Ethics Protocol for Health Research Involving Human Subjects

Please fill the form below with brief summary and give check mark (X/V) inside the box or circle one answer choice which describe the research

P: Protocol sequence number of CIOMS 2016 Protocol – Appendix 1
S: Ethics Eligibility Standard (WHO-2011 and Ethic Research Committee & National Health Development Guideline 2017
C: Checklist
G: CIOMS 2016 Guideline
IC: CIOMS 2016 – Appendix 2

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A. Research Title (p-protokol no 1)*

Treatment towards COVID-19 Patients using Convalescent Plasma Therapy

1. Research Locations :

Gatot Soebroto Indonesia Army Central Hospital, Sulianti Saroso Infectious Disease Hospital, Persahabatan Hospital, Bio Farma, Eijkman Institute

Plan of Research Time (Start – Finish) : April 2020 – April 2021

	Yes	No
2. Is this research multi-centre ?		V
3. If multi-centre, does the research already have ethical approval from other centre / institution ?		V

Identification (p10)

1. Researcher

(Please attach curriculum vitae of main researcher)

Main researcher : Marliana Sri Rejeki, Clinical Pharmacologist, MD
Institution : Gatot Soebroto Indonesia Army Central Hospital

3. Research Member : (attached)
Institution : Gatot Soebroto Indonesia Army Central Hospital

Sponsors (p9)
Name :
Address :

B. Summary of Research Proposal

1. Summary in 200 – 400 words (written in language which can easily understood by common people, not physician / health worker)

This virus began to be detected at the beginning of March 2020 and has already infected 1.677 persons. By April 2020, 103 persons have already recovered meanwhile 157 persons died due to this virus. Globally, neither effective vaccine nor antiviral therapy has been approved as standard treatment for COVID-19 pandemic. Because of this situation, number of cases and deaths increase daily in Indonesia so development of therapy urgently needed to help faster recovery of COVID-19 patients. Convalescent plasma therapy from COVID-19 survivors is a promising strategy for COVID-19 patients' recovery which hospitalized.[1]

Interventional research was done with objectives as producing a good quality convalescent plasma from COVID-19 survivors, and to assess the safety of serial plasma transfusion to severe stage COVID-19 patients and its effect to clinical outcomes. The research questions which submitted are Does plasma from COVID-19 survivors can neutralize virus at in-vitro experiment and produce good quality convalescent plasma ? and Whether convalescent plasma administration from COVID-19 survivors is safe to severe stage COVID-19? Could it produce better recovery, better prognosis and possibly heal COVID-19 ? Hypothesis (answer for research questions) is convalescent plasma therapy is safe and may improve clinical outcome in severe stage COVID-19 patients.

Research and convalescent plasma therapy development divide into 2 activites which are in-vivo experiment (intervention to observe safety of plasma transfusion in COVID-19 patients) then in parallel, in-vitro experiment (convalescent plasma effect on neutralizing virus). Safety of convalescent plasma will be observed in severe stage COVID-19 patients which hospitalized.

Refinement process during in-vitro experiment involve Blood Transfusion Unit at Gatot Soebroto Indonesia Army Central Hospital; testing towards SARS-CoV-2 culture will be held at Eijkman Institute, meanwhile testing for level of convalescent plasma will be done by Bio Farma. Authorization for Blood Transfusion Unit of Gatot Soebroto Indonesia Army Central Hospital are extracting, testing, processing, storing and distributing convalescent plasma.

Development of patients' clinical condition before and after convalescent plasma therapy will be collected from automatic hospital medical record system. Hence, enhancement / alteration of clinical condition as outcomes are patients' clinical condition, improvement of lung lesion from lung imaging, improvement of routine laboratorium parameter and lung function as recovery parameter of COVID-19 patients.[2]

2. Research justification (p3). Please write down why this research need to be done, its benefit for population where this research will be located (Country, Region, Local) – 2/A Standard (Justice)

Results from this research are helping provision of anti-COVID-19 convalescent plasma products in Indonesia by finding right methods to process convalescent plasma from COVID-19 survivors and providing convalescent plasma material for further experiment which is efficacy testing

towards severe stage COVID-19 patients. Another benefit is providing knowledge for science to develop COVID-19 convalescent plasma in Indonesia.

A. Ethical issues might be faced

1. Researchers opinion regarding ethical issues that might be faced in this research and how to handle it (p4) – please adjust it with 7 standard value of ethical eligibility (S)

Social values of this research are providing alternatives to handle urgent matters, giving contribution towards invention of treatment towards severe stage COVID-19 patients, and disseminating its result so that emergency counter measure of COVID-19 can be helped in various areas of Indonesia.

Beside that, in this research, awareness of COVID-19 survivors are needed to give approval after explanation. Donors are not obligated to donate their blood. Donos independently decide whether they agree or disagree to donate their blood which will be converted to plasma. Likewise, hospitalized COVID-19 patients are obligated to give voluntarily approval after explanation. If patients' condition do not enable to give consent, family or legal guardians are asked to give consent. So that, no coercion, no improper persuasion even no exploitation towards donors participation.

Another important ethical issue is related to the less risks and greater benefits for COVID-19 patients. Risks that related to passive convalescent plasma therapy both known risk and theoretical risk.

First, known risk is risk related to blood plasma transfusion, including accidental infection by presence of other infectious disease agents and reaction towards serum such as rare immunologic reaction. However, with advancement technology on blood processing at blood transfusion unit, blood-transmission pathogens can be screened, blood type between donors & recipients can be matched, transfusion reaction can be supressed and also low risk of accidental other known infectious agents transmission. The only risk that reported was 1 COVID-19 patient suffered rash – local red spots and it disappeared in few days after plasma administration. Neither adverse events nor serious adverse events has been reported.

Second, theoretical risk that involving infection escalation phenomenon, which depends on antibody (ADE – Antibody Dependent Enhancement). ADE might happens on several viral diseases and involve disease progression with certain antibodies. For Corona virus, several ADE mechanisms have been described and there is theoretical concern that antibordy towards 1 type of corona virus can escalate other viral infections. Because of convalescent plasma therapy proposal in COVID-19 pandemic will depend on level of good quality neutralizing antibody towards the same virus, COVID – 19, possibility of ADE will be small, or even not at all.

Available evidences for usage of convalescent plasma on patients with SARS1 and MERS showed that plasma transfusion was safe and following infection screening according to blood bank standard.

