therapy
3. Duration of hospital stay
4. The proportion of patients on mechanical ventilation at day 7.(after randomization)

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5. Mortality at day 7 and day 28 (after randomization)

6. Duration of Intensive Care Unit stay

7. Incidence of adverse effects in both groups

8. Presence of antibodies against SARS-CoV-2 in serum on days 0, 3, 7, 14, 21 & 28 after plasma administration, as long as the patient remains in the hospital.

9. Cytokines and acute phase reactants

10. To study the titers in COVID-19 convalescent plasma donors and correlate with duration of illness, the severity of symptoms, duration of hospital stay, drugs used in therapy, duration between recovery, and donation.

Study Centres:

Institute of Liver and Biliary Sciences
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– Collection and testing of Convalescent Plasma

Treatment Centres

Lok Nayak Jai Prakash Hospital (LNJP)

Rajiv Gandhi Super-speciality Hospital

B) Methodology

Donor Plasmapheresis

COVID-19 recovered patients will be counseled and informed regarding convalescent plasma donation. The contact information of those who agree will be sent to the coordinator at ILBS Blood Centre.

- The prospective donor will be contacted and if willing to come for donation, the donor will be provided conveyance if required, to come to ILBS Blood centre for Plasma Donation
- At ILBS the donor will be counseled and the doctor in-charge will explain the procedure to the Donor.
- The donor will be given a Donor Information Sheet and Informed consent will be taken on the document
- The eligibility for plasma donation will be ascertained through Medical History, Physical Examination, and laboratory tests.

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Donor Eligibility for Plasmapheresis

- Virologically documented (PCR positive by nasopharyngeal swab) who is recovered and free of symptoms for 14 days.
- Has tested negative for SARS CoV 2 on two consecutive tests 24 hrs apart.
- Fulfill all criteria of donor eligibility for donor Plasmapheresis under the Drugs & Cosmetics Act 1940 and Rules 1945, amended 11.03.2020
- Females who have been pregnant may be tested for anti-HLA antibodies and eligible if negative for the same.

The following Donors will be excluded

- Do not fulfill all criteria of donor eligibility for donor Plasmapheresis under
- the Drugs & Cosmetics Act 1940 and Rules 1945, amended 11.03.2020
- Females who have been pregnant and have not been tested for HLA antibodies or are HLA antibody positive if tested and previously transfused donors (to prevent TRALI)
- Donors who have taken steroids during treatment for COVID-19

Donor Selection Process

- A detailed medical history of the donor will be taken and documented
- Physical examination (Height, Weight, Blood Pressure, Temperature, adequate veins for phlebotomy)
- Laboratory Testing: complete Blood count, Testing for hepatitis B virus, hepatitis C virus, HIV, malaria, and syphilis) by serology, blood grouping, and antibody screening. Serum protein will be done in repeat donors (Ref: D&C Act and Rules)
- Serum COVID-19 specific IgG antibody positive (with an IgG titre higher than 80).
- All Results Evaluated & Clinically Correlated

The donor is deemed eligible/non-eligible

Plasmapheresis Procedure

- Determine Volume to be collect-approx. 500 ml
- As per the Drugs & Cosmetics Act 1940 and Rules 1945, amended 11.03.2020
- Start Donor Plasmapheresis Procedure(As per SOP)
- Collect Convalescent Plasma

The convalescent plasma will be properly labeled and frozen at -80^{o} C in a separate Deep Freezer. It will not be issued to other patients who are with non-COVID.

- **Label Detail**s: As per the Drugs & Cosmetics Act 1940 and Rules 1945, amended 11.03.2020.
- **Storage condition-** Below -30^{o}C
- **Shelf life: -** 1 Year

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Other Sources of Convalescent Plasma:

Convalescent Plasma collected during a CP donation drive by Delhi Govt. following all rules and regulations of the Drugs& Cosmetics Act 1940 and Rules 1945, amended 11.03.2020 is stored at ILBS and will be used in this trial.

The tests for Donors:

1. **Real-time PCR for** SARS-CoV-2:
   Nasal swab samples will be taken prior to donation and tested for SARS-CoV-2 by real-time PCR method it the donor does not have two negative reports 24 hrs apart.

