PROTOCOL OF STUDY

TITLE:

EFFICACY OF REINFORCING STANDARD THERAPY IN COVID-19 PATIENTS WITH REPEATED TRANSFUSION OF CONVALESCENT PLASMA

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A. PROJECT PROTOCOL

1. SUMMARY

Coronavirus disease 2019 (covid-19) was classified as a pandemic by the WHO in March 2020. The SARS-COV-2 virus is easily transmissible and there is currently no approved treatment with effective results. Although the main epidemiological parameters are currently being studied, apparently the rate of contagion, incidence and mortality rate in severe cases seems to be high. For this reason, there is an urgent need to find a viable therapeutic option. Trying to respond to this need, the objective of this study is to determine the efficacy of standard treatment reinforced with two doses repeated in two consecutive days of plasma from people exvalescing from the COVID-19 disease already discharged and / or with results in negative COVID-19 detection tests, transfused to hospitalized COVID-19 patients, both from the COVID-19 plant and from the ICU of HUSLL and their counterparts in the participating centres, who meet the inclusion criteria and sign the informed consent to participate in the study. To this end, a pilot study of an open-label, phase I, multicentre, open-label clinical trial will be carried out to study the efficacy of strengthening conventional therapy with passive immunization through repeated infusion of plasma compared to exclusive standard treatment in COVID-19 patients. The study will be led by the Son Llàtzer University Hospital, which has designed the project and will act as a coordinating centre. For the evaluation of efficacy, both clinical, immunological and safety criteria will be collected. It is expected to have results in a short period of time from the approval of the corresponding ethics committees.

2. BACKGROUND AND JUSTIFICATION

The first cases of COVID-19 date back to December 31, 2019, when the Wuhan Municipal Health and Sanitation Commission (Hubei Province, China) reported on a group of 27 cases of pneumonia of unknown ethology, with a common exposure at a wholesale seafood, fish and live animal market in Wuhan City, including seven severe cases [1]. The first case, recorded on December 8, 2019, began with the following symptoms: fever, dry cough, dyspnoea and radiological findings of bilateral pulmonary infiltrates [2]. A month later, on January 7, 2020, the Chinese authorities identified as the causative agent of the outbreak a new type of virus of the *Coronaviridae* family that has subsequently been named SARS-CoV-2, whose genetic sequence was shared by the Chinese authorities on January 12 [3]. The disease caused by this new virus has been referred to by international consensus and the WHO as COVID-19 [4].

As it is a pandemic that has affected the whole world at all social levels, the WHO offers a series of reports with updated information, almost daily, with the numbers of cases (classified by infections, deaths, discharged, among others), both globally and classified by countries, can be consulted at (https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200413-sitrep-84-covid-19.pdf?sfvrsn=44f511ab_2). The data consulted on April 14, 2020 (when the initial version 1.0 study was designed) indicated that globally there were: total confirmed cases: 1,773,084, total new confirmed cases: 76,498, total deaths: 111,652, total new deaths: 5,702. In Spain total confirmed cases: 169,496, total new confirmed cases: 4,167, total deaths: 16,972, total new deaths: 619 [5]. According to data from the Spanish Ministry of Health, in the Balearic Islands there were a total of 1,571 infected of which died: 117, cured: 862 (https://covid-19.isciii.es/). As of July 23, 2020, when the study becomes multicentre, and according to the daily report of the WHO (https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200722-covid-19-sitrep-184.pdf?sfvrsn=7680210a_2)[6], worldwide there are a total of confirmed cases: 14,765,256 (since the beginning of the pandemic), total of new confirmed cases per day: 202,726, total deaths: 612,054 (since the beginning of the pandemic). pandemic) and 4,286 new ones per day. In Spain total confirmed cases: 267,551 (since the beginning of the pandemic), total of new confirmed cases: 730 in one day, on July 22, total deaths: 28,426 [7].

People infected with COVID-19 are known to experience immunological and physiological changes that fundamentally affect the airways [8]. At the pathophysiological level, the following symptoms are the most frequent: at the systemic level: fever, cough, fatigue, headache, diarrhoea, hypoxemia, involvement of the cardiac system, lymphopenia, among others. At the level of the respiratory system: pneumonia, acute respiratory distress syndrome [9].

As for its transmission in a span of a few months, COVID-19 has become a pandemic due to its transmissibility, spreading across all continents with a notable daily increase in the number of cases and deaths [10] . Although most infected people exhibit mild illness (80%+), 14% have severe illness and 5% have critical illness. Approximately 10% will require hospital admission, of which approximately 10% will require ICU care, including invasive ventilation due to acute respiratory distress syndrome (ARDS) [11]. While mortality appears to be more common in older people and people with comorbidities, such as chronic lung disease, cardiovascular disease, and diabetes, young people without comorbidities also appear to be at risk of progressing into multi-organ failure and death [12]. There have been a growing number of studies published rapidly online and in academic journals; however, some of these may be of limited quality and are published preliminarily without sufficient review. Therefore, a critical evaluation of existing studies is needed to determine whether the existing evidence is sufficient to support the management strategies currently proposed.

There are several therapeutic approaches to COVID-19 disease: antiviral compounds that inhibit enzymatic systems, those that inhibit the entry of SARS-CoV-2 into the host cell, acting on the mechanisms of interaction between the host and the pathogen, and finally immunomodulators that are supposed to reduce the cytokine storm and associated lung damage. As for therapies, little is known so far about how to definitively treat this disease, in the sense that many laboratories worldwide are working both to improve the detection of the disease and to create a vaccine. It should be noted that no drug is approved by international agencies for COVID-19. The time needed to complete this type of research is much slower than the speed with which the pandemic worsens, so at the moment the main therapies reported in the scientific literature are limited to the use of some antivirals and drugs such as: chloroquine, arbidol, remdesivir and favipiravir. Existing in some articles with tables summarizing the main agents with potential efficacy in the treatment of SARS-CoV-2 (see [13]).. A metanalysis observational studies on passive immunotherapy for SARS and severe forms of influenza indicates a decrease in mortality, but the studies were of low or very low quality and lacked control groups [14]. In Middle East Respiratory Syndrome (MERS), the use of fresh frozen convalescent plasma or immunoglobulins from recovered patients has been discussed [15]. Patients recovered from SARS develop a neutralizing antibody response [15]. Preliminary data indicate that this response also extends to SARS-CoV-2 [16]. Others have argued that plasma from convalescent donors could be an option for the prevention and treatment of COVID-19 disease. In a preliminary series of uncontrolled cases of 5 critical patients with COVID-19 and ARDS, administration of plasma from convalescent COVID-19 donors containing neutralizing antibodies was accompanied by an improvement in their clinical status [17].

There are further examples where convalescent plasma has been successfully used as post-exposure prophylaxis and/or treatment of infectious diseases, including other coronavirus outbreaks (e.g., SARS-1, MERS). Convalescent plasma has also been used in the COVID-19 pandemic; limited data

from China suggest a clinical benefit, including radiological resolution, reduced viral loads and improved survival. Globally, blood centres have a robust infrastructure for conducting collections and building inventories of convalescent plasma to meet growing demand. However, there are major challenges, both regulatory and logistical, encompassing donor eligibility, donor recruitment, collections, and transfusion itself including dose study. Data from rigorously controlled clinical trials of convalescent plasma are also few, underscoring the need to evaluate its use objectively for a range of indications (e.g., prevention versus treatment) and patient populations (e.g., age, disease, comorbidity)[18][19][20]. The joint application of immunotherapy with immune IgG antibodies combined with antiviral drugs as an alternative treatment against COVID-19 has also been studied until more definitive options such as vaccines are available [21]. Therefore, while promising, plasma from convalescent donors has not yet been shown to be safe and effective as a treatment for COVID-19. The effect of strengthening retroviral therapies combined with immunotherapy is also not known exactly [21]. The scientific community indicates that a careful clinical evaluation with this type of therapy should allow to quickly establish whether such passive immunotherapy, administered in the early stages of the disease in patients at high risk of harmful evolution, can reduce the frequency of patient deterioration and, consequently, mortality from COVID-19 [22][23] . Therefore, it is important to study the safety and efficacy of COVID-19 convalescent plasma in clinical trials. In this sense, the present study aims to determine the efficacy of reinforcing standard treatment with infusions of repeated doses of plasma from patients convalescing from the COVID-19 disease already discharged and / or with results in the negative COVID-19 viremia tests, in COVID-19 patients still hospitalized, comparing it with the results obtained with the exclusive standard treatment that is being used in patients infected by COVID-19. Therefore, to evaluate the immunological efficacy of the reinforcement of standard treatment with hyperimmune plasma vs standard therapy without reinforcement.

In April 2020, version 1.0 of this study was designed, which was approved by the corresponding committee and funded by the Health Research Institute of the Balearic Islands in June 2020. In July 2020 due to the context of the increase in the number of infected after the confinement and foreseeing a possible scenario of increase in cases in the coming months, different health centres in the Balearic Islands requested HUSLL to be part of the study, so version1.0 adapts and is presented in this document for implementation as a multicentre study.

3. HYPOTHESIS AND OBJECTIVES

3.1. Hypothesis:

Plasma from people who have been infected and have overcome the COVID-19 disease is expected to have sufficient and compatible levels of antibodies (anti-COVID-19) to neutralize the viral load that a person infected and still convalescing with COVID-19 may present. Therefore, it is expected that the efficacy of the reinforcement of standard therapy with repeated transfusion of immune plasma from COVID-19 convalescents vs standard therapy alone in hospitalized COVID-19 patients will be more effective at the therapeutic level and may be a possible palliative until the discovery of a vaccine. Mitigating the inflammatory phase of the disease and therefore reducing the risk of ARDS.

3.2. Objectives

3.2.1. Main objective:

The objective of the study is to determine the efficacy of reinforcing standard treatment with repeated infusions of plasma from people ex-convalescent of COVID-19 disease (already discharged and/or with negative COVID-19 test results), transfused to COVID-19 patients still hospitalized, both COVID-19 plant and HUSLL ICU (and collaborating centres participating in the multicentre study). Comparing it with the results obtained with the exclusive use of standard treatment, which is being used in patients infected with COVID-19. Therefore, to assess the immunological efficacy of the reinforcement of standard treatment vs standard therapy without reinforcement.

3.2.2 Secondary objectives:

Secondary objectives are related to evaluating not only efficacy at the clinical level, but also tolerance, safety and immunological aspects. Below is a list of the main secondary objectives:

-To assess the serological response to Coronavirus SARS-CoV-2 in patients with plasma transfusion and compare it with patients who have received treatment standard.

-Analyse the influence of the number of antibodies of the donor on the clinical evolution of the recipient.

-Analyse the efficacy of the experimental treatment that will reinforce the standard treatment, comparing it with the exclusive standard treatment at the level of the main clinical parameters during and after the treatment.

-To assess the safety of experimental reinforced treatment, comparing it with standard treatment during and after treatment.

-To assess the tolerance of experimental reinforced treatment, comparing it with standard treatment during and after treatment.

-Evaluate the feasibility of the experimental reinforced treatment.

-To assess the virological response of patients with plasma transfusion versus patients with standard treatments.

-Find if there is a certain patient profile where this therapy is most effective, either by age group, blood group, sex, or presence/absence of other pathologies.

-On the contrary, determine if there is a certain profile of patients (as in the previous case) in which the treatment is less effective.

-To know retrospectively the parameters of antigenemia and viral load of convalescent patients infected by COVID-19.

-Find possible weak points of experimental therapy that need to be studied to be improved in future studies.

4. STUDY DESIGN

4.1. Type and design of the study Pilot study of phase I, open, two-branch, multicentre clinical trial for the study of the efficacy of passive immunization through repeated infusion of plasma from people exvalescing from infection with COVID-19 and/or with a negative viremia result for COVID-19, together with the standard treatment that is currently being scheduled, compared to the exclusive application of standard treatment in currently hospitalized COVID-19 patients. The study will be carried out and coordinated by HUSLL, which may be joined by all health centres interested in participating in the study that meet the requirements to be able to develop it and commit to the conditions of the same. In each centre, the study subjects will be selected among those admitted to both the COVID-19 plant and the ICU (or their counterpart places in each centre). Below is an outline of the study design:

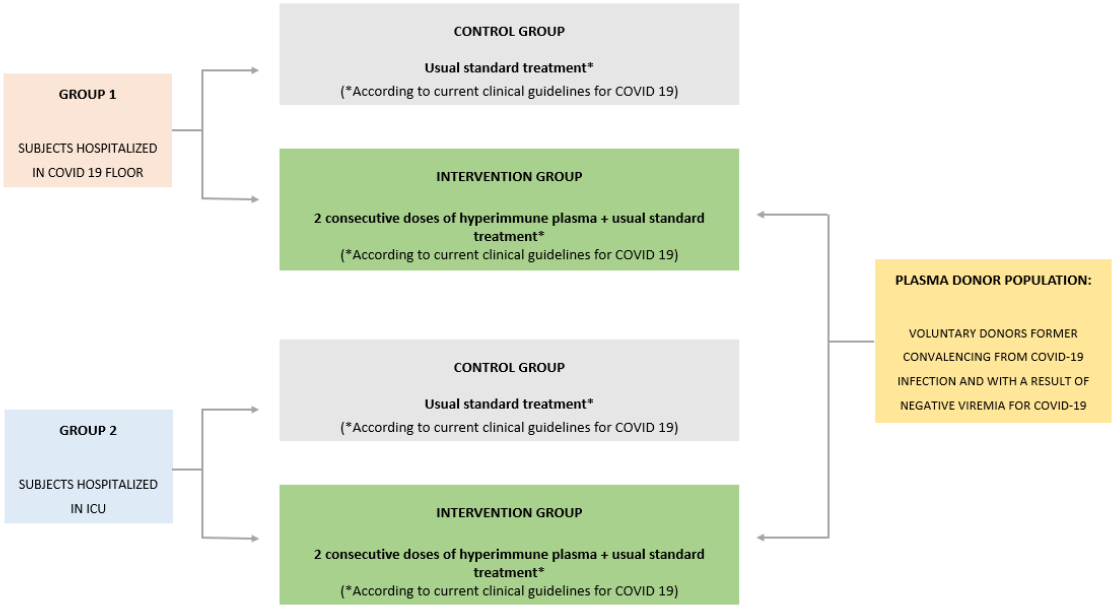

Fig 1. Outline of the design of the study protocol to be carried out.

IMPORTANT NOTE: the scheme refers to the coordinating centre (HUSLL), but the same conditions are extended to all those centres participating in the multicentre study.

The assignment to the control and intervention groups, both in the plant and in the ICU, will be done by means of simple random assignment, using equiprobability calculations through a computer system, in order to guarantee that all subjects have the same probability of belonging to the two groups. The system will be the same in all participating centres. This system will be carried out whenever a plasma stock is available. In the event that the stock runs out, the recruited patients will be part of the control group.

The characteristics of the experimental groups are detailed below:

-*For intervention group*: usual standard treatment (according to clinical guideline for COVID-19), plus two infusions followed by a volume equal to 300 ml of plasma from patients exvalescing from COVID-19 and with negative viremia in the COVID-19 detection test and therefore discharged and / or cured. The infusions will be given on days 1 and 2 of study, after the positive result for COVID-19 of the recipient patient, who will be treated.

-*For control group*: usual standard treatment, according to clinical guideline for COVID-19. This is based on any drug used in clinical practice accepted to date, from retroviral (lopinavir/ritonavir;

darunavir/cobicistat; remdesivir), interferon-α/β, anti-IL-6 monoclonal antibody (Tocilizumab) or oxygen therapy among others. The ratio controls: treated will be 1:2 in favour of the treatment. As treatments have been changing throughout the pandemic, when performing the final analysis, a stratified analysis will be made by type of treatment. That is, infected patients who have been treated with the same drugs will be compared.