Other theoretical risk is antibody administration towards COVID-19 patients assumed can prevent disease by weakening immune system which makes the recipients more vulnerable to re-infection. In this matter, passive antibody administration before vaccination with Respiratory Syncytial virus was reported to lower humoral responses, but not cellular immunity. This matter can be investigated as part of clinical trial by measuring immune responses on they who exposed and treated with convalescent plasma to prevent disease. If the risk was proven to be real, these people can be vaccinated with COVID-19 when vaccine available.

Recipients' risk relate with blood plasma transfusion include immunologic / allergic reaction towards blood plasma. The most severe risk that might happen to recipients is TRALI (transfusion-related acute lung injury). Risk of TRALI can be decreased by better plasma processing with extracting donors' plasma using plasmapheresis process. Meanwhile, anaphylactic shock still can happen even though very rare.

Managements for decreasing risks starting from donor election, donor's blood extraction, plasma processing which also decrease the risk of blood-transmission infectious disease, storing process, and administration process of convalescent plasma which follows valid standard regarding blood plasma transfusion.

Several available historical data up to this moment regarding convalescent plasma shows that this therapy is safe for COVID-19 patients. Thus, with high number of deaths caused by COVID-19 especially on elder patients and vulnerable one, the benefit of this therapy is greater than the risk for vulnerable patients or patients with progressing early stage. However, for every cases which convalescent plasma therapy is considered, assesment of rish and benefit will be done to evaluate individual variables. This consideration has been submitted recently with decision to use mAb in Ebola virus treatment.

Direct benefit that can be felt by patients is improvement of health status which from severe stage at the beginning convert to well condition and shorten hospitalization period.

B. Summary of References :

1. Summary of previous studies according to research topic, including unpublished one which acknowledged by researchers & sponsors; and published research informations, including if animal studies available. One page maximum (p5) – G4.

   Evidences showed that convalescent plasma from COVID-19 survivors can be used for treatment without severe adverse effects. Thus, it might be useful to examine its safety and efficacy of convalescent plasma transfusion on SARS-CoV-2 patients. Challenges in convalescent plasma therapy are availability of enough donor, clinical condition, virus kinetic, and interaction of host and SARS-CoV-2 which has to be explained before considering convalescent plasma as choice of therapy.

   There is an urgent need to decide new therapy for treating severe clinical condition. Hopefully it may lessen deaths, reduce virus spreading and decrease potential of pandemic in the future. Even though currently researchers are developing prevention and specific therapy in vaccinology, monoclonal antibody, peptides, interferon and small molecule medicines to fight SARS-CoV-2; development process still takes few more months to test in-vitro / in-vivo efficacy and also depends on result of its clinical trial.

Open-label randomized clinical trial from antiviral therapy was reported recently. In this research, 199 patients was allocated randomly using antiviral agent lopinavir – ritonavir or treatment standard; this regimen was tested not effective. One of the reasons might be because of registered patients already on IIb stadium (hypoxia stage). Virus pathogenicity may just 1 dominant aspect from overall pathophysiology and patient's inflammatory responses as the main pathophysiology.[3–5]

Symptomatic COVID-19 patients varied from mild until critical; most infection is not severe. Confirmed infected patient has 3 phases of disease severity:[7]

1. Mild (No pneumonia or mild one) was reported in 81% cases
2. Severe (example, with dyspnea, hypoxia, or >50% lung involvement on lung imaging in 24 – 48 hours) was reported in 14% cases.
3. Critical (example, respiratory failure, shock of multi-organ dysfunction) was reported in 5% cases.

Experience from previous pandemics like SARS-CoV-1 showed that convalescent plasma contain antibody that might have neutralizing effect towards relevant virus. On SARS-CoV-2 case, possible mechanism if this therapy was applied is protection arise from neutralized virus by antibody that contained in transfused plasma. However, there might be another possible mechanism such as ADCC (antibody-dependent cellular cytotoxicity) response and/or phagocytosis.[8]

A protocol for convalescent plasma usage in Corona virus Middle East syndrome was made in 2012. One possible explanation for efficacy of convalescent plasma therapy is antibody from convalescent plasma can suppress viremia. Schoofs et.al reported that immunotherapy which mediated by 3BNC117 (broad neutralizing antibody towards HIV-1) increase humoral immunity towards HIV-1.

In-vivo experiments also showed that this antibody effect not only limited in virus clearance and blockage new infection, but also increase clearance of infected cells. Peak of viremia happens on first week of infection in most virus disease. Patients usually develop primary immune response on day 10^{th} – 14^{th}, which followed by virus clearance. Thus, theoretically, convalescent plasma therapy is more effective to be given in early stage of disease. But, other treatment may give effect on relationship between convalescent plasma and level of antibody, including antiviral, steroid, & intravenous immunoglobulin.

Spectrum of symptomatic infection varied from mild until critical; most cases is not severe.

Stadium I (Mild) – Early Infection :[3–5]

Early stage happens when virus inoculate to human body and beginning of disease process. Generally, this stage involve incubation period which related with mild and unspecific symptoms like malaise, fever and dry cough. During this period, SARS-CoV-2 replicate, like building place to live inside the host especially focusing in respiratory system.

Like their older relatives, SARS-COV (which responsible for SARDS pandemic 2002-2003) bind its target using ACE-2 (Angiotensin Converting Enzyme) receptors on human cells. A lot of ACE-2 receptors located on human lung, intestine epithelial, and vessels endothelial. As result of transmission process through air and affinity towards lung ACE-2 receptors, infection usually appears with mild respiratory and systemic symptoms.

Diagnosing Stadium I (Parameter):

- Positive PCR result from respiratory sample
- IgG and IgM SARS-CoV-2 serum testing, with
- Lung CT Scan ,
- Complete blood count (CBC) and liver function test. CBC only reveal lymphopenia and neutrophilia without other significant abnormalities.

Treatment of Stadium I:

- Main objective : eliminate symptoms
- If proper antiviral (like Remdesivir) was proven to be effective, patients' treatment targets are decreasing symptoms duration, minimizing transmission and preventing disease progression.
- If patient can limit the disease severity only up to stadium I, the prognosis and recovery will be very good.

Stadium II (Moderate) – Lung Involvement (Phase IIa – without hypoxia & Phase IIb – with hypoxia):[3–5]

Diagnosing Stadium II :

- CT imaging showed diffuse lung involvement; the principle are virus multiplication and lung local inflammation.
- Patient develops viral pneumonia; with cough, fever, and possibility of hypoxia (defined as PaO2/FiO2 <300 mmHg)
- Imaging with CT-Scan and thorax x-ray reveal bilateral infiltrates or ground-glass opacity.
- Blood test showed severe lymphopenia, along with elevation liver function test.
- Systemic inflammation marker may elevate but not significantly.
- Most patients with COVID-19 Stadium II need to be hospitalized for observation and accurate management.