Antibody Titers of Convalescent Plasma and Patients Plasma by ELISA

For Donors:

The titre of serum neutralizing antibody which is the spike protein antibody, directed against the SARS-CoV-2 RBD (receptor binding domain) proteins. The titre will be done by IgG ELISA or by Rapid IgG antibody titre. The minimum titre of 80 is needed for the use of convalescent in patients.

For recipients:

1. **Real-time PCR for** SARS-CoV-2:
   Nasal swab samples will be taken prior to transfusion and tested for SARS-CoV-2 by real-time PCR method. The test should be positive for eligibility of the recipient along with clinical criteria for COVID-19.

2. Antibody titre: The serum of each recipient will be obtained and IgG antibody titre by enzyme-linked immune-sorbent assay (ELISA) or Rapid IgG antibody method will be tested one day prior to the convalescent plasma transfusion. Changes of IgG antibody titre before and after convalescent plasma transfusion in patients will be studied. The serum will be stored for neutralizing antibody titers by plaque reduction will be done subject to availability.

Study Population:

Adult patients with severe COVID -19 infections defined as WHO Interim Guidance and the Guideline of Diagnosis and Treatment of COVID-19 of National Health Commission of China (version 5.0) with confirmation by real-time RT-PCR assay with severe disease i.e. meeting any 2 of the following criteria

1. Patients on ventilator (in last 24 hours)
2. Respiratory distress, RR ≥30 beats/min
3. Oxygen saturation level less than 93% in resting state
4. Partial pressure of oxygen (PaO_2)/oxygen concentration (FiO_2) ≤ 300 mmHg
5. Lung infiltrates > 50% within 24 to 48 hours

Study Design:

An open label randomized controlled trial.

The study group will comprise of adult patients with severe COVID -19 as detailed above. Randomization will be done in the ratio of 3:1 in with 150 patients in the treatment arm and 50 patients in the control arm. Allocation concealment will be done by Sequentially Numbered Opaque Sealed Envelopes (SNOSE) method.

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Justification for Unequal Allocation

We want to collect the additional safety profile associated with convalescent plasma group hence enrolling more number of cases in this group.

Sample Size calculation:

The study will be designed as an open label RCT with an aim to enrol 150 patients in the treatment arm and 50 patients in the control arm.

Intervention:

Intervention Arm: Two doses of 250 ml Convalescent plasma from recovered COVID-19 patients + Standard of Care will be given to severely sick COVID-19 patients in the treatment arm

Control Arm: Standard of Care will be given to severely sick COVID-19 patients in the control arm

Details of Standard of Care

The Ministry of Health and Family Welfare has issued detailed guidelines for the management of sCOVID-19 based on varying grades of severity which may be periodically updated. For the management of ARDS or sepsis the respective guidelines issued by ARDSNet and Surviving Sepsis campaign will be followed. Other institutional protocols for supportive management will be implemented. (ref: Guidelines on Clinical Management of COVID-19. MoHFW, GoI.2020.)

Monitoring and Assessment: Daily until clinical improvement

Adverse Effects: Will be documented

Stopping rule: None

(C) The expected outcome of the project: We expect convalescent plasma therapy to be a safe and efficacious therapy based on our pilot RCT. This study will determine if there is clinical improvement /mortality benefits and further elaborate on its safety in patients with severe COVID-19

Section 14: Inclusion and exclusion criteria for the admission of patients in the study

Inclusion criteria

Patients with severe COVID-19 (as described above) will be considered for randomization and will be transfused Convalescent Plasma within 3 days of symptom onset (Severe COVID-19)

Severe COVID -19 defined by WHO Interim Guidance and the Guideline of Diagnosis and Treatment of COVID-19 of National Health Commission of China (version 5.0) along with confirmation by real-time RT-PCR assay with severe disease i.e. meeting any 2 of the following criteria-

- Patients on ventilator (in last 24 hours)
- Respiratory distress, RR ≥30 beats/min
- Oxygen saturation level less than 93% in resting state

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- Partial pressure of oxygen (PaO_2)/oxygen concentration (FiO_2) ≤ 300 mmHg
- Lung infiltrates > 50% within 24 to 48 hours