4.2. Patient selection

4.2.1. Inclusion criteria

Plasma donors may be selected from among patients already discharged for COVID-19 in the centres participating in the study (who have not received plasma), as well as by volunteers who meet the requirements for inclusion and non-exclusion, who wish to donate and go to HUSLL or the blood and tissue bank of the Balearic Islands.

The study sample for both the intervention and control group will be extracted from patients who are positive in the real time-polymerase chain reaction (RT-PCR) test for the detection of COVID-19, in any of the participating centres (admitted to the plant or ICU), and who meet the inclusion and non-exclusion criteria, and voluntarily wish to participate, after being informed with the Patient Information Sheet (HIP), and have signed the informed consent (IC).

Both donors and study subjects will be provided with the specific HIP and IQ. Each participating centre will sign a participation agreement, confidentiality commitment and transfer of study results for further analysis, following the usual logistics guidelines of multicentre studies.

1. Below are the inclusion criteria:

For the receiver:

A. Recipients hospitalized in COVID-19 floor:

1. Ability to understand the HIP and sign the IQ of the study.

2. Age greater than or equal to 18 years, male or female.

3. Patient hospitalized in COVID-19 floor (or equivalent areas in each centre) with COVID-19 diagnosis by PCR in nasopharyngeal smear or in any other biological sample.

4. Presence of respiratory symptoms and / or fever associated with COVID-19, with time of evolution of the clinic by COVID-19 equal to or less than 7 days (being day 1 the day of onset of symptoms and including day 7).

5. Presence of pneumonia in chest x-ray and/or $SatO_2 < 94\%$ aa.

6. Sequential Organ Failure Assessment score (SOFA) ≤ 6.

7. Accept the condition of complying with the procedures established in the protocol.

8. That you will remain admitted at least 5 days at the discretion of the clinician, in order to perform the procedures correctly.

B. Recipients hospitalized in ICU:

1. Ability to understand the HIP and sign the IQ of the study. In case of impossibility of signing IC (e.g., intubated patients) the oral IC will be accepted.

2. Age greater than or equal to 18 years, male or female.

3. Patient hospitalized in ICU with COVID-19 diagnosis by PCR in nasopharyngeal smear or in any other biological sample.

4. Presence of respiratory symptoms and / or fever associated with COVID-19, with time of evolution of the clinic by COVID-19 equal to or less than 7 days (being day 1 the day of onset of symptoms).

5. Sequential Organ Failure Assessment score (SOFA) > 6.

6. Accept the condition of complying with the procedures established in the protocol.

7. In addition, for ICU patients, the criteria for admission to the ICU that has been given by the Ministry of Health and the Spanish Society of Intensive Care Medicine will be considered (updated to the current situation). A summary is attached to the following table, and more information is added in Annex IX (also available www.semicyuc.org · www.fepimeti.org ·www.seeeiuc.org).

MAJOR CRITERIA (1 criterion necessary)
Septic shock with the need for vasoactive drugs
Respiratory failure requiring mechanical ventilation
MINOR CRITERIA (3 or more criteria)
Respiratory rate> 30 breaths/minute with conventional oxygen therapy
Pao2/FiO2 < 250 with conventional oxygen therapy
Bilateral infiltrates
Altered level of consciousness
Elevation of urea (<20mg/DL)

Leukopenia (<4000 cells/ml) and lymphopenia
Thrombocytopenia (<100000/ml)
Hypothermia (<36ºC)
Hypotension requiring aggressive resuscitation with fluids
D-dimer > 1 µg/L

In case of overflow situation, the following triage tool will also be considered, based on the use of the SOFA.

Colour Code	Initial Assessment	48 hour Assessment	120 hour Assessment	Priority/Action
Blue	Exclusion Criteria* or SOFA > 11*	Exclusion Criteria Or SOFA > 11 Or SOFA 8 – 11 no	Exclusion Criteria* or SOFA > 11* or SOFA < 8 no	Medical Mgmt +/- Palliate & d/c from critical care
Red	SOFA 7 or Single Organ Failure	SOFA score < 11 and decreasing	SOFA score < 11 and decreasing progressively	Highest
Yellow	SOFA 8 – 11	SOFA < 8 no	SOFA < 8 with < 3 point decrease in past 72h	Intermediate
Green	No significant organ failure	No longer ventilator dependant	No longer ventilator dependant	Defer or d/c, reassess as needed

Patients who do not meet the inclusion criteria may remain in conventional hospitalization and should be re-evaluated. Patients who are classified as "red" have priority admission to the ICU, followed by those classified as "yellow". Patients classified as "blue/black" remain in conventional hospitalization and receive palliative care with active medical therapy at the discretion of the attending physician and according to the opinion of the patient and/or family. Patients should be re-evaluated on days 2 and 5 and re-classified. Decisions beyond day 5 in icu will depend on the availability of resources (these criteria are those dictated by the Spanish Society of Intensive Care Medicine (Semicyuc) for ICUs).

For the donor:

1. Ability to understand the HIP and sign the IQ of the study.

2. Age equal to or greater than 18 years.

3. Compliance with the criteria to be accepted as a plasma donor according to European and Spanish regulations (RD 1088/2005).

4. Presence of IgG antibodies against SARS-CoV-2 delectables in peripheral blood 50 UA/mL.

5. Absence of COVID-19 symptoms in the last 14 days.

6. NEGATIVE SARS-Cov-2 RT-PCR in at least one nasopharyngeal sample.

7. Weight over 50 kg and good venous access.

8. Acceptance for the conservation of serum library samples for the realization of antigranulocyte antibodies; especially in cases in which the recipient presents respiratory clinic.

4.2.2 Exclusion criteria

For the receiver:

A. Recipients hospitalized in COVID-19 plant:

1. Patients with a previous history of allergic reaction to any type of transfusion of blood products.

2. Breastfeeding women or women with pregnancy potential and positive pregnancy test.

3. Patients who have been treated with plasma in the 21 days prior to the screening/baseline visit.

4. Patients who, in the opinion of the researcher, possess any condition that makes the recruitment of the same incompatible.

5. Patients who are at the time of the study, participating in a clinical trial.

6. Patients who have not performed all the procedures in the study.

For the donor:

1. Plasmapheresis in the last 7 days.

2. Blood donation in the last 7 days.

3. Donation of more than 25 L of plasma in the previous 12 months.

4. With the intention of reducing the risk of transfusion-related acute lung injury (LPART/TRALI), only male donors never transfused and women with no history of abortions will be selected.

5. Patients who are at the time of the study, participating in a clinical trial.

4.2.3. Patient withdrawal criteria

The patient will be removed from the study when any of the following circumstances are met:

-Patients who have not had both plasma infusions.

-Unacceptable toxicity.

-Withdrawal of the IC.

-Completion of the study.

-Exitus.

Patients will be informed that they can leave the study at any time without affecting their medical care in the future. The reason and date of departure of the study will be recorded in the patient's medical history.

4.2.4. Research treatment

1. Description of the processing

Plasma of convalescent patients with antibodies against Coronavirus SARS-CoV-2 compatible with receptor. **This plasma will reinforce the standard treatment that will be prescribed in these patients, following the guide of "Clinical management of COVID-19 patients", where the usual medications in these patients and their management are detailed.**

2. Labelling and storage of research processing

The plasma will be labelled and stored as set forth in the apheresis section of the receiver.

3. Administration of study treatment

600 ml of plasma from ex-convalescent patients' compatible ABO group shall be administered peripherally or centrally intravenously every 24 hours on days 1 and 2 from treatment assignment, divided into two doses of 300 ml each. The 600 ml of plasma will ideally come from a single donor patient, failing that plasma from different donors may be administered if they are from the same compatible ABO group, recording the final titration of the two doses administered.

5. Accounting of the study treatment

The principal investigator of the study will be responsible for the registration of the transfused plasma units using the accounting form. Patient code, identification code of the administered plasma unit, expiration date and date of administration must be recorded. This form must be kept together with the documentation of the study in case of audit or inspection.

6. Description of control treatment

The control treatment will consist of what is indicated in the COVID-19 management protocols according to usual clinical practice and in accordance with the clinical management protocol of the patient hospitalized for COVID-19. The full duration of the treatment will be determined by what is specified in the protocols. All medication will be provided by the pharmacy service of the Son Llàtzer University Hospital (or where appropriate the pharmacy services corresponding to each centre participating in the study), following usual clinical practice.

7. Criteria for discontinuation of study treatment

The following situations will lead to permanent discontinuation of study treatment:

- Exitus.
-Life-threatening toxicity to the patient, including infusion-related reactions.

8. Concomitant medication

Any concomitant medication is allowed for the treatment of concomitant pathologies presented by the patient as well as the symptoms associated with COVID-19, including standard anticoagulant treatment that is prescribed under normal conditions (if applicable).

9. Prohibited medication

There is no contraindicated medication in the study treatment.

4.2.5. Recruitment of convalescent donors

The recruitment of donors will be carried out by the Hospital Transfusion Services, the Son Llàtzer University Hospital and the Blood and Tissue Bank of the Balearic Islands. Donors will be identified using local, regional or national registries of cured COVID-19 patients. It is also foreseen the recruitment in the family environment of these patients, that is, to study if in the environment of the donor patient there was any other possible donor who met the criteria of inclusion and exclusion, and who after being informed decides to participate voluntarily.

The selection of donors will have several phases:

1. Telephone pre-selection. The donor candidate will be contacted by telephone, informed of the objectives of the study, and if interested, an interview will be conducted to assess whether he meets the selection criteria as a plasma donor and those specific to this trial. Those who meet criteria will be called for a face-to-face appointment.

Alternatively, participation in the study will be proposed upon discharge of the patient by his doctor.

2. First appointment and extraction of analytics.

to. The donor will fill in the usual blood donor form and the pre-selection form for the trial.

b. You will receive the patient information document and sign the informed consent of the trial.

c. The use of the standard blood donor form does not mean that this procedure can be considered a regular plasma donation. These donors must NOT be registered in the plasma donor circuit of the Transfusion Centres.

d. The following samples shall be taken from you:

- Nasal and pharyngeal smear for RT-PCR of Coronavirus SARS-CoV-2.
- Serum sample 6 ml for the quantitative determination of antibodies against Coronavirus SARS CoV-2.

ii. EDTA tube 5 ml for determination of anti-SARS-Cov-19 antibodies

iii. Usual tubes for performing microbiological and immunohematology determinations typical of a regular blood donor.

iv. EDTA tube for blood count.

and. An appointment will be given for plasmapheresis, considering that the microbiological results, both general blood donor and SARS-Cov-2 specific, must be checked and correct.

3. Confirmation call, When the Extraction Centre has all the results, the donor is called to confirm their appointment for plasma extraction. Donors who do not meet any of the analytical requirements will be informed and discarded.

4.2.6. Plasmapheresis of ex-convalescent donors

1. On the day of the appointment, a confirmation will be made that the selection criteria have not changed, and it will be confirmed that the analytical tests are correct.

2. Blood pressure, temperature and heart rate will be taken. Donors with a temperature greater than 37.0ºC will not be accepted. Hyper/hypotensive, tachycardia or bradycardia donors will be accepted at the discretion of the Haematologist responsible for the extraction.

3. The donation will be assigned a SIN (Single identification Number; or number of donation).

4. Each of the extraction bags and the documentation related to this donation will be labelled with this NUMBER WITHOUT.

5. An extraction of 600 mL of plasma without leukocytes (< 1 x 106 leukocytes per unit extracted) shall be carried out using any apheresis machine with its corresponding validated sets or kits (CE Marking) for the extraction of plasma for transfusion use. The specific protocol of each commercial house will be used.

Due to the new orders of the Ministry of Health, the Blood and Tissue Bank of the Balearic Islands will be in charge of the treatment of the sample (inactivation, classification, plasmapheresis and sending to the relevant centre). This institution is responsible for generating a plasma bank with anti-SARS-Cov2 antibodies from ex-convalescent COVID-19 donors. These donors will be selected by the Blood and Tissue Bank of the Balearic Islands as Son Llàtzer University Hospital, who will make the extractions and send the sample for treatment to the Blood and Tissue Bank. The apheresis product obtained in Son Llàtzer University Hospital shall be used as a priority in Son Llàtzer University Hospital. For the rest of the participating centres, apheresis products from the plasma bank of the blood and tissue bank will be used.

4.2.7 Processing of plasma units

(IMPORTANT: the rules of the document *RECOMMENDATIONS FOR OBTAINING PLASMA FROM CONVALESCENT DONORS OF COVID-19 of* the Ministries of Health will be followed[24]**)**

1. The plasma units (identified with the SIN) will be stored at 20ºC (butanediol plates, or similar) if they are to be processed before 8h; or frozen (< -20ºC) if they are going to be processed after 8h.
2. Before the pathogen inactivation process, the 600 mL units shall be separated into two 300 mL bags; using sin as traceability. Each of the 300 mL bags is labelled with the SIN followed by subcode 01 and 02.
3. The 300 mL bags shall be subjected to a pathogen reduction process (inactivation), using any pathogen inactivation system validated for the treatment of plasma for transfusion use. The inactivation process will be carried out in accordance with the specific procedures of each commercial house.
4. If the plasma has been previously frozen, it shall be thawed, inactivated and re-frozen within a period of not less than 2h.
5. All processes, from plasma extraction to final storage after inactivation, shall be carried out maintaining a closed system to ensure the sterility of the product, using a sterile tube connection system, validated for the use of transfusion products. Handling of products within a flow chamber as a closed system is not accepted.

-Labelling of plasma units of convalescent donors

1. Inactivated units will be labelled using the SIN code and subcode 01 or 02.
2. The labelling of devices shall preferably follow the criteria set out in the ISBT128 coding of blood products. The labels will include all the information required for any blood product according to the European guidelines1.
3. Product coding will ideally be done by assigning a new ISBT128 product code that identifies plasma units as specific from COVID19 convalescent donors. The product codes will be:
- E9746 = Apheresis CONVALESCENT PLASMA| NS/XX/<=-25C| Riboflavin-treated| COVID-19
4. In addition, the labels shall include the following information specific to that investigation product:
PLASMA FROM ALTRUISTIC DONORS CONVALESCING FROM COVID-19
INVESTIGATIONAL PRODUCT FOR USE EXCLUSIVELY WITHIN THE CONPLAS-19 CLINICAL TRIAL
SARS-CoV-2 RNA PCR NEGATIVE; SARS-CoV-2 IgG POSITIVE
STORAGE AND DISTRIBUTION OF PLASMA UNITS FROM CONVALESCENT DONORS
Plasma units will be stored and transported following European indications (up to 36 months at a temperature of -80ºC or 3 months between -18ºC and -25ºC). During transport, it will be ensured that the plasma is kept frozen until its delivery to the receiving centre.

4.2.8. Transfusion of plasma units from convalescent donors

The transfusion procedure will follow the requirements established for any transfusion within the usual clinical practice, ensuring ABO compatibility and always being carried out under the structure of a hospital Transfusion Service and under the supervision of a specialist in Haematology and Hemotherapy. The usual traceability records will be maintained using the computer transfusion management systems available in the Transfusion Services, or alternatively using a specific computer system for the management of the units of this clinical trial.
The adverse effects associated with the infusion of the plasma units of this research study will be recorded following a Hemovigilance procedure with follow-up of the transfusion until 24h after the transfusion (See attached annex, included in the Safety section of this EC).

4.2.9. Adverse events

4.2.9.1. Monitoring and recording of adverse events.

An adverse event (AA) is any harmful, unintended, or unfavourable medical event that occurs or worsens in a patient over the course of a study. It may be a new concurrent disease, the worsening of a concomitant disease, an injury, or any concomitant deterioration of the patient's state of health, including its analytical results regardless of its cause. Any worsening (i.e., any adverse and clinically significant variation in the frequency or intensity of an ailment that was present prior to study treatment) should be considered an AA. The diagnosis or syndrome is recorded in the Data Collection Notebook (CRD).