Treatment of Stadium II:

- Main treatment includes supportive cares and available antiviral therapy like Remdesivir
- In most Pneumonia COVID-19 cases, procalcitonin serum level ranged from low until normal.
- On early stadium II (without significant hypoxia), avoid corticosteroid usage.
- In situation when hypoxia occur, there is possibility that mechanical ventilation will be needed.
- Anti-inflammation therapy usage like corticosteroid might be helpful and can be used wisely.
- Thus, Stadium II need to be divided with IIa phase (without hypoxia) and IIb phase (with hypoxia)

Stadium II (Critical) – Systemic Hyperinflammation [3–5]:

Small percentage of COVID-19 patients will progress to Stadium III (critical):

- Manifested as non-lung systemic hyper-inflammation syndrome.
- Systemic inflammation markers increase apparently
- T-helper, T-cell suppressor and T-cell regulator decrease.
- Cytokines and inflammation biomarkers such as IL-2, IL-6, IL-7, granulocyte colony-stimulating factor, macrophage inflammation protein 1-α, tumor necrosis factor- α, C-reactive protein, ferritin and D –dimer increase significantly on more severe patient.
- Troponin and NT-pro BNP (N-terminal pro-brain natriuretic peptide) might be increase.
- HLH (haemophagocytic lymphohistiocytosis)-like form might happens.
- Vasoplegic shock, respiratory failure and even cardiopulmonary collapse can be seen in this stadium.
- Systemic organs involvement, even myocarditis will manifest during this stadium.

Treatment of Stadium III:

- Depending on immunomodulatory agent usage to decrease systemic inflammation before producing multi-organ dysfunction.
- Corticosteroid can be given along with cytokines inhibitor like Tocilizumab (IL-inhibitor) or Anakinra (IL-1 receptors antagonist)
- Intravenous immunoglobulin (IVIG) plays a role in modulating immune system which under hyper-inflammation condition.
- Overall, prognosis and recovery of critical stadium very poor and therapy would possibly improve the outcome

Open-label randomized controlled trial from antiviral therapy just reported recently. In this trial, 100 patients was allocated randomly to antiviral agent lopinavir-ritonavir or treatment standard; this regimen was found not effective.

One of the reasons might be because of registered patients already on IIb stadium (hypoxia stage). Virus pathogenicity may just 1 dominant aspect from overall pathophysiology and patient's inflammatory responses as the main pathophysiology

C. Field Conditions

1. Brief description regarding research location (please look P-2)

   a) Donor recruitment from COVID-19 survivors. Blood Transfusion Unit of Gatot Soebroto Indonesia Army Central Hospital isolates blood plasma from donor then examines the plasma for blood type & pathogens contained.
   b) Examining convalescent plasma for antibody neutralizing act by in-vitro towards SARS-CoV-2 culture (Done at Eijkman Institute)
   c) Testing level of antibody in convalescent plasma (Done at Bio Farma – Government Corporate)

Information regarding availability of eligible facility for save and precise research:
Bio Farma has production facilities which certified with Good Manufacturing Practice.

Demographic / Epidemiologic Information which relevant with research location:
Plasma extraction will be done in Jakarta at Gatot Soebroto Indonesia Army Central Hospital. Meanwhile, plasma development process to be end product will be done at Bio Farma in Bandung.

D. Research Design

1. Research objectives, hypothesis, research questions, assumption and research variables (P-1; S-1,2)

Research objectives:

1) Producing a good quality convalescent plasma from COVID-19 survivors, and
2) Assess the safety of serial convalescent plasma transfusion in severe stage COVID-19

Proposed hypothesis is convalescent plasma administration is safe and possibly improve clinical outcome of severe stage COVID-19 patients.

Proposed research questions

1) Does plasma from COVID-19 survivors can neutralize virus during in-vitro examination and produce good quality convalescent plasma?
2) Does convalescent plasma from COVID-19 survivors safe and could possibly produce better recovery, better prognosis and heal COVID-19?

Research variables:

1) Progression / improvement of clinical symptoms : fever, cough, breathing difficulty, chest pain, sore throat, nausea, vomit, diarrhea, anosmia, erythema, conjunctivitis, ILI (influenza-like illness).
2) Progression/Improvement of lung lesion from lung imaging.
3) Progression/Improvement of routine laboratory test criteria: CRP, procalcitonin, Complete blood count, leukocyte count, leukocyte differential count, SGOT, SGPT, blood gas analysis, ureum, creatinine, e-GFR, blood glucose.

2. Detail description of Research Design

This research is an interventional experimental study by evaluating prospectively before and after convalescent plasma administration on COVID-19 patients. There are 2 groups (phase) consist of donor and recipient group.

Donor group consists of mild COVID-19 survivors. Donor eligibility criteria : 1) Positive history of COVID-19 which already declared healthy, 2) 14-28 days after recovery or 14 days after repeated negative nasopharyngeal swab, 3) Negative PCR result, 4) Male / female donor which free from HIV, Hepatitis B & Hepatitis C, 5) Signing informed consent form for COVID-19 Survivors Plasma Donor

Recipient group consists of severe COVID-19 patients which still hospitalized.

Donor is COVID-19 survivors with inclusion criteria as follows:
1. Age: ≥ 18 until ≤ 60 years old
2. Complete resolution of symptoms for minimum 14 days before plasma donation or 14 days after repeated negative nasopharyngeal swab.
3. Donor has been declared negative from twice nasopharyngeal swab.
4. Positive history of hospitalization with mild symptom of COVID-19 or independent self-isolation with mild symptoms COVID-19 and already confirmed with RT-PCR (Real Time-Polymerase Chain Reaction)
5. Female donor candidate not is not pregnant (negative result of serum pregnancy test). HLA examination was done if pregnancy history was positive previously. Female with negative pregnancy history more prioritized.
6. Approving NAT (Neutralizing Antibody Titers) examination. If NAT examination can be done before transfusion, optimal titer which greater than 1:80 is more preferred.

Blood Transfusion Unit will classify donor candidates who fulfill criteria as follows:
1. Blood type (ABO) and Rhesus (RhD) identification.
2. Blood screening towards HIV, HBV, HCV, syphilis and other infections which considered necessary using immunoassay method and / NAT if possible.
3. Hemoglobin level examination
4. If possible, titration of total COVID-19 antibody and COVID-19 neutralizing antibody might help donor qualification, especially if donor willing to donate their plasma continuously.
5. Erythrocyte antibody screening examination, if possible.