Exclusion criteria

- Patient/ family members who do not give consent to participate in the study.
- Patients with age less than 18 years
- Patients presenting with multi-organ failure
- Pregnancy
- Individuals with HIV and Viral Hepatitis and Cancer
- Extremely moribund patients with an expected life expectancy of less than 24 hours
- Hemodynamic instability requiring vasopressors
- Previous history of allergy to plasma
- Cirrhosis
- Severe renal impairment with GFR< 30ml/min or recipients of RRT, peritoneal dialysis
- Patients with uncontrolled diabetes mellitus, hypertension, arrhythmias and unstable Angina

Transfusion of COVID-19 Convalescent Plasma

Dose-250 ml
Frequency – 2 doses on consecutive days
Duration –Start by day 3 of symptom onset in eligible patients

Blood Group Compatibility

ABO identical plasma will be the first choice followed by ABO compatible plasma.

In case compatible plasma is not available reduction of titers will be done using an ABO antibody immune-adsorption column.

Patient Monitoring

All included patients will be randomized to receive either 500 ml of convalescent plasma in two doses of 250 ml on two consecutive days along with the standard of care or standard of care alone

Clinical information of all enrolled patients including symptoms at presentation, time to presentation to the hospital, and development of pulmonary symptoms will be recorded. The details of comorbid diseases as measured by the Charlson index of co-morbidity and Acute Physiology and Chronic Health Evaluation II (APACHE II). Details of cross-sectional imaging, chest-x-ray, bacterial or fungal co-infections, and details of antibiotic treatment will be recorded. Development of complications including shock, acute kidney injury, acute coronary syndrome, myocarditis, acute respiratory distress syndrome, need for mechanical ventilation and nosocomial infection will be recorded. The use of high-flow oxygen, non-invasive, and invasive ventilation will follow standard guidelines and will be recorded. The details of antiviral treatment will be recorded for all enrolled patients.

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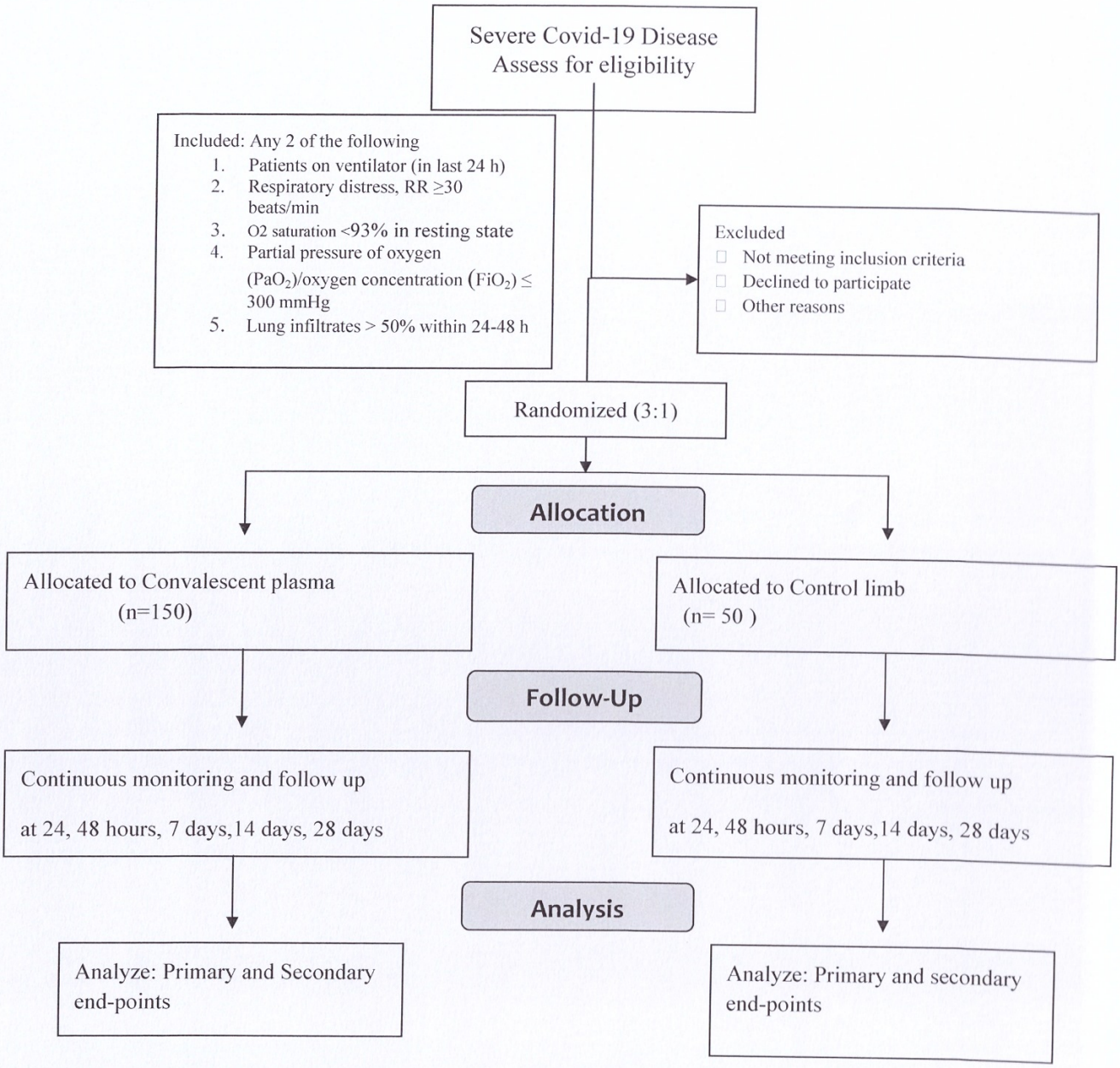
Flow Chart