The investigator must record all non-serious and severe AAs related to the study treatment that occur from the signing of the informed consent up to 30 days after the last dose of the investigational treatment. Severe AA (AAG) that occurs after the signing of the informed consent but before initiating treatment should also be recorded.

The assessment of the AA will include the following aspects:

- Gravity: An AAG is all AA thathttps://correu.ssib.es/owa/ - _msocom_1 :

1. Deathrolls.
2. Threaten life (an AA that, in the opinion of the investigator, carries an immediate risk of death).
3. Hospitalization or prolongation of hospitalization is necessary (hospitalization is defined as a hospital admission, regardless of the length of stay). Scheduled hospitalization, for socio-sanitary reasons or, for this study, that derived from COVID-19, will not be considered an AAG.
4. Persistent or significant disability or disability (substantial impairment of the patient's ability to perform normal activities).
5. Give rise to a congenital anomaly or birth defect.
6. It is an important medical event.

-Severity: The severity/intensity of adverse events (AA) is classified based on the patient's symptoms according to the current version of the toxicity criteria
common for adverse events (CTCAE, Version 5.0);
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

- Causal relationship: The relationship will be defined as **suspicious** in a situation where there is a reasonable possibility that the administration of the investigational medicinal product caused the adverse event. When there is a remote or low probability that the event is related to the study drug then the relationship will be defined as non-suspicious**.**

-Duration: The start and end dates of the AA must be determined.

- Measures adopted: The actions carried out as a result of the AA and in reference to the study treatment must be indicated. Concomitant treatment should also be recorded if concomitant treatment is required.
- Outcome: The researcher will communicate the outcome of the events, whether it is an AA or an AAG (total recovery, recovery with sequelae, fatal, not recovered / continuous).

4.2.9.2. Reporting of adverse events

The sponsor or designated person is responsible for reporting the AAG to the Research Ethics Committee and for providing it with all relevant initial and follow-up information about the event. The researcher must keep a copy of all AAG information in his or her file, including correspondence with the sponsor and the Research Ethics Committee.
The researcher must keep copies of all AAG information in a file, including correspondence with the sponsor.
The sponsor or designated person shall notify the relevant Authorities of all relevant and unexpected information on AAG suspected of being related to the study medication, causing death or threatening life, as soon as possible and in any case within a maximum period of seven days of becoming aware of them. Relevant follow-up information on these cases will be notified subsequently, within an additional eight days.

Any other serious and unexpected event suspected to be related to the study medication, as soon as possible, but within a maximum period of fifteen days after the investigator becomes aware of them. The researcher should keep a copy of all relevant security information in his or her file.

-Contact details of the promoter (coincides with the fact that he will be the person in charge of communicating the AA):
Maria Arrizabalaga Asenjo
Son Llàtzer University Hospital, Internal Medicine Service
marrizab@hsll.es

Phone: +34 871 202 095, 34 871 202 038

4.2.10. Sample size calculation

In the first version of the study, the sample size has been calculated considering the context of the first COVID outbreak and taking into account that it was a unicentric study, so the following was considered:

Given that this is a unicentric study in which the experimental treatment is applied in certain phases and on specific days, and that depends on the ability to obtain donors and patients with specific characteristics, added to the context in which it is carried out, in which the number of patients hospitalized in HUSLL decreases every day, adding the factor that in the Balearic Islands the number of hospitalized has been lower, added to not having any definitive data so far that allows us to calculate the sample size safely and due to the urgency of the situation. It is required to collect the plasma sample from patients discharged from HUSLL and apply it to all those hospitalized patients who agree to participate in the study after being informed and signing the informed consent, both those hospitalized in the COVID-19 plant and in the HUSLL ICU. This is further justified if we consider the fact that currently in HUSLL there are less than 100 patients admitted for COVID-19, which is a low number, taking into account also that not everyone will want to participate. Therefore, plasma must be collected, and treatment applied to all those who sign the informed consent.

In this new version of the study (version 2.0) the context of the study changes, since it is a multicentre study, and the epidemiological framework is slightly better known. Therefore, the sample size is estimated as follows:

Since from the beginning of the pandemic to the present day no effective treatment against SARS-Cov-2 infection has been found; whereas it has also been shown that the disease has a high probability of progressing rapidly into more severe forms, causing death even in vulnerable groups; whereas the forecast for late summer-start autumn 2020 is being met; whereas there are no prevalence/incidence numbers or any other type of definitive numerical data that allows canonical sample size calculations to be made; whereas the few studies that have been published on the treatment of hyperimmune plasma infection have shown a positive trend towards decreasing symptoms and severity; and that finally we continue to find ourselves in a health emergency situation; so for all these reasons this study is transformed into a multicentre study, at the request of the participating centres. Therefore, it is required, in order to estimate with maximum efficiency, the effect of this therapy, the maximum number of donors and the maximum number of possible recipients. Each case is explained below:

-*For donors*: it is required to collect the plasma sample from the maximum number of people who meet the requirements to be donors. This aims to create an anti-SARS-Cov-2 hyperimmune plasma bank, so that not only for this study, but for serious situations in which all the possibilities available so far have been exhausted, this therapy can be used as an alternative. The difficulty of finding suitable donors, who not only meet the requirements to be donors, but also have a sufficient antibody titration, forces us to make accurate donor lists in order to have this type of sample in sufficient quantity. Being a multicentre study, more doses of plasma will be needed to be able to supply all the centres. Considering that the ratio is 1 donor or 1 donation for each recipient.

-*For recipients*: as it is unknown how many patients can progress in the coming weeks/months with COVID-19, it is required to propose participation in the study to all patients who are diagnosed with COVID-19 and admitted to the plant or ICU for COVID-19 of all participating centres. In this way, the maximum number of patients can be collected, in order to cover a sufficient sample size in the two branches of comparison of the study (control and treatment). As patients are admitted, they will be proposed to participate by explanation and with the HIP, and if they sign the IC, they will become part of it.

4.3. Development of the study: work plan and data collection

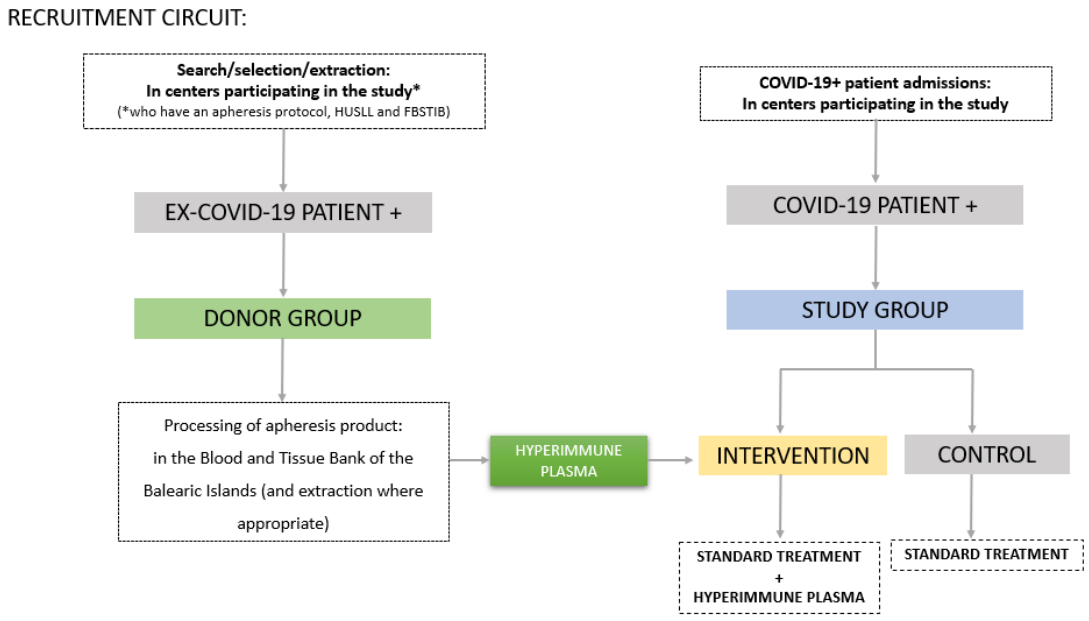

Fig 2. Outline of the development of study.

4.3.1. Stages of study and evaluation of the response

a) The study procedures for the patient receiving treatment shall be carried out as follows:

1. Baseline visit/screening:

- Review of inclusion and exclusion criteria: HIP and CI signature.
- Vital signs: Blood pressure, Heart rate, Respiratory rate, Temperature, and oxygen saturation.
- Complete physical examination.

- Review of relevant medical history.
- Rx of Tx
- Electrocardiogram.
- Weight, height, Body mass index.
- ECOG.
- Complete hematimetry.
- Coagulation study, D-dimer.
- Arterial blood gas.
- Biochemical analysis: Glucose, creatinine, glomerular filtration (CKD-EPI), sodium, potassium, chlorine, or rhea, urate, calcium, ferritin, C-reactive protein, AST, ALT, GGT, FA, LDH, CPK, troponin, procalcitonin.
- Inflammatory parameters: IL-6.
- Serology HIV, HVC, HVB, SYPHILIS.
- Imaging tests according to usual practice.
- Real Time-PCR for detection of Coronavirus SARS-COV-2 in nasal smear and pharynx.
- Quantitative determination of antibodies (IgG, IgM) against Coronavirus SARS-COV-2.
- Immunohematological study (ABO Group, Rh, Indirect Coombs).
- Concomitant medication evaluation.

2. Treatment initiation visit (First dose: day 1): Marked procedures (*) do not need to be repeated if performed at baseline in the previous 7 days:

- Study treatment assignment: if it is an intervention group, first plasma infusion.
- Vital signs (TA, FC, FR, Tª) pre-infusion and post-infusion*.
- Complete physical examination*.
- ECOG*.
- Hematimetry*.
- Biochemical analysis*.
- Inflammatory parameters*.
- Concomitant medication evaluation.
- Evaluation of emerging adverse effects.

3. Visit of Day 2:

- if it is an intervention group, second plasma infusion.
- Concomitant medication evaluation.
- Evaluation of emerging adverse effects.

4. Visit of Day 3:

- Vital signs (TA, FC, FR, Tª).

- Physical examination.
- ECOG.
- Hematimetry.
- Biochemical analysis.
- Inflammatory parameters.
- Nasal and pharyngeal smear for RT-PCR of Coronavirus SARS-COV-2.
- Quantitative determination of antibodies (IgG, IgM) against Coronavirus SARS-COV-2.
- Concomitant medication evaluation.
- Evaluation of emerging adverse effects.
- Clinical/virological response evaluation.

5. Visit of Day 7:

- Vital signs (TA, FC, FR, Tª).
- Physical examination.
- ECOG.
- Hematimetry.
- Biochemical analysis.
- Inflammatory parameters.
- ECG.
- Nasal and pharyngeal smear for RT-PCR of Coronavirus SARS-COV-2
- Quantitative determination of antibodies (IgG, IgM) against Coronavirus SARS-COV-2.
- Concomitant medication evaluation
- Evaluation of emerging adverse effects.
- Clinical/virological response evaluation.

6. Visit of Day 14:

- Vital signs (TA, FC, FR, Tª).
- Physical examination.
- Hematimetry.
- Biochemical analysis.
- Nasal and pharyngeal smear for RT-PCR of Coronavirus SARS-COV-2.
- Quantitative determination of antibodies (IgG, IgM) against Coronavirus SARS-COV-2.
- Concomitant medication evaluation.
- Evaluation of emerging adverse effects.
- Clinical/virological response evaluation.

7. Visit of Day 21/end of study (at discharge):

- Vital signs (TA, FC, FR, Tª).
- Physical examination.

- Rx of Tx to assess evolution/resolution of infiltrates.
- ECG.
- ECOG.
- Hematimetry.
- Biochemical analysis.
- Inflammatory parameters.
- Real Time-PCR for SARS-COV-2 viral load study.
- Quantitative determination of antibodies (IgG, IgM) against Coronavirus SARS-COV-2.
- Concomitant medication evaluation.
- Evaluation of emerging adverse effects.
- Clinical/virological response evaluation.

IMPORTANT: In cases where the patient is discharged after 7 days, visits on day 14 and day 21 can be made on an outpatient basis, in outpatient consultations or day hospital, after appointment with the patient.

Screening visits and day 1 may overlap on the same date threaten life the inclusion criteria are confirmed and none of the exclusion is met.

There will be a margin of +/- 24 hours to perform the procedures of visits 7, 14 and 21 (to be able to adjust the appointments in external consultation).

The study procedures for study subjects (control and treatment groups) can be reviewed in summary form in the following table:

Procedure	Study days						
	Screening/ Basal	Day 1*	Day 2	Day 3	Day 7	Day 14	Day 21
DATE							
Signature of informed consent	X						
Medical history review	X						
Physical examination	X	X*		X	X	X	X
Vitals signs	X	X*		X	X	X	X
Weight, Height, BMI	X						
ECOG	X	X*		X	X	X	X
ECG	X				X		X
ABO/Rh Group	X						
Hematimetry	X	X*		X	X	X	X
Coagulation	X	X*		X	X	X	X
Biochemistry	X	X*		X	X	X	X
Study of inflammatory parameters	X			X	X		X
Serology Important IgG/IgM anti-COVID	X			x	x	x	x
Quantitative titration antibodies	X			X	X	X	X
COVID PCR	X			X	X	X	X
Chest Rx	x						x
AE Review	X	X	X	X	X	X	X
Concomitant review	X	X	X	X	X	X	X
Clinical response	X			X	X	X	X
PLASMA TRANSFUSION		X	X				

Table 3. Summary of procedures in the study subjects.

LEGEND:

-DATE: indicate the patient's follow-up date.
-Screening/Basal VISIT**:** this visit corresponds to the moment the patient signs the informed consent.
-DAY 1: corresponds to the time of the first plasma transfusion.

EXPLANATION:
- SCREENING/BASAL VISIT AND DAY 1 MAY COINCIDE. In this case it is not necessary to repeat the determinations of day 1. The marked procedures (*) do not need to be repeated if they were performed at the screening visit in the previous 7 days.

b) The study procedures for the plasma donor subject are as follows:

1. Basal visit:

- Review of inclusion and exclusion criteria: HIP and CI signature.
- Extraction of nasal/pharyngeal smears for the determination by RT-PCR of Coronavirus SARS CoV-2.
- Serum extraction for determination of antibodies (IgG, IgM) SARS-COV-2.
- Serological determinations.
- Complete physical examination.

2. Visit for the performance of plasmapheresis: Performance of the procedures as set out in point 4.2.6

4.3.2. Duration of the study

In version 1.0 of the study, the estimated study duration period was 3 months from the date of compliance with the Clinical Research Ethics Committee (in Spain CEIm) Research Ethics Committee (CEIm) and Spanish Agency for Medicines and Health Products (in Spain AEMPS). In this version 2.0 the study period is extended to recruit a sufficient n to be able to estimate the effectiveness of the treatment or failing that until the competent authorities so determine. The follow-up period for patients will be 21 days from the start date of the study and if necessary, it will be extended as long as necessary, in order to ensure patient safety.