Recruited recipients are they who fulfill inclusion and exclusion criteria as follows: [3,4, 8,9, 17,23]

Recipient inclusion criteria:
1. Age : ≥ 18 until ≤ 60 years old
2. Confirmed case with RT-PCR from nasopharyngeal swab.
3. Classified as severe COVID-19
   - Severe COVID-19 fulfill at least one condition below:
     - Breathing difficulty or severe pneumonia treated supportively with quick progressivity and high viral load
     - Respiratory rate >30 times/minute
     - Blood oxygen saturation <93% or with PaO2/FiO2 <300 (PaO2 measured in mmHg and FiO2 measured as inspired oxygen fraction)
     - Arterial PF ratio < 300 and/or lung infiltrate >50% in 24-48 hours.
     - Not yet or already supported with mechanical ventilation
4. Hospitalized severe stage COVID-19 patients with comorbidities will be given immediately.

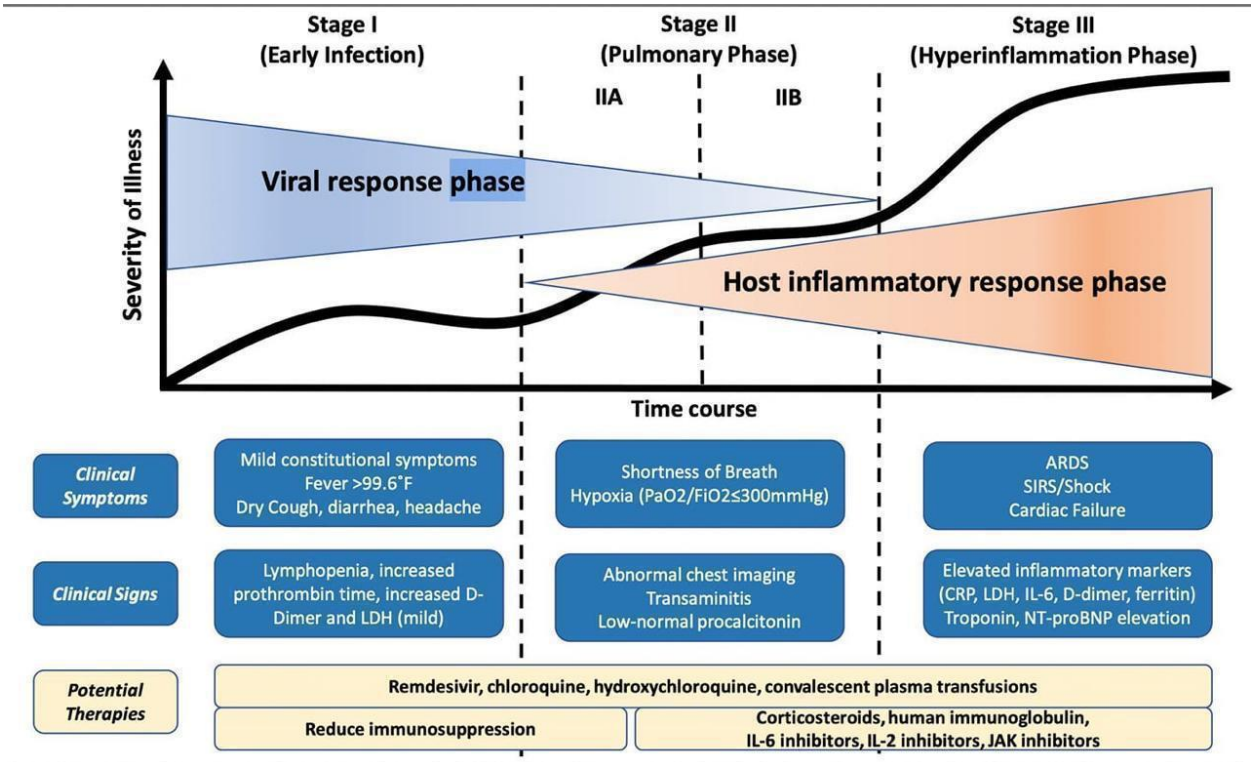
Recipient exclusion criteria:
1. Pregnant patient
2. Having contraindication towards transfusion or any history of cross reaction previously towards blood product transfusion.

Donor's convalescent plasma is extracted from subjects who fulfil inclusion criteria.Ten ml serology sample is extracted for Blood Transfusion Unit of Gatot Soebroto Indonesia Army Central Hospital. Another 200 ml plasma is extracted using apheresis method which will be divided into 2 bags @100 ml then it will be tested for blood type & pathogen. Antibody titer examination was

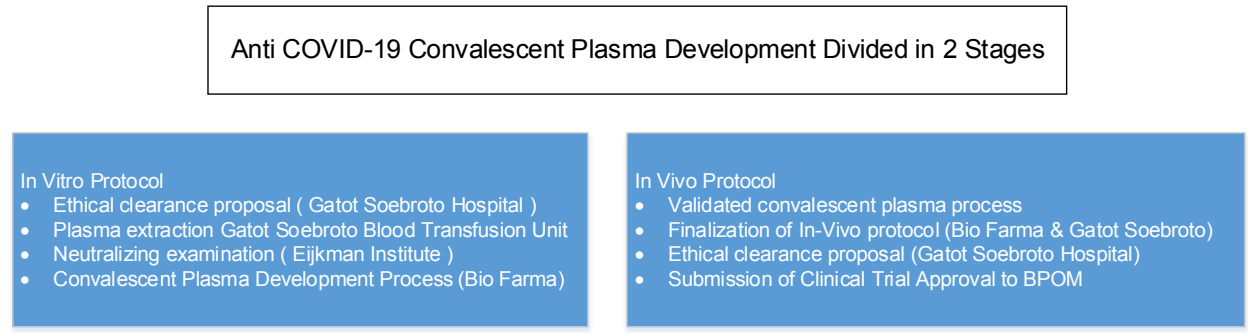
done using 2 ml sample at Bio Farma and neutralizing test using 3 ml sample was done at Eikjman Institute.

In urgent condition, plasma can be transfused to COVID-19 patients before 6 hours. In not urgent condition, plasma can be kept at -70ºC degree so it turns to 200 ml frozen plasma. If the plasma will be used, thawing done at 30-37ºC then it can be transfused to COVID-19 patients before 6 hours.

Disease Severity Spectrum
Basic for Timing of COVID-19 Convalescent Plasma Therapy



Cited from[7]



Research and convalescent plasma therapy development divide into 2 activites which are in-vivo experiment (intervention to observe overall effects towards COVID-19 positive subjects) then in parallel, in-vitro experiment (convalescent plasma effect on neutralizing virus). Safety and efficacy of convalescent plasma will be observed in severe stage COVID-19 patients which hospitalized.