- All variables shall be expressed in mean (SD) or median (range)
- Variables will be compared by Mann- Whitney U test
- For Categorical variables, we will use Chi-Square or Fisher's test
- Survival analysis will be done using Cox-proportional regression analysis

The actuarial probability of survival shall be calculated by Kaplan- Meier graph and compared by the log-rank test.

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Section 15: Work Plan with the schedule of activities giving milestones

An RCT which will be completed within 4 months

Section 16: Permission from Drug Controller of India for use of drug/vaccine/device in the study, wherever applicable-

ILBS Blood Centre has a license for Plasmapheresis and approval of DCGI

Section 17: Safety of the proposed interventions, drugs, or vaccine to be tested including results of relevant laboratory and animal toxicity and safety trials, and results of studies carried out in humans

Human studies have been done and reported rare SAEs*, it has been approved by CDC under emergency Investigational New Drug Applications (eINDs)

*(Joyner MJ, Wright RS, Fairweather DL, senefeld JW, Bruno KA, klassen SA et al. Early Safety Indicators of COVID-19 Convalescent Plasma in 5,000 Patients. MedRziv. doi.org/10.1101/2020.05.12.20099879)-See review of literature

Section 18: Description of plans to withdraw or withhold standard therapy in the course of research-No

Section 19: For research carrying more than minimal risk, an account of plans to provide medical therapy for such risk or injury –Insurance cover for patients

The donor may have any of the adverse events related to Plasmapheresis donation (similar to healthy apheresis donors) – Detailed in Donor Information Sheet

Patients may have any of the adverse events related to plasma transfusion- Patient Information Sheet

Section 20: Budget Estimates – None

Section 21: Other research projects with investigators -None

Place: New Delhi

Signature & Designation of PI/Co-PI/Collaborator

Date: 24/05/2020.

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References in support of the proposed study:

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Annexures

1. Donor Information and Consent Form
2. Patient Information and Consent Form
3. Plasmapheresis License
4. Plasmapheresis- Donor Selection and Procedure
5. Apheresis Registration Form
6. Additional Donor Information
7. Transfusion Monitoring of Convalescent Plasma
8. Case Report Form
9. IEC approval ILBS
10. Bio-data of Investigators
11. Executive Summary
12. Form CT04
13. PI Undertaking Meenu
14. Reference paper 1
15. Reference paper 2
16. Reference paper 3
17. Standard of Care

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