4.3.3. Primary and secondary variables

The variables that will be collected will be those related to the study of the efficacy, tolerance, safety and clinical effects of the treatment. Below is the list of encoded variables:

VARIABLE NAME	UNITS	CODING	VALUE
Diagnostic date			Date
Date of birth			Date
Age	years		Number
Presence of concomitant disease		0	Yes
		1	No
Concomitant disease specifies			Name

Sex		0	Man
		1	Woman
Weight	Kg		Number
Height	cm		Number
Body mass index	Kg/cm^2		Number
Physical examination		0	Normal
		1	Clinically insignificant abnormality
		2	Clinically significant abnormality
Physical scans specify			Number
Blood pressure	mmHG		Number
Heart rate	lpm		Number
Respiratory rate	rpm		Number
Temperature	ºC		Number
Oxygen saturation	$\%O_2$		Number
ECOG		0	Asymptomatic. Fully active.
		1	Intense activity restriction. Capable of daily work.
		2	Ambulatory and capable of self-care. Unable to work. Lifted more than 50% of the time awake.
		3	Capable of some self-care. Bed-chair life more than 50% of the time awake.
		4	Total disability. Chair-bed 100% of the time awake.
		5	Dead.
Electrocardiogram		0	Normal
		1	Abnormal. Clinically not significant.
		2	Abnormal. Clinically significant.
Concomitant medication		0	No
		1	Yes
Chest X-ray			Assessment
Concomitant medication specifies			Name
ANALYTICAL PARAMETERS			
Haemoglobin	g/dl		Number
Haematocrit	%		Number

Leukocytes	x10^9/l		Number
Absolute lymphocytes	x10^9/l		Number
Absolute neutrophil count	x10^9/l		Number
Monocytes	x10^9/l		Number
Eosinophils	x10^9/l		Number
Basophils	x10^9/l		Number
Medium Corpuscular Volume	fl		Number
Platelets	x109/l		Number
Prothrombin time	s		Number
Activated Partial Thromboplastin Time (APTT)	s		Number
INR			Number
Fibrinogen	mg/dl		Number
D-dimer	mg/dl		Number
Glucose	mg/dl		Number
Creatinine	mg/dl		Number
Glomerular filtration (CKD-EPI)	ml/min		Number
Sodium	mEq/l		Number
Potassium	mEq/l		Number
Chlorine	mEq/l		Number
Calcium	mg/dl		Number
Urea	mg/dl		Number
Urate	mg/dl		Number
Albumin	mg/dl		Number
Total proteins	mg/dl		Number
Iron	µg/dl		Number
Ferritin	ng/ml		Number
Ferry	mg/dl		Number
transferrin saturation index	%		Number
Reactive protein C	mg/dl		Number
AST	U/L		Number
ALT	U/L		Number
GGT	U/L		Number

LDH	U/L		Number
FA	U/L		Number
CPK	U/L		Number
Troponin I			Number
Procalcitonin			Number
IL-1			Number
Blood pH arterial blood gas			Number
PO_2	mmHg		Number
HIV Serology		0	Negative
		1	Positive
HVB Serology		0	Acute infection
		1	Chronic infection
		2	Past infection
		3	Immunized
		4	Negative
CMV Serology		0	Negative
		1	Positive
Syphilis Serology		0	Negative
		1	Positive
INMHEMATOLOGIC STUDY			
AB0 Blood Group		0	A
		1	B
		2	AB
		3	0
Rh		0	Present
		1	Absent
Irregular Blood Group antibodies		0	Negative
		1	Positive
DIAGNOSTIC/MICROBIOLOGICAL PROCEDURES			
Quantitative titration of SARS-COV2 antibodies (IgG/IgM)		UA/mL	Number
RT-PCR SARS-COV-2		0	Negative
		1	Positive

Time to RT-PCR negativization	Days		Number
CLINICAL CRITERIA			
Pleural effusion		0	Negative
		1	Positive
PSI score		1	Valuation not required
		2	<=70
		3	71 - 90
		4	91 - 130
		5	>130
WHO Progression Scale		0	Uninfected; no viral RNA detection.
		1	Asymptomatic; viral RNA detection
		2	Symptomatic. Independent
		3	Symptomatic. Need for assistance
		4	Hospitalized. Oxygen-free
		5	Hospitalized. Oxygen with mask or nasal tips
		6	Hospitalized. Oxygen by non-invasive ventilation (NIV) or high flow.
		7	Intubation or mechanical ventilation. PO2/ FIO2>= 150; or SpO2/ FO2> 200
		8	Mechanical ventilation (pO2/FIO2< 150, or SpO2/FIO2< 200), or vasopressor (norepinephrine >0.3 microg/Kg/min)
		9	Mechanical ventilation (pO2/FIO2< 150, or SpO2/FIO2< 200), or vasopressor (norepinephrine >0,3 microg/Kg/min) o dialysis o ECMO
% of patients requiring ICU admission			Number
15-day mortality rate			Number
Mortality rate at 30 days			Number
Days of hospitalization			Number
SECURITY CRITERIA			
Emerging adverse effects (ASD) ≥ GIII		0	No
		1	Yes
Type TEAE SPECIFY			Name
Cumulative rate/incidence of ASD ≥ GIII in experimental branch			Number

Cumulative rate/incidence of emerging adverse events (ASD) any grade in experimental branch			Number
Hospital discharge date			Date
Exitus		0	Yes
		1	No

Table 1. Variables that will be included in the database of the study.

4.3.4. Work plan and data collection

TASKS	YEAR 2020					Responsible units
MONTHS	1	2	3	4	Months Successive	
Design version 1.0, CI approval, CEIm, communication to the AEMPS, application for financing	x					Haematology, Internal Medicine, Intensive Medicine, Research Unit, Microbiology
Obtaining IdISBa financing		x				Haematology, Internal Medicine, Research Unit
Revision version 1.0, writing version 2.0 (multicentre study)			x			Haematology, Internal Medicine, Research Unit
Commissioning		x				Haematology, Internal Medicine, Intensive Medicine, Research Unit, Microbiology
Patient Recruitment		x	x	x	x	Haematology, Internal Medicine,
Experimental phase		x	x	x	x	Haematology, Internal Medicine, Intensive Medicine, Microbiology, Clinical Analysis
Data collection		x	x	x	x	Coordination of Haematology trials
Data analysis			x	x	x	Research Unit
Dissemination of results			x	x	x	Haematology, Internal Medicine, Intensive Medicine, Research Unit

Table 2. Schedule of the phases of the study.

5. DATA ANALYSIS: STATISTICS

A descriptive analysis of all variables will be performed. With the categorical variables, the global percentages and frequencies will be estimated. Normality tests and graphs will be used to determine if the quantitative variables follow a normal distribution. Normal distribution variables shall be expressed as mean ± standard deviation and those without normal distribution shall be expressed as median and interquartile range. To describe the significance and associations between variables after the intervention, parametric and non-parametric tests will be used as appropriate (the student's t test of paired samples or the Wilcoxon test for quantitative variables and the ANOVA test for paired samples or Friedman test for qualitative variables). The correlations will be examined by the correlation of Spearman or Pearson ranges and a multivariate analysis will be performed to assess the effect of other factors such as the confusion/interaction effect, as well as to assess the possible construction of predictive models. A p-value < 0,05 shall be considered an indicator of a significant difference. SPSS v.23 software will be used for data analysis.

6. ETHICAL ASPECTS

6.1. General considerations

The study will be conducted in accordance with the standards of Good Clinical Practice and Guidelines of the International Conference on Harmonization [ICH]. In accordance with the criteria of good clinical practice, the subjects will be duly informed of all those details concerning their participation in the study and will freely give their written consent. For the use of the data contained in this register, as in any scientific research project, it will be necessary:

- Approval by the Clinical Research Ethics Committee (in Spain CEIm) local of the study author centre.

- Approval by the Scientific Committee, a body that will be constituted to give scientific performance to the database.

Scientific responsible for the registry: Dr. Joan Bargay, Haematology Service, Son Llàtzer University Hospital.

The clinical trial shall be conducted in accordance with the protocol, the principles set out in the current revised version of the Declaration of Helsinki (Annex 1) and the applicable regulatory requirements, in particular the ICH Good Clinical Practice Guidelines (1996), Regulation (EU) No

536/2014 on clinical trials with medicinal products for human use, and the applicable local regulations (in Spain, the Royal Decree on Clinical Trials 1090/2015).

The ICH guidelines require the approval of the health authorities and the favourable opinion of an accredited Clinical Research Ethics Committee (in Spain CEIm) before the inclusion of patients in clinical trials. Prior to the start of the study, the protocol, informed consent, materials to be used for patient recruitment (if applicable), and any other written information in connection with the trial provided to the patient will be approved by the CEIm.

AMENDMENTS TO THE PROTOCOL:

Any modification of the study protocol shall always take the form of an amendment or addendum in writing. For its formalization, it must be issued in writing to the CEIm and the Health Authorities for approval before the proposed changes are implemented. After approval by the CEIm, the AEMPs will be immediately informed of the study, for its correct classification and obtaining supporting documentation.

6.2. Patient Information and Type of Informed Consent

Each participating subject must voluntarily give their written consent before the start of the study in order to be included in it. To do this, researchers must ensure that the patient receives adequate verbal and written information regarding the nature, purpose and possible consequences of the study in a language understandable to him. Subjects must also be informed of their full freedom to withdraw at any time without prejudice. They will be allowed to ask the questions they deem appropriate and will be given time to consider their decision.

The patient information and informed consent to be provided for the study are in ANNEXES I and II. The investigator shall retain the informed consent form, signed, and dated by the patient, of all subjects included in the clinical trial.

6.3. Confidentiality

All data will be treated maintaining confidentiality in accordance with current legislation on the protection of personal data. Subjects will be identified only by code. The data of the subjects

included in it will be treated in accordance with Organic Law 3/2018, of December 5, on the Protection of Personal Data and guarantee of digital rights.

6.4. Study insurance

The study is covered by the healthcare insurance of the Health Service of the Balearic Islands, who will cover possible complications if they occur.

7. PRACTICAL CONSIDERATIONS: LIMITATIONS

7.1. Conditions for data collection, handling, processing and corrections

All patient data generated in this study will be collected in the CRD which has been specifically designed to collect the clinical, diagnostic test and radiological analysis data that are necessary for this study.

The principal investigator will be responsible for properly archiving and maintaining the data and all documentation related to the conduct of the study.

7.2. Conditions of publication

The information obtained from this study will be analysed together and before its publication must be evaluated by all the researchers participating in the study. In each publication that derives from this study, the contribution in terms of tasks, of each member of the research team, in it, will be specified.

8. SCIENTIFIC RELEVANCE AND APPLICABILITY

There is currently no proven effective therapy to treat COVID-19 infection, having become a global pandemic that affects not only the health of the world's population, but also its economy. Until an effective vaccine against this virus is found, it is vital to find therapies that, although they do not have the efficacy of a vaccine, serve as a palliative to mitigate the consequences of the infection and

/ or prevent progression to more severe stages of the disease. As has happened in other epidemics, treatment with hyperimmune plasma could be a reinforcement therapy along with the usual treatments, which could serve as palliative therapy, trying to avoid the aggravation of the disease. Since the writing of version 1.0 of this study (end March-start April 2020), epidemiologically two events have occurred, on the one hand a decrease in the number of cases, due to the confinement effect, and on the other hand the reversal of this same fact, due to the effect of post-confinement social contact. Currently, at the end of July 2020, there is a scenario in which new cases and small outbreaks arise every day in an increasingly exponential way, so a new great preoutbreak is expected in the coming months. Hence, the interest on the part of other centres in being part of the study arises, as this is the first and only one in the Balearic Islands, of these characteristics, which has the approval of all the competent authorities. That is why this amendment is being tabled, which aims to make the study multicentre.

At the level of infectivity, it could also be useful since these patients when receiving anti-COVID-19 antibodies, could be less infective, and therefore in this way contribute to reduce the rate of contagion. A factor that not only affects the health of people, but also the development of the daily activities of the population and therefore its economy. The study is one more among the many that are suddenly being carried out throughout the world, however, any effort to contribute to the scientific research of this disease is fundamental and is not in any case vein, since little is known about the therapeutic part of this infection. Therefore, any possible effort to generate knowledge is clearly justified.

On the other hand, it is reflected in the scientific articles that the scientific community is also calling for this type of study , specifically, they indicate that guidance would be needed to direct blood banks to begin prioritizing collections of CONVALESCENT COVID-19 donors; accelerate the availability of these products for therapeutic use; create a data collection, analysis and regulatory infrastructure to identify factors predicting therapeutic efficacy and report relative levels of convalescent plasma vs H-Ig production; and remove regulatory barriers that, for example, currently limit the use of pathogen reduction technology for convalescent plasma collections or that require multi-month inventory reserves for H- pharmaceuticals. For all these reasons, the study presented could contribute to the provision of data referring to the above.

9. FINANCING-PROMOTER

This study in its version 1.0 was presented in the special call*: call for expressions of interest for research and innovation projects in relation to COVID-19* of Health Research Institute of the Balearic Islands, in April 2020. Being financed in May 2020 with € 17,000 for its execution.

Below is the funding that was requested in the call and that appears in version 1.0 of this study:

The Son Llàtzer University Hospital will act as promoter, represented by the Principal Investigator, Maria Arrizabalaga, belonging to the Internal Medicine service of the Son Llàtzer University Hospital and member of the Infectious Diseases research group of Health Research Institute of the Balearic Islands. For practical purposes, the IP or, failing that, a delegated person will be responsible for notification to the ethics committee or regulatory agencies.

The Son Llàtzer University Hospital is committed to providing some technical means necessary to carry out the study, such as the techniques that must be performed in the blood bank, the application of drugs for the treatment of patients, the viremia tests (RT-PCR) for the detection of COVID-19. However, some additional material means will be lacking, which we currently lack, and for which an economic investment will have to be made. To this end, aid will be requested in the *call for expressions of interest for research and innovation projects in relation to COVID-19* of Health Research Institute of the Balearic Islands

The following are some of the necessary materials that must be purchased:

-Kit for the quantification by ELISA of Antibodies (IgG/IgM) in serum of patients (COVID-19),

1 box = 1 plate of 96 wells price: 690€ *3 boxes (due to making copies) = 2070 €

-Thermo Scientific™ Vertical Deep Freezer -86 °C 88000 series shape™ with security and alarm system: 16.441 €

- Antibodies for study of immune profile/markers of inflammation:

TNF-alpha; IL-6; IL-1: 1500 €

- Laboratory consumables: 1000 €

- Consumable material to preserve samples: 600 €

- PPE for sample handling: 500 €

- Sample courier for category A 1 refrigerated box: 1300 €

Total estimated according to prices consulted with commercial houses as of 17/04/2020, € 23,411, prices can be adjusted as the material is requested once the specific commercial houses have been chosen.

Financial aid is essential to collaborate with the expenses that the Son Llàtzer University Hospital will already assume, and to be able to finance these expenses in whole or in part.

In version 2.0 it is added that, for its part, also, due to new ministerial orders, Blood and Tissue Bank of the Balearic Islands undertakes to perform the plasmapheresis of the donors, and manage the samples of possible donors belonging to the different centres participating in the study.

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B. ANNEXED DOCUMENTS

Annex I. Recipient Patient Information Sheet (HIP-RECIPIENT)

PATIENT INFORMATION SHEET FOR CONDUCTING CLINICAL TRIALS

Version 2.0 August 13, 2020

STUDY TITLE: ***Study of the efficacy of strengthening standard therapy for COVID-19 patients with repeated transfusion of immune plasma from COVID-19 convalescents vs exclusive standard therapy in hospitalized COVID-19 patients.***
PROMOTER: Son Llàtzer University Hospital
PRINCIPAL INVESTIGATOR:
Maria Arrizabalaga Asenjo (Adjunct Specialist Physician, MI-infectious): marrizab@hsll.es
Joan Bargay Lleonart (Head of Haematology Service): jbargay@hsll.es
CENTER: Son Llàtzer University Hospital

INTRODUCTION

We are writing to inform you about a study in which you are invited to participate. The study has been approved by the Research Ethics Committee of the Balearic Islands, in accordance with current legislation, and is carried out in compliance with the principles set forth in the Declaration of Helsinki and the standards of good clinical practice.