In-vivo research – plasma which already pass quality control used in COVID-19 patient. Its safety and efficacy towards hospitalized severe stage COVID-19 patients was observed, then in parallel in-vitro research is done. In-vitro research including donor election, plasma characterization, virus inactivation, and efficacy testing of plasma until it is declared pass quality control.

Refinement process during this in-vitro research involving Blood Transfusion Unit at Gatot Soebroto Indonesian Army Central Hospital; examination towards SARS-CoV-2 culture was done at Eijkman Institute, meanwhile evaluation of convalescent plasma antibody level was done by Bio Farma. Process sequence in this stage is by drawing COVID-19 survivors' plasma donor in amount 200 ml. Then virus deletion was done and the plasma was given to severe COVID-19 patients. More plasma donor from COVID-19 survivors will increase data which collected and analyzed.

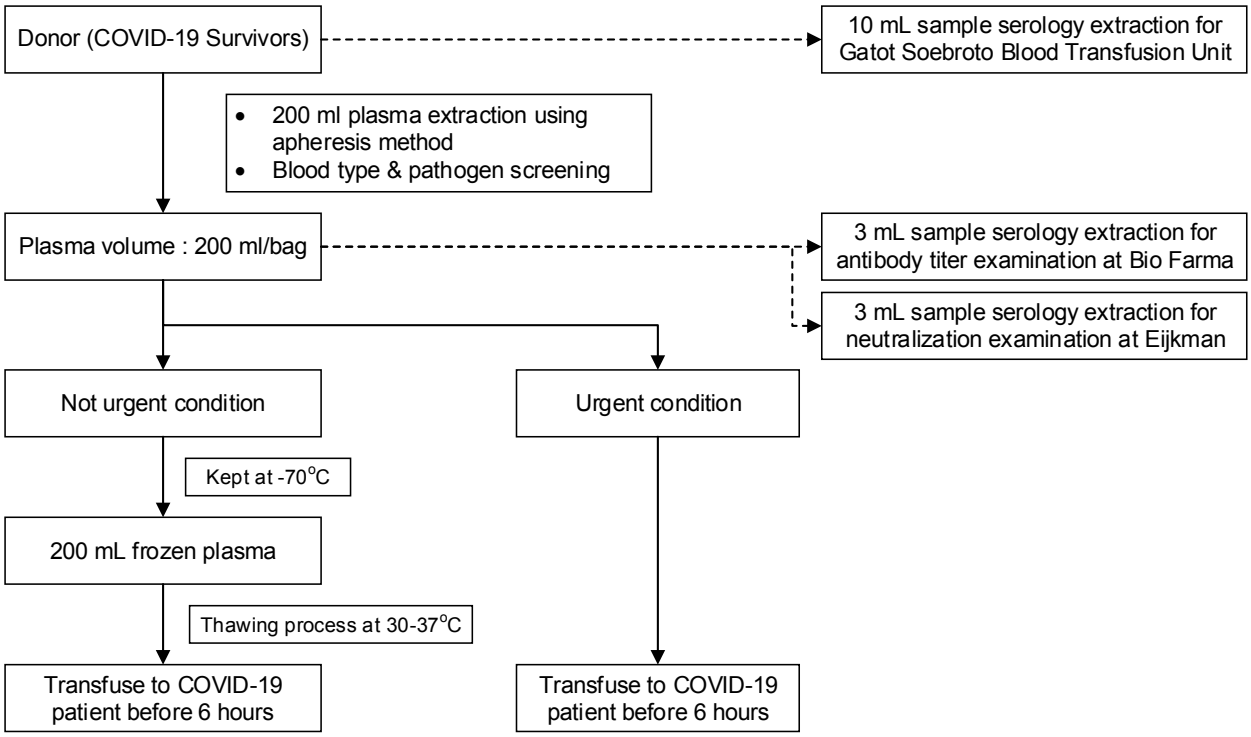
Measured variables:

1. Progression / improvement of clinical symptoms : fever, cough, breathing difficulty, chest pain, sore throat, nausea, vomit, diarrhea, anosmia, erythema, conjunctivitis, ILI (influenza-like illness).

2. Improvement of lung lesion from lung imaging

3. Improvement of routine laboratory test criteria: CRP, procalcitonin, complete blood count, SGOT, SGPT, blood gas analysis, ureum, creatinine, e-GFR, blood glucose, D-dimer, IL-1, IL-6 and IL-8.

COVID-19 Plasma Apheresis Research Plot



3. If clinical trial, description has to include whether treatment group is allocated randomly or nor (including randomization method) P5-21 and whether it is blinded or not. (*If not clinical trial, it is enough to write : irrelevant*)(*p12)*

Irrelevant

Sampling

1. Number of subject needed according research objectives and its calculation based on statistic.

Sample number needed ranged from 5 – 10 subjects (amended) in each treatment group (mild and severe stage). This sample is an early study. Analysis of this trial use T-test independent which is comparative test or comparison test to know whether if there is any significant mean difference between 2 interval data groups. Two independent groups described earlier is 2 unpaired groups which means source of data come from different source.

4. Participant / subject criteria and exclusion / inclusion justification (P-3)

Donor is COVID19 – survivors (COVID-19 patients whom already declared healthy) with inclusion criteria as follows:
1. Age: ≥ 18 until ≤ 60 years old
2.Complete resolution of symptoms for minimum 14 days before plasma donation or 14 days after repeated negative nasopharyngeal swab.
3.Donor has been declared negative from twice nasopharyngeal swab
4. Positive history of hospitalization with mild symptom of COVID-19 or independent self-isolation with mild symptoms COVID-19 and already confirmed with RT-PCR (Real Time-Polymerase Chain Reaction)
5. Female donor candidate not is not pregnant (negative result of serum pregnancy test

Blood Transfusion Unit then will classify donor candidates who fulfill criteria as follows:
1. Blood type (ABO) and Rhesus (RhD) identification.
2. Blood screening towards HIV, HBV, HCV, syphilis and other infections which considered necessary using immunoassay method and / NAT if possible.
3. Hemoglobin level examination
4. Erythrocyte antibody screening examination, if possible.