Our intention is only that you receive the correct and sufficient information so that you can evaluate and judge whether or not you want to participate in this study. To do this, read this fact sheet carefully and we will clarify any doubts that may arise after the explanation. In addition, you can consult with the people you deem appropriate. If you have any questions, please contact:
Maria Arrizabalaga Asenjo Son Llàtzer University Hospital, Internal Medicine Service, 2nd floor, 871 202095.
Joan Bargay Lleonart, Son Llàtzer University Hospital, Hematology Service, 3rd floor, 871 202138.

OVERVIEW

The Haematology/Internal Medicine Service of this hospital is conducting a clinical research study. This consists of studying the efficacy and safety of plasma treatment of convalescent patients infected with COVID-19administered for two days together with the standard treatment available.

The objective is to determine the clinical benefit of plasma treatment of ex-convalescent patients infected with COVID-19.

You are invited to participate in the study, in which all patients at the Son Llàtzer University Hospital with COVID-19 will participate.

The study is approved by an accredited Clinical Research Ethics Committee and by the Spanish Agency for Medicines and Health Products. It will be carried out following the Declaration of Helsinki and the requirements established in Royal Decree 1090/2015, of

December 4, which regulates clinical trials with medicines, the Ethics Committees of Research with medicines and the Spanish Registry of Clinical Studies.

The study consists of the administration of compatible plasma from ex-convalescent COVID-19 patients, that is, people who have passed the infection and now have antibodies against the virus that causes the disease but are negative in the tests for the COVID-19 virus (that is, they do not have a viral load in patients with the active COVID-19 disease.

This administration will be carried out on two consecutive days from the moment of signing the informed consent. Each infusion will consist of 300 ml of plasma intravenously, from a single donor negative for COVID-19 viremia.

This plasma infusion with active antibodies against the virus that causes COVID-19 disease can give you the benefit of improving the response to the disease.

In addition to plasma treatment, the responsible physician will provide you with all currently available treatments for COVID-19 disease.

The duration of the study will be 21 days from the start of plasma treatment.

If you choose to participate in the trial, you will be tested to see if you qualify for it. This will be done at the selection visit. If you meet the requirements of the trial, you can begin your participation. During the study, a whole series of laboratory and diagnostic tests will be carried out as shown in the following table:

Procedure	Study days						
	Screening/ Basal	Day 1*	Day 2	Day 3	Day 7	Day 14	Day 21
DATE							
Signature of informed consent	X						
Medical history review	X						
Physical examination	X	X*		X	X	X	X
Vitals signs	X	X*		X	X	X	X
Weight, Height, BMI	X						
ECOG	X	X*		X	X	X	X
ECG	X				X		X
ABO/Rh Blood Group	X						
Hematimetry	X	X*		X	X	X	X
Coagulation	X	X*		X	X	X	X
Biochemistry	X	X*		X	X	X	X
Study of inflammatory parameters	X			X	X		X
Serology Important IgG/IgM anti-COVID	X			x	x	x	x
Quantitative titration antibodies	X			X	X	X	X
COVID PCR	X			X	X	X	X
Chest Rx	x						x
AE Review	X	X	X	X	X	X	X
Concomitant review	X	X	X	X	X	X	X
Clinical response	X			X	X	X	X
PLASMA TRANSFUSION		X	X				

For the collection of blood samples during the study, the usual procedure will be followed in each participating centre.

Plasma donors will be chosen by the doctors responsible for the study following the recommendations of the Scientific Committee for Transfusion Safety (SCTS), the recommendations of the Blood and Tissue Bank of the Balearic Islands and following the transfusion protocols of the Blood Bank of the Son Llàtzer University Hospital. Donor plasma will be tested to ensure the presence of antibodies against the COVID-19 disease virus.

All patients admitted to the inpatient units (inpatient units for COVID-19 patients and intensive care units) will be requested to participate in the study.

What are the expected benefits and potential risks of this study?

The benefit of this study is to be able to determine the efficacy of reinforcing the standard treatment with repeated infusions of plasma from people convalescing from the COVID-19

disease already discharged and / or with results in negative COVID-19 detection tests, transfused to COVID-19 patients still hospitalized, both COVID-19 floor and Son LLátzer University Hospital ICU, comparing it with the results obtained with the exclusive standard treatment that is being used in patients infected with COVID-19 of the same characteristics as the treatment group. Therefore, to evaluate the immunological efficacy of standard treatment reinforcement vs standard therapy without reinforcement.

Risks arising from the study.

Participating in this trial may involve certain risks, derived from the drugs used or from plasma transfusion. If you participate in this trial, you or your family members should immediately notify the study physician or your collaborators if you have unusual health problems, injuries, or side effects, even if you believe they are not due to the trial or the study drug.

Procedures performed during this clinical trial may result in certain discomfort. Most tests are used in routine clinical practice to evaluate a disease like yours.

Risks arising from plasma transfusion.

A very low risk (less than 1 per 95,000 transfusions), but not zero, of contracting infections with hepatitis C, hepatitis B, human immunodeficiency (AIDS) or other less frequent viruses. Although the selection of donors is very careful and the precautions to detect contaminated blood are maximum, there is an initial phase in infectious diseases (window period) in which infectious agents are not detectable in the blood and therefore make there always a minimum possibility of contagion.

Transfusion reactions. By allergic type processes due to the effect of certain components (proteins) of the donor that are foreign to the recipient. Mild reactions (fever, chills) are relatively common and easy to treat. Very rarely these reactions can be severe or very serious and compromise the patient's life (respiratory failure, severe hypotension, or even cardio-respiratory arrest).

What if your partner is pregnant when you start this trial?

In case of pregnancy, you should inform the doctor of the study immediately. On the other hand, in order to collect information about the pregnant woman or the baby, in the case that is considered appropriate, the study doctor will notify the sponsor of the pregnancy and as well as the information sheet will be provided to the patient and the informed consent for the pregnant woman.

Study procedures

The following describes the known risks and side effects of the tests or procedures related to the trial.

Blood draw: Possible side effects of a blood draw are tenderness, pain, bruising, bleeding, or infection at the injection site. Drawing blood can also make you nauseous or dizzy.

Electrocardiogram (ECG): An ECG is a record of the normal electrical activity of the heart, which is obtained by putting electrodes (stickers connected to wires) on the skin of the chest, arms, and legs. Sometimes stickers cause mild skin irritation.

ALTERNATIVE TREATMENTS

At present, apart from the standard treatment to be used for COVID-19, there are no other alternative treatments approved by the authorities and laboratories or the European Union. The study doctor will give you more information if you wish.

OTHER RELEVANT INFORMATION

The treatment of COVID-19 disease with plasma from convalescent patients is not currently approved by the Spanish and European health authorities. This treatment is beginning to be applied in the different hospitals in Spain and Europe under the protection of clinical trials and observational studies. However, there is no previous extensive experience of plasma treatment of convalescent patients as it is a new health emergency.

Any new information regarding the treatment of the study and that may affect your willingness to participate in the study, which is discovered during your participation, will be communicated to you by your doctor as soon as possible.

If you decide to withdraw consent to participate in this study, no new data will be added to the database and may require the destruction of all previously retained identifiable samples to prevent further analysis, although those responsible for the study may continue to use the information collected about you until that time, unless you expressly object.

You should also know that you can be removed from the study in case those responsible for the study consider it appropriate, either for safety reasons, for any adverse event that occurs due to the medication under study or because they consider that you are not complying with the established procedures. In either case, you will receive an adequate explanation of the reason for your withdrawal from the study.

If you are removed from the study for any of the reasons stated, the only thing that will change will be that you will not receive the reinforcement with immunological therapy, that is, you will not receive the plasma transfusion, but you will continue with the treatment scheduled for your disease following the protocols for COVID-19 patients.

By signing the attached consent sheet, you agree to comply with the study procedures that have been exposed to you.

CONFIDENTIALITY

Responsible for the file: health service of the Balearic Islands.

Purpose of collection: Clinical trial

Legitimation: Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights.

Recipients: There is no transfer of data to third parties.

Rights: access, rectify and delete data, as well as opposition, limitation of treatment and portability to third parties.

Additional information: www.hsll.es

The treatment, communication, and transfer of personal data of all participating subjects will comply with the provisions of Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights in Spain.

In accordance with the provisions of the legislation, you can exercise your rights of access, rectification, deletion, opposition, limitation of data processing, including to transfer your data to an authorized third party (portability), for which you must contact the person

responsible for the treatment: Maria Arrizabalaga Asenjo, Internal Medicine Service-infectious diseases, Son Llàtzer University Hospital, Floor 1. Carretera Manacor Km 4,07198 Palma marrizab@hsll.es Tel: 871202000. Your data will be processed electronically and will be incorporated into an automated file of personal data whose responsible is the General Secretariat of the Health Service of the Balearic Islands, with headquarters at Street of la Reina Esclaramunda, 9, 07003 Palma, dpd@ibsalut.caib.es, which complies with all the security measures of restricted access to the objective described in this document.

To ensure the confidentiality of the information obtained, your data and the sample will be identified by a code and only the study doctor and collaborators will be able to relate this data to you and your medical history. Therefore, your identity will not be disclosed to any person except in case of medical emergency, requirement of the Health Administration or legal requirement.

Only the essential data necessary to carry out the study will be transmitted to third parties and other countries, and that in no case will contain information that can directly identify you, such as name and surname, initials, address, Social Security number, etc. If this assignment occurs, it will be for the same purposes of the study described and guaranteeing confidentiality at least with the level of protection of the legislation in force in our country.

Access to your personal information will be restricted to the study doctor/collaborators, health authorities, the Research Ethics Committee of the Balearic Islands, and authorized personnel, when they need it to verify the data and procedures of the study, but always maintaining the confidentiality of the same in accordance with current legislation.

You can file a claim with the Spanish Agency for Data Protection if you consider that your data protection rights have been violated.

FINANCIAL COMPENSATION

Your participation in the study will not entail any expense.

Your doctor will not receive any financial compensation for your participation in this study and has stated that there is no conflict of interest.

VOLUNTARY PARTICIPATION

You should know that your participation in this study is voluntary and that you can decide not to participate or change your decision and withdraw consent at any time, without giving any explanation, as well as request the destruction of the sample without altering the relationship with your doctor or the treatment you should receive.

If you decide to revoke your consent, no new data will be collected, nor will new analysis of the sample be carried out, but this revocation will not affect the research carried out so far.

SURE

The study in which you participate is covered by the healthcare insurance of the Health Service of the Balearic Islands, who will cover possible complications if they occur.

COLLECTION OF BIOLOGICAL SAMPLES

The blood samples that are collected will be used both for their usual treatment and for the development of this study.

The samples will be collected by the nursing service of the corresponding hospitalization unit. These samples will be analysed in the corresponding services of the centre in which you are admitted.

At the end of the research, part of the biological samples will be stored in the microbiology service of the Son Llàtzer University Hospital.

The possible risks arising from the procedure carried out to obtain these samples are covered by the insurance of the study mentioned above in the "insurance" section.

The sample will be coded and treated confidentially for the duration of this study, using a code that only the researcher and staff of your team can link with you to preserve your identity.

In case any additional data or sample is necessary, your doctor will contact you to request your collaboration again. You will be informed of the reasons and will be asked again for consent, if necessary.

It will not receive any economic benefit from the donation of the samples and the transfer of the data provided, nor will it be entitled to possible commercial benefits of the discoveries that may be achieved as a result of the research carried out.

The samples will be analysed in the biochemical and microbiology analysis laboratory of the Son Llàtzer Hospital and will be stored for 1 year, in anticipation that some additional analysis related to the objectives of the study will be necessary. During this process, the person responsible for the samples will be the promoter of the study.

In case of conservation of the samples for future uses, they will be stored in the Microbiological Analysis Service for 1 year.

At the end of the investigation, your sample may be:

1. Destroyed.
2. Anonymized (i.e., the link that links the sample to you will be completely destroyed, so that neither the researcher nor any other person on the team will be able to identify again who your sample belongs to).
3. Incorporated into a collection, whose managers are the main researchers Maria Arrizabalaga Asenjo and Joan Bargay Lleonart. This collection is in the Microbiology Service of Son Llàtzer University Hospital, so that it continues to be used in the study of the COVID-19 disease.
4. Stored in the biobank of the Son Llàtzer University Hospital to be used in other research, possibly not related to the initial study for which it consented. Samples may be transferred from the biobank for authorized projects, possibly also abroad, with a prior favourable opinion of the scientific committee and the ethics committee of the biobank. You can contact the biobank to gather information about the projects in which your samples have been used.

GRATITUDE

Whatever their decision, both the promoter and the research team want to thank you for your time and attention. You are contributing to the best knowledge and care of your disease which in the future can benefit many people.

Annex II. Informed consent of receiver (CI-RECEIVER)

INFORMED CONSENT TO THE PATIENT FOR THE CONDUCT OF CLINICAL TRIALS

Version 2.0 August 13, 2020

STUDY TITLE: ***Study of the efficacy of strengthening standard therapy for COVID-19 patients with repeated transfusion of immune plasma from COVID-19 convalescents vs exclusive standard therapy in hospitalized COVID-19 patients.***
PROMOTER: Son Llàtzer University Hospital
PRINCIPAL INVESTIGATOR:
Maria Arrizabalaga Asenjo (Adjunct Specialist Physician, MI-infectious): marrizab@hsll.es
Joan Bargay Lleonart (Head of Haematology Service): jbargay@hsll.es
CENTER: Son Llàtzer University Hospital

I, *(first and last name)* _____

_____

☐ I have read the information sheet that has been given to me.

☐ I have been able to ask questions about the study.

☐ I have received enough information about the study.

☐ I have spoken to: *(name of the researcher).*

☐ I understand that my participation is voluntary.

☐ I understand that I can withdraw from the study and request the destruction of my sample, if it has not been anonymized:

1. Whenever.
2. Without having to give explanations.
3. Without this having an impact on my medical care.

☐ I understand that, if I decide to withdraw from the study, the results obtained up to that point may continue to be used but that no further analysis of my sample will be carried out, if it has not been anonymised.

If the results of the research provide data that may interest me or my relatives: (*indicate one of the boxes*)

☐ I want to be informed.

☐ I do not want to be informed, but I accept that my doctor contacts my relatives if these results may affect them.

☐I understand that I have the rights of access, rectification, deletion, opposition, limitation of data processing, including to transfer my data to an authorized third party (portability), in accordance with the provisions of Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights.

☐ I freely consent to participate in the study and consent to the access and use of my data under the conditions detailed in the patient information sheet.

At the end of the research my sample may be:

1. ☐ Destroyed.
2. ☐ Anonymized (i.e., the link that links the sample to you will be destroyed, so that neither the researcher nor any other person on the team will be able to identify again who your sample belongs to).
3. ☐ Incorporated into a collection whose head is the researchers Maria Arrizabalaga Asenjo and Joan Bargay Lleonart, which is in the Microbiology Service of Son Llàtzer University Hospital, so that it continues to be used in the study of the COVID-19 disease.
4. ☐ Stored in the biobank of the Son Llàtzer University Hospital to be used in other research, possibly not related to the initial study for which it consented. Samples may be transferred from the biobank for authorized projects, possibly also abroad, with a prior favourable opinion of the scientific committee and the ethics committee of the biobank. You can contact the biobank to gather information about the projects in which your samples have been used.

Patient Signature	: Researcher's signature:
Name:	Name:
Date:	Date:

INFORMED CONSENT TO THE PATIENT FOR THE CONDUCT OF CLINICAL TRIALS (Representative)

Version 2.0 August 13, 2020

STUDY TITLE: ***Study of the efficacy of strengthening standard therapy for COVID-19 patients with repeated transfusion of immune plasma from COVID-19 convalescents vs exclusive standard therapy in hospitalized COVID-19 patients.***
PROMOTER: Son Llàtzer University Hospital
PRINCIPAL INVESTIGATOR:
Maria Arrizabalaga Asenjo (Adjunct Specialist Physician, MI-infectious): marrizab@hsll.es
Joan Bargay Lleonart (Head of Haematology Service): jbargay@hsll.es
CENTER: Son Llàtzer University Hospital

I, *(name and surname_____),*" as representative of *(participant's first and last name_____*

_____

☐ I have read the information sheet that has been given to me.

☐ I have been able to ask questions about the study.

☐ I have received enough information about the study.

☐I have spoken to: *(name of the researcher_____*.

☐ I understand that patient involvement is voluntary.

☐ I understand that I can withdraw from the study and request the destruction of my sample, as long as it has not been anonymized:

1. Whenever.
2. Without having to give explanations.
3. Without this having an impact on my medical care.

☐ I understand that, if the patient decides to withdraw from the study, the results obtained up to that point may continue to be used but that no further analysis of his sample will be carried out as long as it has not been anonymized.

☐ In my presence he has been given *(name of the participant)* all relevant information adapted to his level of understanding and agrees to participate. I agree to (*participant's name)* participating in this study and consent to the access and use of the data under the conditions detailed in the patient information sheet.

If the results of the research provide information that may interest me or my relatives: (*indicate one of the boxes*)

☐ I want to be informed.

☐ I do not want to be informed, but I accept that my doctor contacts my relatives if these results may affect them.

☐ I understand that *(name of the participant*_____

_____

At the end of the investigation, your sample may be:

1. ☐ Destroyed.
2. ☐ Anonymized (i.e., the link that links the sample to you will be destroyed, so that neither the researcher nor any other person on the team will be able to identify again who your sample belongs to).
3. ☐ Incorporated into a collection whose head is the researcher Maria Arrizabalaga Asenjo and Joan Bargay Lleonart, which is in the Microbiology Service of Son Llàtzer University Hospital, so that it continues to be used in the study of the COVID-19 disease.
4. ☐ Stored in the biobank of the Son Llàtzer University Hospital to be used in other research, possibly not related to the initial study for which it consented. Samples may be transferred from the biobank for authorized projects, possibly also abroad, with a prior favourable opinion of the scientific committee and the ethics committee of the biobank. You can contact the biobank to gather information about the projects in which your samples have been used.

Signature of the representative:

Name:
Date:

Signature of the researcher:

Name:
Date:

Annex III. Donor Patient Information Sheet (HIP-DONOR)

PATIENT INFORMATION SHEET FOR CONDUCTING CLINICAL TRIALS

Version 2.0 August 13, 2020

STUDY TITLE: *Study of the efficacy of repeated transfusion of COVID-19 Convalescent Immune Plasma vs standard therapy in hospitalized COVID-19 patients*
PROMOTER: Son Llàtzer University Hospital
PRINCIPAL INVESTIGATOR:
Maria Arrizabalaga Asenjo (Adjunct Specialist Physician, MI-infectious), marrizab@hsll.es
Joan Bargay Lleonart (Head of Haematology Service), jbargay@hsll.es
CENTER: Son Llàtzer University Hospital

INTRODUCTION

We are writing to inform you about a study in which you are invited to participate. The study has been approved by the Research Ethics Committee of the Balearic Islands, in accordance with current legislation and is carried out with respect to the principles set forth in the Declaration of Helsinki and the standards of good clinical practice.

Our intention is only that you receive the correct and sufficient information so that you can evaluate and judge whether or not you want to participate in this study. To do this, read this fact sheet carefully and we will clarify any doubts that may arise after the explanation. In addition, you can consult with the people you deem appropriate. If you have any questions, please contact:

1. Maria Arrizabalaga Asenjo, Son Llàtzer University Hospital, Internal Medicine Service, 2nd floor. Tel. 871 202095
2. Joan Bargay Lleonart, Son Llàtzer University Hospital, Haematology Service, 3rd floor. Tel. 871 202138

OVERVIEW

The haematology and Internal Medicine Service of this hospital is carrying out a clinical research study. This consists of studying the efficacy and safety of plasma treatment of convalescent patients with COVID-19 disease administered for two days together with the standard treatment available.

The objective is to determine the clinical benefit of plasma treatment of convalescent patients with COVID-19 disease.

You are invited to participate in the study, in which all patients of the Son Llàtzer University Hospital with the COVID-19 disease will participate.

The study is approved by an accredited Clinical Research Ethics Committee and by the Spanish Agency for Medicines and Health Products. It will be carried out following the Declaration of Helsinki and the requirements established in Royal Decree 1090/2015, of December 4, which regulates clinical trials with medicines, the Ethics Committees of Research with medicines and the Spanish Registry of Clinical Studies.

The study will include two sets of participants, donors, and recipients. Recipient participants are patients with COVID-19 disease, who will receive plasma treatment from convalescent patients with COVID-19 disease (donors).

You would participate as a plasma donor.

Plasma extraction will be carried out by apheresis, which is the process used to extract a blood component intended for transfusion, or for the treatment of some diseases that require the removal of a component from the blood.

The apheresis procedure consists of connecting the donor by venous route (1-2 accesses) to a cell separator machine, using a team of sterile collection bags and tubes. The blood reaches the cell separator, where it is processed and the product to be collected is selected, the rest of the blood is returned to the donor. Depending on the type of collection machine and the product that is intended to obtain apheresis can last between 30 minutes and 2 hours.

The donor selection criteria are the same as those established for blood donation. This procedure is performed under the supervision of medical and nursing personnel experienced in this type of donation.

If you decide to withdraw consent to participate in this study, no new data will be added to the database and may require the destruction of all previously retained identifiable samples to prevent further analysis, although those responsible for the study may continue to use the information collected about you until that time, unless you expressly object.

By signing the attached consent sheet, you agree to comply with the study procedures that have been exposed to you.

BENEFITS AND RISKS ARISING FROM YOUR PARTICIPATION IN THE STUDY

By participating in this study, you will not get any benefit to your health. While we hope that their participation can benefit a better understanding of the efficacy of standard treatment with repeated dose plasma infusions of patients convalescing from COVID-19 disease in patients with COVID-19 disease.

Possible side effects from a venipuncture are tenderness, pain, bruising, bleeding, or infection at the injection site. Drawing blood can also make you nauseous or dizzy. The most common possible side effects of an apheresis are muscle cramps, which are solved with some ease by supplying calcium. Other very low frequency side effects derived from an apheresis are hypotension due to extracorporeal circulation, malaise or syncope.

CONFIDENTIALITY

Responsible for the file: Health Service of the Balearic Islands

Purpose of collection: Clinical trial

Legitimation: Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights in Spain.

Recipients: no third parties

Rights: access, rectify and delete data

Additional information: http://www.hsll.es/

The treatment, communication, and transfer of personal data of all participating subjects will comply with the provisions of Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights in Spain.

In accordance with the provisions of the legislation, you can exercise your rights of access, rectification, deletion, opposition, limitation of data processing, including to transfer your data to an authorized third party (portability), for which you must contact the person responsible for the treatment: Maria Arrizabalaga Asenjo, Internal Medicine Service-infectious diseases, Son Llàtzer University Hospital, Floor 1. Carretera Manacor Km 4,07198 Palma marrizab@hsll.es Tel: 871202000. Your data will be processed electronically and will be incorporated into an automated file of personal data whose responsible is the General Secretariat of the Health Service of the Balearic Islands, with headquarters at Calle de la Reina Esclaramunda, 9, 07003 Palma, dpd@ibsalut.caib.es, which complies with all the security measures of restricted access to the objective described in this document.

Your data will be processed electronically and will be incorporated into an automated file of personal data who's responsible is the Health Service of the Balearic Islands, which complies with all the security measures of restricted access to the objective described in this document.

To guarantee the confidentiality of the information obtained, your data and the sample will be identified by a code and only the study doctor and collaborators will be able to relate this data to you and your medical history. Therefore, your identity will not be disclosed to any person except in case of medical emergency, requirement of the Health Administration or legal requirement.

Only the essential data necessary to carry out the study will be transmitted to third parties and other countries, and that in no case will contain information that can directly identify you, such as name and surname, initials, address, Social Security number, etc. In the event that this assignment occurs, it will be for the same purposes of the study described and guaranteeing confidentiality at least with the level of protection of the legislation in force in our country.

Access to your personal information will be restricted to the study doctor/collaborators, health authorities, the Research Ethics Committee of the Balearic Islands, and authorized personnel, when they need it to verify the data and procedures of the study, but always maintaining the confidentiality of the same in accordance with current legislation.

You can file a claim with the Spanish Agency for Data Protection if you consider that your data protection rights have been violated.

FINANCIAL COMPENSATION

Your participation in the study will not entail any expense. Your doctor will not receive any financial compensation for participating in this study and has stated that there is no conflict of interest.

VOLUNTARY PARTICIPATION

You should know that your participation in this study is voluntary and that you can decide not to participate or change your decision and withdraw consent at any time, without giving any explanation, as well as request the destruction of the sample, without altering the relationship with your doctor or the treatment you should receive.

If you decide to revoke your consent, no new data will be collected, nor will new analysis of the sample be carried out, but this revocation will not affect the research carried out so far.

COLLECTION OF BIOLOGICAL SAMPLES

When participating in this study, a plasma extraction will be done by apheresis, in the Blood Bank of the Son Llàtzer University Hospital, apheresis cabinet, haematology Service, 3rd floor. The plasma sample will be used as a treatment for patients participating in this study (recipients) affected with COVID-19 disease.

The possible risks derived from the procedure carried out to obtain this sample are covered by the insurance of the study, which is that of the Health Service of the Balearic Islands.

The sample will be coded and treated confidentially for the duration of this study, using a code that only the researcher and staff of your team can link with you to preserve your identity.

In case any additional data or sample is necessary, your doctor will contact you to request your collaboration again. You will be informed of the reasons and will be asked again for consent, if necessary.

It will not receive any economic benefit from the donation of the samples and the transfer of the data provided, nor will it be entitled to possible commercial benefits of the discoveries that may be achieved as a result of the research carried out.

The samples will be analysed in the Biochemical analysis and microbiology laboratory of the Son Llàtzer University Hospital and will be stored for 1 year, in anticipation that some additional analysis related to the objectives of the study will be necessary. During this process, the person responsible for the samples will be the promoter of the study.

In case of conservation of the samples for future uses, they will be stored in the Microbiology Service of the Son Llàtzer University Hospital for 1 year.

At the end of the investigation, your sample may be:

☐ Destroyed.
☐ Anonymized (i.e., the link that links the sample to you will be destroyed, so that neither the researcher nor any other person on the team will be able to identify again who your sample belongs to).
☐ Incorporated into a collection whose managers are Maria Arrizabalaga Asenjo (Adjunct Specialist Physician, MI-infectious, marrizab@hsll.es) and Joan Bargay Lleonart (Head of haematology Service, jbargay@hsll.es) of the Son Llàtzer University Hospital, so that it continues to be used in the study of the COVID-19 disease.
☐ Stored in the biobank (Biobank of the Son Llàtzer University Hospital) to be used in other research, possibly not related to the initial study for which it consented. Samples may be transferred from the biobank for authorized projects, possibly also abroad, with a prior favourable opinion of the scientific committee and the ethics committee of the biobank. You can contact the biobank to gather information about the projects in which your samples have been used.

GRATITUDE

Whatever their decision, both the promoter and the research team want to thank you for your time and attention. You are contributing to the best knowledge and care of your disease which in the future can benefit many people.

Annex IV. Informed consent of donor (CI-DONOR)

INFORMED CONSENT FOR CLINICAL TRIALS

Version 2.0 August 13, 2020

STUDY TITLE: *Study of the efficacy of repeated transfusion of COVID-19 Convalescent Immune Plasma vs standard therapy in hospitalized COVID-19 patients*
PROMOTER: Son Llàtzer University Hospital
PRINCIPAL INVESTIGATOR:
Maria Arrizabalaga Asenjo (Adjunct Specialist Physician, MI-infectious), marrizab@hsll.es
Joan Bargay Lleonart (Head of haematology Service), jbargay@hsll.es
CENTER: Son Llàtzer University Hospital

I, _____

☐ I have read the information sheet that has been given to me.

☐ I have been able to ask questions about the study.

☐ I have received enough information about the study.

☐ I have spoken to: _____

☐ I understand that my participation is voluntary.

☐ I understand that I can withdraw from the study and request the destruction of my sample, if it has not been anonymized:

1. Whenever.
2. Without having to give explanations.
3. Without this having an impact on my medical care.

☐ I understand that, if I decide to withdraw from the study, the results obtained up to that point may continue to be used but that no further analysis of my sample will be carried out, if it has not been anonymised.

If the results of the research provide data that may interest me or my relatives: (*indicate one of the boxes*)

☐ I want to be informed.

☐ I do not want to be informed, but I accept that my doctor contacts my relatives if these results may affect them.

☐ I understand that I have the rights of access, rectification, deletion, opposition, limitation of data processing, including to transfer my data to an authorized third party (portability), in accordance with the provisions of Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights in Spain.

☐ I freely consent to participate in the study and consent to the access and use of my data under the conditions detailed in the patient information sheet.

At the end of the research my sample may be:

☐ Destroyed.
☐ Anonymized (i.e., the link that links the sample to you will be destroyed, so that neither the researcher nor any other person on the team will be able to identify again who your sample belongs to).
☐ Incorporated into a collection whose managers are Maria Arrizabalaga Asenjo (Adjunct Specialist Physician, MI-infectious, marrizab@hsll.es) and Joan Bargay Lleonart (Head of haematology Service, jbargay@hsll.es) of the Son Llàtzer University Hospital, so that it continues to be used in the study of the COVID-19 disease.
☐ Stored in the biobank (Biobank of the Son Llàtzer Hospital) to be used in other investigations, possibly not related to the initial study for which he consented. Samples may be transferred from the biobank for authorized projects, possibly also abroad, with a prior favourable opinion of the scientific committee and the ethics committee of the biobank. You can contact the biobank to gather information about the projects in which your samples have been used.

Patient Signature: Researcher's signature:

Name: Name:
Date: Date:

INFORMED CONSENT FOR CLINICAL TRIALS (REPRESENTATIVE)

Version 2.0 August 13, 2020

STUDY TITLE: *Study of the efficacy of repeated transfusion of COVID-19 Convalescent Immune Plasma vs standard therapy in hospitalized COVID-19 patients*
PROMOTER: Son Llàtzer University Hospital
PRINCIPAL INVESTIGATOR:
Maria Arrizabalaga Asenjo (Adjunct Specialist Physician, MI-infectious), marrizab@hsll.es
Joan Bargay Lleonart (Head of haematology Service), jbargay@hsll.es
CENTER: Son Llàtzer University Hospital

I, _____

as a representative of _____

_____

☐ I have read the information sheet that has been given to me.

☐ I have been able to ask questions about the study.

☐ I have received enough information about the study.

☐ I have spoken to: _____

_____

☐ I understand that the participant's participation is voluntary.

☐ I understand that I can withdraw from the study and request the destruction of my sample, if it has not been anonymized:

1. Whenever.
2. Without having to give explanations.
3. Without this having an impact on my medical care.

☐ I understand that, if the patient decides to withdraw from the study, the results obtained up to that point may continue to be used but that no further analysis of my sample will be carried out, if it has not been anonymised.

☐ In my presence, _____

_____ I agree that _____

_____

_____

In the event that the results of the research provide data that may interest me or my relatives: (*indicate one of the boxes*)

☐ I want to be informed.

☐ I do not want to be informed, but I accept that my doctor contact my relatives if these results may affect them.

☐I understand that I have the rights of access, rectification, deletion, opposition, limitation of data processing, including to transfer my data to an authorized third party (portability), in accordance with the provisions of Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights in Spain.

☐ I freely consent to participate in the study and consent to the access and use of my data under the conditions detailed in the patient information sheet.