Recruited recipients are they who fulfill inclusion and exclusion criteria as follows: [3,4, 8,9, 17,23]

Recipient inclusion criteria:
1. Age: ≥ 18 until ≤ 60 years old
2. Confirmed case with RT-PCR from nasopharyngeal swab.
3. Classified as severe COVID-19
    - Severe COVID-19 fulfill at least one condition below:
        - Breathing difficulty or severe pneumonia treated supportively with quick progressivity and high viral load
        - Respiratory rate >30 times/minute
        - Blood oxygen saturation <93% or with PaO2/FiO2 <300 (PaO2 measured in mmHg and FiO2 measured as inspired oxygen fraction)
        - Arterial PF ratio < 300 and/or lung infiltrate >50% in 24-48 hours.
        - Not yet or already supported with mechanical ventilation
4.Hospitalized severe stage COVID-19 patients with comorbidities will be given immediately.

Recipient exclusion criteria:
1. Patient in pregnant condition
2. Having contraindication towards transfusion or any history of cross reaction previously towards blood product transfusion.

Donor's convalescent plasma is extracted from subjects who fulfil inclusion criteria. Ten ml serology sample is extracted for Blood Transfusion Unit of Gatot Soebroto Indonesia Army Central Hospital. Another 200 ml plasma is extracted using apheresis method which will be divided into 2 bags @100 ml then it will be tested for blood type & pathogen. Antibody titer examination was done using 2 ml sample at Bio Farma and neutralizing test using 3 ml sample was done at Eikjman Institute.

In urgent condition, plasma can be transfused to COVID-19 patients before 6 hours. In not urgent condition, plasma can be kept at -70^{o}C degree so it turns to 200 ml frozen plasma. If the plasma will be used, thawing done at 30-37^{o}C then it can be transfused to COVID-19 patients before 6 hours.

5. **Vulnerable group sampling** : Reason to involve pediatric patients or adult patients who not capable to give agreement after explanation of vulnerable group, and preventive measurement if the risks happen. (P-15 until 19)(*p15*)

This research does not involve pediatric or adult patients who unable to give approval after explanation.

Intervention (For qualitative secondary data data user, enough to write "irrelevant" then proceed to "benefit")

Description and explanation of all interventions (treatment administration methods, including administration route, dosage, dosage interval, and treatment duration of usable product)

In this intervention research, 5 – 10 patients will be recruited. Subject will be given 100 ml convalescent plasma on day 0, 3, 6 which originated from COVID-19 donor (healthy condition with antibody neutralizing titer ≥ 1/80) as additional treatment. Early justification is safety of convalescent plasma transfusion and secondary justification is clinical symptoms improvement and laboratory parameters within 3-5 days after transfusion.

6. Plan and justification to continue or stop treatment standard during trial (p4 and 5)

Research will be stopped if recipient suffer from serious adverse effects such as TRALI, anaphylactic shock.

7. Another treatment that might be given/allowed or becoming contraindication during trial.

In this trial, patient already treated with medication:

- Azithromycin 500 mg/24H IV (5 – 10 days)
- Chloroquine 500 mg/12H (5-10 days) or
  Hydroxychloroquine 200 mg/12H (5-10 days)

*) Note: If electrocardiogram show abnormal result, it is contraindication for Chloroquine or Hydroxychloroquine (Cardiologist will be consulted)

- Methisoprinol 100 mg/kgBW/day (divided in 4 dosage)
- Multivitamins which contain Zinc and Vitamin C. For example :
  Surbex Z 1 tab/12H, or Seloxy AA 1 tab/12H
- Cernevit 1 vial/24H (3 days)
- Omeprazole injection 40 mg/24H
- Intravenous fluid drops : Crystalloid solution
- If breathing difficulty (+), oral bronchodilator will be given.
- Mucolitic / Expectorant: Fluimucyl 600 mg/12H effervescent tab.
- Antipyretic if fever
- Hepatoprotector if there is abnormal liver function

8. Other clinical or laboratory test which is necessary to be done

Laboratory data including white blood cell count, lymphocyte count, chemical parameter which evaluate liver and renal function, cycle threshold point, inflammation factor C-reactive protein (CRP), procalcitonin, lung imaging test.

E. Outcome Monitoring

1. Sample from standardized case report form, recording method of therapeutic response (description, evaluation method and measurement frequency),follow-up procedure, and if possible, proposed measurement to define subject compliance who receive the treatment (see appendix)(p17)

Measured variables:

1. Progression / improvement of clinical symptoms : fever, cough, breathing difficulty, chest pain, sore throat, nausea, vomit, diarrhea, anosmia, erythema, conjunctivitis, ILI (influenza-like illness) on day 1
2. ,4,7 and 14 after convalescent plasma administration

3. Improvement of lung lesion from lung imaging on day 1, 4, 7 and 28 after first convalescent plasma administration.

4. Improvement of routine laboratory test criteria: CRP, procalcitonin, complete blood count, SGOT, SGPT, blood gas analysis, ureum, creatinine, e-GFR,blood glucose, D-Dimer, IL-1, IL-6 and IL-8 on day 1,4,7 and 14 after first convalescent plasma administration.

BLOOD EXAMINATION RESULT TABLE of RESEARCH SUBJECT

Patient Name :
Gender : M / F
Date of Birth :
Address :
Medical Record Number:

Type of Examination	**Result**			
	Examination before Convalescent Plasma **Date.....**	**Day 1 After Convalescent Plasma** **Date.....**	**Day 3 After Convalescent Plasma** **Date.....**	**Day 6 After Convalescent Plasma** **Date.....**
Clinical symptoms				
Laboratory parameter : -CRP -PCT -CBC -SGOT -SGPT -Blood gas analysis -Ureum -Creatinin -e-GFR -Blood glucose -D-dimer Biomarkers: -IL1,IL,IL8				
Lung imaging parameter				
	Examiner, (.....)	Examiner, (.....)	Examiner, (.....)	Examiner, (.....)

F. Termination of Research and Its Rationale

1. Rule and criteria when subject can be terminated from research/clinical trial or in multi-centre trial, when a centre / institution can be deactivated, and when the trial can be terminated (not to be continued)

Convalescent plasma administration is stopped if subject suffer risk related with blood plasma transfusion, including immunologic / allergic reactions towards blood plasma. The most severe risk that might happen to recipients is TRALI (transfusion-related acute lung injury). Risk of TRALI can be decreased by better plasma processing with extracting donors' plasma using plasmapheresis process. Meanwhile, anaphylactic shock still can happen even though very rare. Mild adverse effects which might happen are fever and arise of purpura.

G. Adverse Event and Complication (Unexpected Event)

Recording and reporting adverse events / reactions, and complication handling requirement (P-4, 6)

Format attached

1. Risks known from adverse events, including risk related with each intervention plan and related with medicine, vaccine or procedure that will be tested. (P-4, 5)

Before convalescent plasma administered to subject, informed consent was done towards patient / family regarding adverse effect risk, disease prognosis and measurement action that if adverse events happen. The most severe adverse effect might happen is TRALI (transfusion-related acute lung injury) with incidence rate 1:5.000 and also anaphylactic shock even though very rare. Mild adverse effects which might happen are fever and arise of purpura.