At the end of the research my sample may be:

☐ Destroyed.
☐ Anonymized (i.e., the link that links the sample to you will be destroyed, so that neither the researcher nor any other person on the team will be able to identify again who your sample belongs to).
☐ Incorporated into a collection whose managers are Maria Arrizabalaga Asenjo (Adjunct Specialist Physician, MI-infectious, marrizab@hsll.es) and Joan Bargay Lleonart (Head of haematology Service, jbargay@hsll.es) of the Son Llàtzer University Hospital, so that it continues to be used in the study of the COVID-19 disease.
☐ Stored in the biobank (Biobank of the Son Llàtzer Hospital) to be used in other investigations, possibly not related to the initial study for which he consented. Samples may be transferred from the biobank for authorized projects, possibly also abroad, with a prior favourable opinion of the scientific committee and the ethics committee of the biobank. You can contact the biobank to gather information about the projects in which your samples have been used.

Signature of the representative: Signature of the researcher:

Name: Name:
Date: Date:

INFORMED CONSENT FOR CLINICAL TRIALS
(BEFORE WITNESS)

Version 2.0 August 13, 2020

STUDY TITLE: *Study of the efficacy of repeated transfusion of COVID-19 Convalescent Immune Plasma vs standard therapy in hospitalized COVID-19 patients*
PROMOTER: Son Llàtzer University Hospital
PRINCIPAL INVESTIGATOR:
Maria Arrizabalaga Asenjo (Adjunct Specialist Physician, MI-infectious), marrizab@hsll.es
Joan Bargay Lleonart (Head of haematology Service), jbargay@hsll.es
CENTER: Son Llàtzer University Hospital

I,_____

I declare under my responsibility that _____

☐ You have read (or have been read, in the event that the patient cannot read), the information sheet that has been given to you.

☐ He has been able to ask questions about the study.

☐ You have received sufficient information about the study.

☐ You have spoken to: _____

☐ He states that he understands that his participation is voluntary.

☐ You state that you understand that you can withdraw me from the study and request the destruction of your sample:

1. Whenever.
2. Without having to give explanations.
3. Without this having an impact on my medical care.

☐ He states that he understands that, if he decides to withdraw from the study, the results obtained up to that point may continue to be used but that no new analysis of my sample will be carried out, as long as it has not been anonymized.

In the event that the results of the research provide data that may interest the participant or his relatives: (*indicate one of the boxes*)

☐ The patient states that he wants to be informed.

☐ The patient states that he does not want to be informed, but I accept that the patient's doctor contact his relatives if these results may affect them.

☐ You declare that you understand that you have the rights of access, rectification, deletion, opposition, limitation of data processing, including to transfer your data to an authorized third party (portability), in accordance with the provisions of Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights in Spain.

☐ You have freely expressed your agreement to participate in the study and consent to the access and use of your data under the conditions detailed in the patient information sheet.

At the end of the investigation your sample may be:

☐ Destroyed.
☐ Anonymized (i.e., the link that links the sample to you will be completely destroyed, so that neither the researcher nor any other person on the team will be able to identify again who your sample belongs to).
☐ Incorporated into a collection whose managers are Maria Arrizabalaga Asenjo (Adjunct Specialist Physician, MI-infectious, marrizab@hsll.es) and Joan Bargay Lleonart (Head of haematology Service, jbargay@hsll.es) of the Son Llàtzer University Hospital, so that it continues to be used in the study of the COVID-19 disease.
☐ Stored in the biobank (Biobank of the Son Llàtzer University Hospital) to be used in other research, possibly not related to the initial study for which it consented. Samples may be transferred from the biobank for authorized projects, possibly also abroad, with a prior favorable opinion of the scientific committee and the ethics committee of the biobank. You can contact the biobank to gather information about the projects in which your samples have been used.

Witness Signature:

Name:
Date:

Investigator's signature:

Name:
Date:

Annex V. COLLECTION OF ADVERSE EVENT DATA FOR RESEARCH PRODUCTS

COLLECTION OF ADVERSE EVENT DATA FOR RESEARCH PRODUCTS

Nº CENTER: PROJECT CODE (SPONSOR) :	PATIENT NUMBER:	TYPE OF REPORT: INITIAL TRACKING:	RANDOMIZATION:
SPONSOR ID:	CASE ID:	DATE OF NOTIFICATION:	

I-ADVERSE EVENT INFORMATION.

COUNTRY	DATE OF BIRTH	AGE	SEX	WEIGHT	HEIGHT	SAE START DATE:

CRITERION OF SERIOUSNESS	SAE END DATE
DEATH LIFE-THREATENING: HOSPITALIZATION/PROLONGATION IN ALREADY HOSPITALIZED PATIENT: SIGNIFICANT OR PERMANENT DISABILITY: CONGENITAL ALTERATION: CLINICALLY SIGNIFICANT TRANSMISSION OF INFECTIOUS DISEASE BY A MEDICAL DEVICE:	FATAL/ Date of death: RESOLVED: SOLVED WITH SEQUELS: IMPROVING: PERSISTING: WORSENED: UNKNOWN:

II-RELEVANT INFORMATION OF THE STUDY PROCEDURE

DATE	START TIME	END TIME	DOSE

ACTION TAKEN REGARDING THE STUDY PROCEDURE			
DOSE REDUCTION	START DATE:	END DATE:	CONTINUOUS:

TEMPORARILY INTERRUPTED	START DATE	END DATE:	CONTINUOUS:
PERMANENT INTERRUPTION	START DATE	END DATE:	CONTINUOUS:

HAS THE INTENSITY OF THE EVENT DECREASED DUE TO THE ACTION TAKEN WITH RESPECT TO THE STUDY PROCEDURE?

HAS THE EVENT REAPPEARED AFTER REINTRODUCING THE STUDY PROCEDURE?

DESCRIPTION OF THE ADVERSE EVENT:
EVENT:
SEVERITY: GRADE 1 GRADE 2 GRADE 3 GRADE 4
DESCRIPTION:

POSSIBLE CAUSE OF THE ADVERSE EVENT
PREVIOUS ILLNESS:
STUDY TREATMENT:
OTHER TREATMENTS:
PROTOCOL-RELATED PROCEDURE
OTHER (SPECIFY):

III- CONCOMITANT MEDICATION AND RELEVANT MEDICAL HISTORY

CONCOMITANT MEDICATION	INDICATION OF USE	FREQUENCY	ROUTE	DOSE	START DATE	END DATE	CONTINUOUS

RELEVANT MEDICAL HISTORY	START DATE:	END DATE	CONTINUOUS

RELEVANT MEDICAL TESTS/PROCESSES	RESULT (UNITS)	NORMAL RANGE	DATE OF THE TEST/PROCEDURE

SAE-SPECIFIC MEDICATION	FREQUENCY	ROUTE	DOSE	START DATE	END DATE	CONTINUOUS

IV-INFORMATION ABOUT THE RESEARCHER:

NAME OF THE RESEARCHER	ADDRESS OF THE RESEARCHER	REPORTED BY:	DATE:	SIGNATURE OF THE RESEARCHER	DATE:

Annex VI. List of participating centres and researchers

Project Title: Study of the efficacy of the reinforcement of standard therapy for COVID-19 patients with repeated transfusion of immune plasma from COVID-19 convalescents vs exclusive standard therapy in hospitalized COVID-19 patients

List of participating centres and researchers

Centre Code	Centre Name	Principal Investigator	Collaborating researchers/ Research team
01	Son Llàtzer University Hospital	Joan Bargay Lleonart (Hematologic) * Maria Arrizabalaga Asenjo (Internal Medicine)	COORDINATING RESEARCH TEAM: - José María Guerra Hernando (jmguerra@hsll.es) (Haematology) * - Manuel Raya (Internal Medicine) - Maria Aranda (ICU) Ext1558 - Josep Borràs Vives (jborras@hsll.es), Magdalena Flexas, Jordi Perales (Coordination of Clinical Trials of Haematology)* -Maria Fiorella Sarubbo (mariafiorella.sarubbo@hsll.es), Khaoulah El Haji, Aina Vidal (Research Unit). RESEARCHERS OF THE COORDINATING CENTER: - Martí Mascaró Riera (Haematology) * - Gemma Rialp (ICU-HUSLL) - Marcio Borges (ICU -HUSLL) - Sonia Velasco Rodríguez (Nursing Coordinator of Blood Bank-haematology) - Víctor López Nieto (blood bank nursing team). - Ana Cruz (Internal Medicine floor Coordinator) - María Victoria Fernández-Baca Gutiérrez del Alamo and Carmen Gallegos (Microbiology Laboratory) - Maria Antonia Bautista Gili, Enrique Girona Llobera, Teresa Jiménez (Blood and Tissue Bank Foundation of the Balearic Islands
02	Blood and Tissue Bank Foundation of the Balearic Islands	Maria Antonia Bautista Gili, Enrique Girona Llobera, Teresa Jiménez	
03	Manacor Hospital	Albert Vallès	
04	Inca Hospital	Catalina Gual Reynés	
05	Mateu Orfila General Hospital	Eduardo Martínez de Castro Hurtado	Laura Calonge Raventós, Pilar Galán Álvarez, Juan Tena Aniés
	Can Misses Hospital	Francisco Javier Vercher Agustí	

***IDISBA RESEARCH GROUP IN YOUR CASE:** Some of the researchers of the study belong to the IdISBA group *Study of monoclonal gammapathies and myelodysplastic syndromes.*

Annex VII. Commitment signature sheet of the centres assigned to participate in the study

Project Title: Study of the efficacy of the reinforcement of standard therapy for COVID-19 patients with repeated transfusion of immune plasma from COVID-19 convalescents vs exclusive standard therapy in hospitalized COVID-19 patients

Research Project Code: CO-PLASMA-20

Version number and date: 2.0, September 03, 2020

This signature constitutes the approval of the protocol and the accompanying documents and provides the necessary assurance that the study will be carried out in accordance with the conditions stipulated in the protocol, including the conditions relating to confidentiality, and in accordance with local legal and regulatory requirements and with the applicable regulations and ICH guidelines.

Centre Name: _____

Principal Investigator's Signature	Date of signature (MM -DD -YYYY)
Name of the Researcher (capital letters)	
Principal Investigator's Signature	Date of signature (MM-DD- YYYY)
Name of the Researcher (capital letters)	
Principal Investigator's Signature	Date of signature (MM-DD- YYYY)
Name of the Researcher (capital letters)	
Principal Investigator's Signature	Date of signature (MM-DD- YYYY)
Name of the Researcher (capital letters)	

IMPORTANT: the Commitment Signature Sheet completed by each centre is added as an attachment to the protocol.

Procedure of collection of immune plasma of convalescent COVID-19

1. Definition

A study is being carried out in our Hospital to obtain plasma from convalescent Covid-19 donors, for its infusion in patients who have an active Covid19 infection at risk of progression to severe respiratory failure.

The collection of immune plasma from convalescent Covid-19 donors will be carried out in two phases:

1. **BASELINE INTERVIEW WITH THE DONOR**
2. **PLASMA EXTRACTION BY APHERESIS**

2. Baseline interview with the donor

It consists of the first phase of the procedure.

2.1 OBJECTIVES OF THE INTERVIEW

1. Make a correct selection of the donor according to the donor selection criteria.
2. The Donor will be informed of the process at all times.
3. Obtain a venous blood sample that meets the quality requirements necessary for its analytical determination.

2.2 RESOURCES

HUMAN RESOURCES:

1. Haematologist of the haematology and Hemotherapy Service of Son Llàtzer University Hospital. HSLL.
2. Nurse/Due of the haematology and Hemotherapy Service HSLL

MATERIAL RESOURCES:

1. Previously issued printed analytical requests
2. Identification labels of laboratory, microbiology and haematology.
3. Study Informed Consent **(CI-Donor) Annex 1**
4. Donor Patient Information Sheet **(HIP-DONOR) Annex 2**
5. Material necessary for venipuncture: needles/popcorn of different sizes, vacutainer hood, tourniquet rubber (SMART), antiseptic, gauze, and tape
6. Analytical tubes

7. Sterile gloves
8. Double compartment bag for sample transfer
9. Container for sharp material

ESTIMATED DURATION

1. Interview with doctor: 15 minutes
2. Assessment of veins and blood collection by nursing: 15 minutes.

PHYSICAL SPACE REALIZATION

1. Apheresis cabinet. haematology and hemotherapy service

2.3 DESCRIPTION

PREVIOUS ACTIONS

1. The donor will be summoned a week before by the Secretary of haematology, after management of the haematologist responsible for the identified patient-donors (either from donors who come from internal medicine or haematology)

ACTIONS

2. Interview with the doctor, in which we will proceed to:
    1. Inform the objective of the study and the phases of it.
    2. Report complications arising from the procedure and request informed consent.
    3. Perform the standard pre-donation interrogation of plasma derivatives.
    4. Make analytical requests:
        1. Group ABO, Rh (D) and irregular antibodies.
        2. Blood count, biochemistry including total proteins, liver tests, determination of immunoglobulin levels
        3. Serology: chronic HBV profile; Hepatitis C, antibodies; HIV (1+2), antibodies and/or antigen; lue profile.
        4. Determination of COVID19 antigenemia. It will be made in a petition that will include description "donor plasma protocol COVID-19"
    5. Weight greater than 50 kg should be checked at the interview. The donor should be advised to avoid eating high-fat meals 12 hours before donation. The haematologist will perform the patient assessment for the extraction of 600 ml of plasma.
    6. Information will be collected from the donor on whether he takes regular medication, mainly ACE inhibitors. At the end, an email will be sent to Microbiology (vfernandez-baca@hsll.es) with the history number and the names and surnames of the donors of the day, to carry out the Covid19 serology test quantitatively.

7. Nursing assessment of the state of the patient's veins.
8. Blood draw by nursing for the requested tests:
    1. Hand washing with soap and water or hydroalcoholic solution.
    2. Placement of disposable gloves.
    3. Place the compressor on the selected arm, select the most suitable vein for venipuncture.
    4. Disinfect the puncture area as standard.
    5. Label the extracted tubes and fill in the requests.

SUBSEQUENT ACTIONS

1. After the verification of the requested tests, by the haematologist who performs the interview, the donor will be summoned in apheresis by the Secretary of haematology, through the coordination of the responsible haematologist and the supervisor of the service. At this time clinical trial coordination will inform

2.4 POTENTIAL COMPLICATIONS

1. Anxiety (hyperventilation picture, vasovagal reaction)
2. Pain and/or bruising due to blood draw.
3. Complications of apheresis donation and donation (vasovagal reaction, peripheral nerve injury, citrate reaction, haemolysis, etc.)

2.5 RESULT CRITERIA

1. The donor will state that he is informed of the study to be carried out.
2. Reduced donor anxiety
3. The blood sample necessary to carry out the requested analytical determinations will be obtained.

2.6 RELATED FILES

1. Annex 1: Donor Informed Consent (CI-DONOR)
2. Annex 2: Donor Patient Information Sheet (HIP-DONOR)
3. Annex 3: Informed consent of transfer of data of the convalescent donor of plasma covid 19 for Blood and tissue bank of the Balearic Islands

3. PLASMA EXTRACTION BY APHERESIS

3.1 DEFINITION

The collection of hyperimmune plasma from convalescent Covid-19 donors will be carried out by apheresis, a procedure that consists of circulating the blood extracted from the donor through a sterile and single-use plastic extracorporeal circuit, with the aim of centrifuging and selectively obtaining one or more blood components, in this case hyperimmune plasma.
With this system we will be able to process large volumes of blood, restoring the rest of the blood components not necessary for the study.

3.2 OBJECTIVES

1. Perform the apheresis procedure as effectively as possible, obtaining the desired quantity and quality of the product.
2. The Donor will be always informed of the process.
3. Reduce/eliminate signs and symptoms of possible side effects.