H. Complication Handling (p-14)

Detail plan if there is risk more than minimal risk / physical wound, make detail plan, insurance availability, treatment facility / medical fee availability. Compensation if disability / death happen.

If adverse effect arise, then subject will be hospitalized at hospital and become responsibility of researcher team and hospital.

Management for minimize risks starting from donor election, donor sampling, plasma processing including minimize risk of blood-transmission contagious infection, storing process, labelling process, transporting plasma from Blood Transfusion Unit Gatot Soebroto Indonesia Army Central hospital to ward; dosage and how administer convalescent plasma following valid standard of blood plasma transfusion.

I. Benefits

1. Personal benefit of research to subject and others (P-4)

- Benefit for Donor: Donating their blood plasma as contribution for humanity in developing convalescent plasma therapy to save other lives.
- Benefit for others / COVID-19 patients: One step forward of treatment availability to heal / save COVID-19 patients' life and shorten hospitalization period.

2. Research benefits for population including new knowledge which resulted from trial (P-1, 4)

For Population

This trial outcome can help availability of anti COVID-19 convalescent plasma product where this therapy give benefits such as:

- Finding method to process convalescent plasma from COVID-19 patients
- Providing convalescent plasma material for further testing which is efficacy test towards patient if the development succeed. There will be another further trial regarding this matter.

For science

- Providing information for basic knowledge to develop COVID-19 convalescent plasma in Indonesia
- As national even international publication materials

J. Sustainability of Benefits Guarantee (p28)

1. Possibility of continuity access if intervention outcome produces significant benefits, available modality, available parties who need treatment continuity, organization who will pay the expenses, and duration (P-6, 14)

Specimen guarantee – In not urgent condition, plasma can be stored at -70^{o}C degree so it will convert to 200 ml frozen plasma for a year and can be administered to other patient in other research centre. Storage will be set at -70^{o}C and locked; it only can be accessed by authorized staff.

K. Informed Consent

1. Proposed method to gain informed consent and planned procedure to communicate research information to subject candidates including name and guardian position for those who unable to give consent. (P-9)

   Informed consent is delivered to donor and recipient with persuasion and explanation regarding benefits and objectives of research.

3. For pregnant woman : Available planning to observe mother and child health for short and long term. (P-14, 19)

   Irrelevant, pregnant woman is not allowed to donor

L. Guardian (p-10, 16,17)

1. Presence of legal guardian if subject candidate unable to give informed consent (P-10, 16, 17)

   There will be request for valid legal guardian if patient unable to give consent after explanation; but for donor, donor consent is more preferred.

4. Presence of parents or guardian if children understand the informed consent but not reach legal age to make decision

   Irrelevant

M. Persuasion

1. Description of persuasion / incentive to subject candidate for participating such as money, gift, free service or others. (P-13)

   Both donor and recipient as subject independently decide whether will participate or not. If donor eligibility criteria is not fulfilled, subject will be informed by physician in charge at our Blood Transfusion Unit. Donor will receive package that consist of milk, vitamin and biscuits as gratitude.

5. Plan, procedure and person in charge to inform participant's benefits and risks ; or regarding other research with same topic which can influence continuity subject participation during trial (P-9)(p33)

   Donor requirement information will be informed by Blood Transfusion Unit Gatot Soebroto Indonesia Army Central Hospital staff

Please contact us at Blood Transfusion Unit Gatot Soebroto Indonesia Army Central Hospital:

a. Dwi Novianingtyas, Clinical Pathologist, MD / 0821.1228.7478 / dwinovinobi@gmail.com
b. Jenie Erawati Muchti, M.Ked (Clin.Path), Clinical Pathologist, MD / 0813.1484.2822 / muchti.jea@gmail.com

6. Planning to inform research outcomes to subject or participant (P-24)

N. Confidentiality

2. Recruitment process (for example through advertisement); and steps to keep privacy and confidentiality during recruitment (P-3)

Donor's name and identity will be classified

7. Protection steps for keeping private data confidential and respecting people privacy including caution to prevent leakage of confidential family genetic test result except permitted by relevant one.

Information which delivered to Bio Farma only blood type and time of sampling; no information regarding donor identity. Thus, patient identity as subject will also be classified.

8. Information about coding (if exist); to make subject's identity, storing information (place, time and how) and also by whom the data can be opened if emergency happen. (P-11, 12)

Coding technique for donor identity:
Sample sequence number / 4 digits of medical record number / date / month / COVID19-RSPAD/2020

Coding technique for recipient identity:
Sample sequence number / 4 digits of medical record number / date / month / COVID19-RSPAD/2020

9. Possibility for further usage of personal data or biological material

None

O. Analysis Planning

1. Description regarding statistic analysis plans, including intern analysis plan if needed, and criteria if or under which condition whole research will be terminated prematurely.

This sample is an early stage of trial. Trial analysis use T-dependent test which is comparative test or difference test to know whether any significant mean difference according normal curve. If data distribution is abnormal, then analysis use Wilcoxon signed rank test.

P. Safety Monitoring

1. Planning to monitor continuity of medicine safety or other intervention which done in the trial; and if needed, independent committee establishment for data and safety monitoring (P-4).

Recipient monitoring:
1. Progression / improvement of clinical symptoms : fever, cough, breathing difficulty, chest pain, sore throat, nausea, vomit, diarrhea, anosmia, erythema, conjunctivitis, ILI (influenza-like illness)
2. Improvement of lung lesion from lung imaging
3. Improvement of routine laboratory test criteria : CRP, procalcitonin, complete blood count, SGOT, SGPT, blood gas analysis, ureum, creatinine, e-GFR,blood glucose, white blood cell count

Specimen guarantee which is storage place set at -70^{o}C degree, locked and only can be accessed by authorized staff.

All the adverse event and severe adverse event will be reported to responsible ethics committee within 24 hours since the event took place (SAE).

This research is monitored by appointed KEPPK team.

Q. Conflict of Interest

1. Regulation to resolve financial / other conflicts which could influence researcher / other staff decision ; informing it to institution committe regarding possible conflict interest; committe communicate it to ethical committe and then communicate it to researcher regarding further steps which necessary to be done.

   This is a non-profit research

R. Social Benefit

For research which is done at poor resource, sponsor contribution for capacity building , scientific & ethic study; health research. Assurance that capacity building purpose according to expectation of participant and community where the research is done.