3.3 RESOURCES

HUMAN RESOURCES:

1. Responsible for the indication: Haematologist responsible for the extraction of plasma within the study.
2. Responsible for the execution: Nurse/DUE and Nursing Assistant. haematology and Hemotherapy Service.

MATERIAL RESOURCES

1. Apheresis processor: HAEMONETICS MCS+
2. Software card (PPP&FFP) and pump adapter
3. Plasma collection equipment (792P)
4. Sphygmomanometer, stethoscope and second-hand clock or failing that digital device for TA and pulse shots.
5. Thermometer
6. Scale
1. 1 ACDA bag
2. Centrifuge adapter (same as for erythropheresis)
3. Oral calcium in tablets or effervescent.
4. 2 adapters and a vacutainer system hood
5. Extraction tubes that will accompany the product
6. Sterile and disposable gloves
7. Syringes of different sizes (5ml, 10ml)
8. Venous compressor
9. Ampoules of S.F. of 10 ml
10. 2 fistulas of 16G
11. Sterile gauze, antiseptic solution and tape

12. Containers for disposal of sharp material

ESTIMATED DURATION

1. Assembly and priming of the equipment**: 15 min.**
2. Process: **35/40 min (Depends on the donor's haematocrit)**
3. Subsequent actions: **10 min**

PHYSICAL SPACE REALIZATION

1. Apheresis cabinet. haematology and hemotherapy service

3.4 DESCRIPTION

PREVIOUS ACTIONS

It is important to notify the haematologist of the Transfusion Centre (BSTIB) on the same day that the appointment for plasmapheresis is confirmed for the correct scheduling of the treatment of the component, which includes the technique of reducing plasma pathogens, the analysis of the donation unit and the freezing of the two units obtained until their distribution.

1. We will present ourselves upon the arrival of the donor and inform us of the procedure to which he will be subjected.
2. We will check that the donor has correctly signed the informed consent and the screening questionnaire.
3. We will check that all the analyses requested in the baseline consultation have been carried out (ABO and RH EAI group, biochemistry with liver function, blood count, serology: HBV, HCV, HIV, treponema). In case of doubt with the results comment with haematologist responsible for the extraction)
4. Wash hands with soap and water or hydroalcoholic solution.
5. Glove placement

6. Taking ta, Tª, FC, weighing and carving the donor. The extraction should not exceed 13% of the donor's volume (70 kg, can extract 637 ml; 50 Kg 455 ml).
7. Assembly of the equipment: (before assembly confirm that the protocol card that we have to use for plasma collection and pump adapters is inserted into the machine).
8. The procedure is a single puncture (a single route), using the PPP protocol with filter (*Platelet Poor Plasma*; Platelet-Poor Plasma) and the necessary material is as follows:

    1. The plasmapheresis team. Plasma equipment for the PPP protocol (792P)
    2. ACD anticoagulant solution of 500 ml.

1. Preparation of the apheresis machine*:*

1. Once the MCS+ is started, the detected protocol card will be shown on the screen.
2. A series of checks will automatically be carried out on all the safety components of the MCS+.

3. Select Protocol: LNG25B/1BD6
4. The operator must close, open and re-close the centrifuge cover for checking check that the centrifuge adapter is on.
5. The possibility of choosing between two disposables will appear on the screen, with the MODIFY key we will move through the options. We will use the EXTRACT key to select the disposable **792P.**
6. We will install the disposable as indicated on the screen of the MCS+, first we will insert the bowl, making sure of its correct installation, to avoid any type of friction, we will close the lid and pre-install the tube of the blood pump.
7. We will pass the bloodline through the air detector (BLAD) and through the red valve. We will place the filter on its support and pass the tubing through the air detector and the donor line (DLAD 2) and the donor (DLAD 1)
8. We will install the bowl output line in the sensor line, we will pass the output line through the yellow valve.
9. We will hang the plasma bag on the scale, with the entrance at the top.
10. We will pre-install the Anticoagulant pump and pass its output line through the anticoagulant air detector (ACD)
11. We will install the filter in the donor pressure sensor (DPM), pressing and turning a quarter turn clockwise.

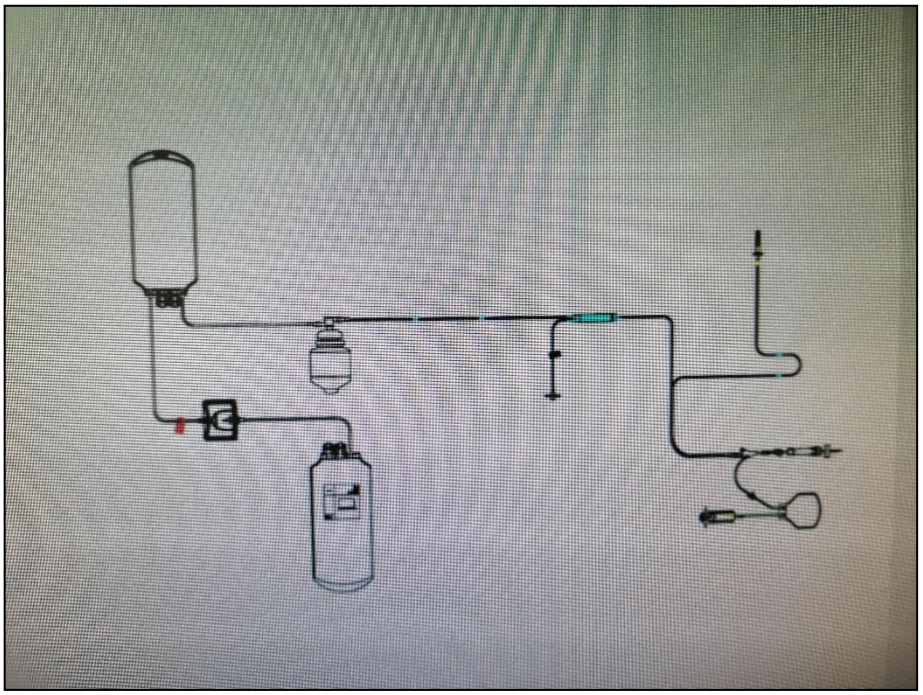


Fig.1: Assembly scheme of the apheresis machine equipment

12. Once the equipment is assembled, we will check it and follow the indications on the screen, pressing extraction to load the pumps.
13. Before the priming sequence we will be asked to check, that the needle line is well nailed and that we pierce the ACD bag.
14. We will purge the equipment by pressing the primed key, it will be purged with anticoagulant, until the DLAD1 and DLAD2 sensors detect liquid.
15. Finishing the priming, the main screen will appear. To check the programming parameters, we will press MODIFY.

16. With the modify fabric we will select the parameter that we want to change, and with the keys + 0 – we will increase or decrease the values.

COMMENTS ON THE APHERESIS TEAM

1. If the container is opened, but the equipment is not removed, closing the wrapper tightly with adhesive tape, it could be used until the expiration date.
2. If mounted and not used, without having purged it, it can be used for up to 24 hours.
3. If the equipment is assembled and purged, it can be used for up to 4 hours.

Separator type	**Reprimanded assembled equipment**	**Mounted equipment primed**
Haemonetics	**24 hours**	**4 hours**

ACTIONS

1. Once the machine is prepared, before starting the procedure, we will properly disinfect the area to be punctured and proceed to it, safely fix the needle of the equipment.
2. We will perform the extraction of the satellite tubes for the processing of the unit in the Community Bank (FBSTIB), which will be **4 tubes in total (3 tubes of EDTA, of 4.5 ml, of 9 ml, of 6 ml, and a tube of biochemistry of 9 ml)** that will be identified with the same numbering of the donation in each of them, for the analysis of the donation in Blood and tissue bank of the Balearic IslandsThe donation will be analysed the next day, which will mean delaying the availability of the two aliquoted units of frozen plasma by 24 hours.
3. Once the procedure has begun, some parameters can be changed, such as: cuff pressure, extraction and return speed and maximum plasma in each cycle to be collected.
4. We must ensure that the plasma to be collected, has an optimal appearance, in case of doubt it will be communicated to the haematologist responsible for the procedure. Lipemia must have been prevented with a recommendation not to ingest fats 12 hours before donation.

Characteristics of the plasma considered suitable for illumination:

Red blood cell count	Residual levels suitable for concentrations of 15 x 10^9 red blood cells per litre
Leukocyte count	Residual levels suitable for concentrations of 1 x 10^9 leukocytes per litre
Platelet content	Residual levels suitable for concentrations of 2.1 x 10^{12} platelets per litre
Aspect	NO Lipemic, NO Hematic

5. Always monitor the donor, check for signs and symptoms of potential complications (described below)

SUBSEQUENT ACTIONS

6. Once the procedure is finished (sound signal) remove the needle.
7. Write down the donor's data and machine parameters on **the donation registration sheet (Annex 5)**
8. Aseptically pinch the collected plasma bag, leaving the segment as long as possible after security sealing to facilitate the processing work at the Community Bank.
9. Assign the product the numbering of the donation (**SIN, single identification number**): the labels will be specific for this type of donation, which have been provided by the Community Bank. Important: the 600 mL plasma bag and the 4 donation tubes will be identified with the labels provided by Blood and tissue bank of the Balearic Islands.
10. The surplus will be sent together with the documentation and the products to be used in the processing of the two 300 mL plasma aliquots and for inactivation with the pathogen reduction technique.
11. The ABO and Rh(D) blood group will be noted on the label of the final plasma bag, the date and time of completion of the collection of the plasma unit (with black marker suitable for food use.
12. Check the punctured area and protect it aseptically.
13. Remove the equipment from the machine and dispose of it in the specific containers.
14. Take TA and FC and offer a snack to the donor.
15. Remove gloves and perform proper hand hygiene.
16. The plasma unit will be placed between the butanediol bags provided by the FBSTIB in the container intended for transport, to guarantee the storage temperature of +20ºC, from extraction to processing in the fractionation area. In the same container and together with the plasma bag, the 4 tubes of the donation will be placed, inside an anti-spill bag.
17. The transport will be carried out in a specific container specifically identified for the study of COVID19 convalescent plasma, with sufficient time to process (within 3 hours of extraction) accompanied by a copy of the donation record sheet **(Annex 5)** that must be signed by the haematologist responsible for the extraction). The check-list form **(Annex 4)** will be reviewed prior to submission.
18. As far as possible the product will arrive before 12 noon to the Blood and tissue bank of the Balearic Islands, we will use the NACEX courier, which we will notify at least 24 hours in advance. The messaging contact details are:

    NACEX messengers
    Phone: 971 222232- 618 34 17 54
    Subscriber No.: 94707 Office: 700
19. Donor and product data will be entered into the hemotherapy service's e-delphine program.

3.5 POTENTIAL COMPLICATIONS

1. By the apheresis itself: vasovagal reactions, citrate poisoning, hypovolemia, haemolysis, chills and feeling cold.
2. Hypotension
3. Hypocalcaemia
4. Anxiety

3.6 RESULT CRITERIA

5. The donor will declare to be informed of the procedure to which he will be subjected.
6. Reduced donor anxiety
7. Apheresis is performed as safely as possible.
8. The donor will not suffer unnecessary risks.
9. Pre and post apheresis data will be recorded on each donor's registration sheet.
10. The product will be treated with maximum security for its transfer and processing.

3.7 RELATED FILES

Annex 5 : ***Immune plasma collection record sheet*** .
Annex 4**:** Request for processing, inactivation, freezing and distribution of COVID-19 convalescent plasma.

4. PROCESSING OF THE COVID-19 PLASMA UNIT in the FBSTIB ONCE RECEIVED AFTER ITS EXTRACTION.

The procedure will be carried out using personal protective equipment (PPE) and the cleaning and disinfection measures of the laboratory area.

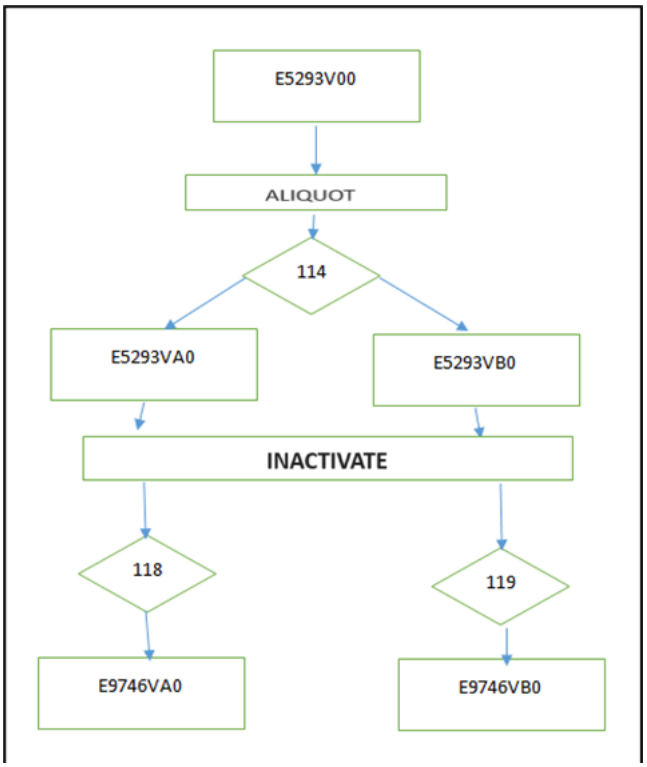
The steps to follow are:

1. Reception of the convalescent plasma unit
2. Check documentation and inactivation request:
3. Check end time collection
4. Single identification number (SIN): Check that additional codes have been sent (minimum 4 per 600 mL unit)
5. Each 600 mL unit shall be allocated in 2 300 mL units (refer to the FR-FRA-XX aliquotation procedure)
6. Add transfer bag equipment using sterile sealant.
7. Label each satellite bag with an additional code and add subcode 01 and 02.
8. Aliquoted by gravity distributing a volume of between 250 and 300 mL in each aliquot.
9. Add the inactivation equipment to each aliquot and attach the corresponding numbering to the final bag.
10. Proceed to plasma inactivation according to usual procedure (PR-FRA-62)

Product obtained: **E9746 Plasmapheresis of convalescent plasma COVID-19, treated with riboflavin, aliquot 1 and Aliquot 2**

11. Freeze in quick freezer before 8 hours from the time of collection (PR-FRA-68)
12. Once frozen, the hospital transfusion service that sent it for collection will be contacted
13. If collection by the hospital transfusion service is delayed, it shall be stored in a separate room, segregated from the transfusion plasma of normal donors.
14. Add the conditions of carriage (refer to the distribution procedure PR-DIS-XX)

Initial Product	Transformation	Final Product	
E5293V00	**114**	E5293VA0	E5293VB0
E5293VA0 (52931)	**118**	E9746VA0 (97461)	
E5293VB0 (52932)	**119**	E9746VB0 (97462)	



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Annex IX. Procedure for inclusion and recruitment of recipient patients in the CO-PLASMA-2020 study

For the inclusion of recipient patients in the study, the following procedure should be carried out:

1. Once the patient has signed the Informed Consent (IC), **the inclusion of the patient must be notified** by sending an email to co-plasma-2020@hsll.es with the following information:
    1. Name of the responsible investigator and the doctor responsible for the patient.
    2. Date of signature of the IC
2. The principal investigator and the physician responsible for the patient will be answered to the branch of study and the patient code in the study that will be assigned to that patient.
3. **In the event that the patient is in the experimental branch**, the doctor responsible for the patient must make the **request for hyperimmune plasma** through the corresponding computer system (depending on the centre) thus activating the plasma management that will be requested from the Blood and tissue bank of the Balearic Islands.

Ctra. Manacor, Km 4 - 07198 Palma de Mallorca - Tel: 871 202 000 - Fax: 871 202 027 - www.hsll.es