10. Research protocol / document delivered to ethical committee including description of community involvement planning and it shows which resources allocated to involving activitity. The document describe what will be and has been done; when and by whom to ensure that population clearly mapped for simplify their involvement during research, to ensure that purpose of research

    Protocol attached

S. Data Rights

1. Especially if sponsor is private sector,legal contract which declared to whom publication right research result belong; and obligation for joint preparation and research outcome report draft is given to researcher. (P-24) (B dan H, S1,S7)

Publication belongs collectively between Gatot Soebroto Indonesia Army Central Hospital, Bio Farma and Eijkman.

T. Publication

Planning of result publication on certain field (such as epidemiology, genetic, sosiology) which has risk to be in contrary with community, population, family and certain ethnic benefit; minimalize harm of this group by keeping data confidentially during and after trial; and publish research trial by always considering their dignity

Lancet or Pubmed

If the research result is negative, making sure that the result will be available through publication or by reporting it to drug administration authority. (P-24)

If the result is negative, it will be reported to Bio Farma BoE, Gatot Soebroto Indonesia Army Central Hospital directors and it will be coordinated with Indonesia Health Ministry.

U. Funding

Resource and amount of research fund, sponsor institution, and financial commitment description from sponsor to research institution, researcher, research subjects, and if exist, to community (P-25)

Early research funding is supported by Bio Farma, Simultaneously, collaboration agreement is prepared between Bio Farma, Gatot Soebroto Indonesia Army Central Hospital and Eijkman Institute.

V. Ethical Commitment

11. Main researcher declaration that all principles written in this guideline will be obeyed.

    Main researcher and other researchers will obey all principle that written in this guideline.

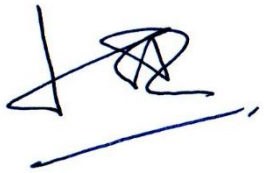
12. (Track Record) History of previous ethic protocol proposal and its result (content with title and date of research and ethical committe review result)

    None

13. Declaration that if there is evidende of data fraud, it will be handled according to policy sponsor for taking necessary action.

    If there is evidence of data fraud, it will be handled according to sponsor policy for taking necessary action

Main researcher signature
Jakarta, April 4th 2020



Marliana Sri Rejeki, Clinical Pathologist, MD

W. References

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13. Tim TPK Covid-19 Indonesia. *Penatalaksanaan Terapi Plasma Konvalesen bagi Pasien Covid-19*. (2020).

AB. Appendix

1. Main Researcher Curriculum Vitae

Researcher Team from Gatot Soebroto Hospital (GS Hospital)

No.	Name	Institution	Position in Team	Job Description	Information
1	Marliana Sri Rejeki, Clinical Pharmacologist, MD	GS Hospital	Main Researcher	Responsible for report of all research technical activity at GS Hospital	EL-GCP: 872/EL-GCP/AKEPIN/2020
2	Familia Bela, Pathologic Anatomist, MD	GS Hospital	Researcher	Responsible for report of all research technical activity at GS Hospital	
3	Triono Sundoro, MD	GS Hospital	Advisor	Consultant and responsible for all research technical activity at GS Hospital	
4.	A. Budi Sulistya, Otolaryngologist, MD, MARS	GS Hospital	Advisor	Consultant and responsible for all research technical activity at GS Hospital	
5	Nana Sarmadi, Obstetric & Gynecologist, MD	GS Hospital	Supervisor and Research Coordinator	Consultant and responsible for all research technical activity at GS Hospital	
6.	Dr. Agus Yunianto, Neuro Surgeon, MD	GS Hospital	Supervisor	Consultant and responsible for all research technical activity at GS Hospital	
7.	Dr.Handrianto Setiajaya, Neuro Surgeon, MD	GS Hospital	Research Coordinator	Consultant and responsible for all research technical activity at GS Hospital	
8.	Lukman Ma'ruf , Neuro Surgeon, MD, M.Kes., M.H	GS Hospital	Supervisor	Consultant and responsible for all research technical activity at GS Hospital	
9	Retno Wihastuty, Pulmonologist, MD	GS Hospital	Researcher	Consultant and responsible for all research technical activity at GS Hospital	
10.	Ratna Andriyana, Pulmonologist, MD	GS Hospital	Researcher	Consultant and responsible for all research technical activity at GS Hospital	

12.	Martina Lily, Clinical Pathologist, MD	GS Hospital	Researcher	Consultant and responsible for all research technical activity at GS Hospital	
13	Dwi Novi, Clinical Pathologist, MD	GS Hospital	Researcher	Consultant and responsible for all research technical activity at GS Hospital	
14	Jenie, Clinical Pathologist, MD	GS Hospital	Researcher	Consultant and responsible for all research technical activity at GS Hospital	
15	Wisvici Yosua Samin, Pediatrician, MD, M.Sc	GS Hospital	Researcher	Responsible for report of all research technical activity at GS Hospital	

Researcher Team from PT. Bio Farma

No.	Name	Institution	Posision in Team	Job Description
1	Dr. Neni Nurainy, Apt	PT. Bio Farma (Persero)	Main Researcher	Responsible for all research technical activity at Bio Farma
2	Dr. Novilia Sjafri Bachtiar, MD., M.Kes	PT. Bio Farma (Persero)	Researcher	Responsible for assisting all research technical activity at Bio Farma
3	Dyah Widhiastuti, MD, M.Kes	PT. Bio Farma (Persero)	Researcher	Responsible for assisting all research technical activity at Bio Farma
4	Acep Riza Wijayadikusumah PhD	PT. Bio Farma (Persero)	Researcher	Responsible for assisting all research technical activity at Bio Farma
5	Hidayat Setiaji MSc.	PT. Bio Farma (Persero)	Researcher	Responsible for assisting all research technical activity at Bio Farma

Researcher Team from Eijkman

No.	Name	Institution	Position in Team	Job Description
1.	Prof Dr Amin Soebandrio,MD, Internist	Eijkman	Researcher	Responsible for assisting all research technical activity at Eijkman
2	Frilasita A Yudhaputri SSi. MBiomed. Sc Sisi	Eijkman	Main Researcher	Responsible for assisting all research technical activity at Eijkman
3.	Prof Dr David Handoyo Mulyono, MD, Internist, Finasim	Eijkman	Researcher	Responsible for assisting all research technical activity at Eijkman
4.	Dr. Tedjo Sasmono	Eijkman	Researcher	Responsible for assisting all research technical activity at Eijkman

2. Case Report Form Sample : Irrelevant

** Sequence Number on CIOMS 2016 Guideline*