Test subject's information for participation in a medical-scientific study

The CoV-Early study: a study into the usefulness of plasma in the treatment of infection with the new coronavirus (SARS-CoV-2)

Official title: Convalescent plasma therapy from recovered patients to treat COVID-19 early in SARS- CoV-2 disease. (CoV-Early study)

Introduction

Dear Sir/Madam,

We are asking you to participate in a medical scientific study. Participation is voluntary. Your written permission is required to participate.

You are receiving this letter because an infection with the coronavirus (SARS-CoV-2 / COVID-19) has been demonstrated in your case. Before you decide whether you want to participate in this study, you will be explained what the study entails. Please read this information carefully and ask the researcher for an explanation if you have any questions. You can also ask the independent expert referred to at the end of this letter for additional information. You can also talk about it with your partner, friends, or family. General information about participating in a medical scientific study can be found on the website of the Dutch government: www.rijksoverheid.nl/mensenonderzoek.

1 General information

This study was set up by researchers from the Erasmus University Medical Centre in Rotterdam and the Leiden University Medical Centre in Leiden, in collaboration with (the Dutch blood bank). Six-hundred and ninety participating patients are required to complete this study. A large number of hospitals in the Netherlands are participating in this study.

The medical ethics review committee of Erasmus MC has approved this study. General information about the review of study can be found in the brochure “Medical scientific research”: https://www.rijksoverheid.nl/documenten/brochures/2014/09/01/medisch-wetenschappelijk-onderzoek- algemene-informatie-voor-de-proefpersoon

2 Purpose of the study

Currently, the treatment of COVID-19 consists of supportive measures. This means that patients are admitted to hospital if necessary, receive nursing care and receive additional oxygen for support if necessary and/or, in some cases, they are ventilated in intensive care. For hospitalized patients, it has since been demonstrated that treatment with dexamethasone reduces the risk of death. However, there is not yet any proven treatment for patients who not yet been admitted to hospital with COVID-19. The purpose of this study is to investigate whether the administration of plasma from patients who have been cured of COVID-19 to patients with COVID-19, but who

have not yet been admitted to, hospital leads to a faster recovery. This is investigated by giving half of the patients pasma from patients who have recovered from COVID-19 and by giving the other half plasma from healthy blood donors (placebo). In this way, the disease progression between the two groups can be compared in the most reliable way.

The study focuses specifically on patients with an increased risk of a more serious course of the coronavirus. You are receiving the information about this study because you are at an increased risk of a more serious course of the disease.

Besides, we would want to know how your lungs recover after experiencing COVID-19 and we would want to investigate how your immunity (the defense) to COVID-19 was built up. We also want to investigate the consequences of COVID-19 on the daily functioning in patients aged 70 years or older after the infection had been cured.

3 Background to the examination

The current standard of treatment for the coronavirus is that patients who are moderately to severely ill are cared for in a nursing ward or intensive care unit if necessary. Despite the best possible care, about 20% of all patients admitted to hospital still die. That is why a better treatment for the corona virus is being searched for. Antibodies from patients who have already recovered from the SARS-CoV-2 virus are likely to be effective in clearing the virus in other patients as well. Giving this effective treatment early in the course of the disease (before admission to hospital) could prevent increases in illness, hospitalization and even death.

Antibodies are proteins that are produced by our immune system when a patient contracts an infection with a virus and with the purpose of fighting the virus. These antibodies are located in the plasma (that is the part of the blood without the blood cells). The immune system needs a few days to weeks to produce sufficient antibodies. Therefore, patients who have been infected with the virus already have antibodies against the coronavirus. Patients who have only recently been ill with this virus have not yet produced any antibodies. In this study, we want to give plasma with antibodies, from people who have been infected with the coronavirus in the past, to patients who have only recently become ill. We hope to demonstrate that this leads to a faster recovery from COVID-19 and therefore this will lead to less frequent hospitalization and fewer fatalities among the patients. This is certainly important for elderly people for whom hospitalization or admission to intensive care is too drastic in case of a serious illness and for whom it is additionally important to focus on a treatment that prevents a serious course of the disease.

An earlier study, conducted in 2003 during the SARS outbreak in Hong Kong, showed that patients with SARS-CoV virus, who received plasma from people who had already experienced the virus, recovered more quickly. We do not yet know whether this is also the case for patients with COVID-19. Previous studies in the Netherlands in COVID-19 patients showed that most patients with COVID-19 already produce antibodies themselves when they have to be admitted to hospital and therefore this made it unlikely that treatment with plasma is still useful at that stage. Therefore, we believe that plasma treatment works best if it is given as early as possible, before a patient needs to be admitted to a hospital.

In addition, it is unclear how quickly and how completely people's lungs and condition recover after experiencing a COVID-19 episode. It is also not entirely clear how resistance to the corona virus is accrued and how long it will remain present. It is also unclear in, elderly patients, what the effect of the infection is on daily functioning after experiencing a COVID-19 episode. These are all aspect of COVID-19 that we hope to learn about in the COV-Early study.

4 What participation entails:

For you, the study will take at least 28 days in total. The study consists of a suitability examination (screening), a treatment phase and a follow-up phase.

In short, this means that after you have given consent to participate in this study, you will come to the hospital for half a day. Blood is drawn to determine your blood group. A cotton swab is also used to test for the presence of the virus (in the nose and throat). You will have plasma administered and then you can go home. You will be phoned 3 times to find out how you are doing. Finally, if you don't mind we also want to sample blood 3 months later but that is not a requirement.

There are also a few of additional studies for which you can choose as to whether or not to participate. These additional examinations are not part of the main study. You can indicate your choice on the consent form (p.13).

This concerns the following additional examinations

- Examination of daily functioning and quality of life after an COVID-19 infection, is only done in a group of people over the age of 70.
- Examination into the rate of virus disappearance from the body and the development of resistance (immunity) against COVID-19 infection in the first 4 weeks after plasma administration
- Examination into long term resistance against COVID-19 (up to 1 year after infection)
- Examination into the long-term effects of COVID-19 infection on the lung function.

Screening
If you want to participate in the study, you or your attending physician (e.g., GP) must contact the research team to determine if you are indeed a suitable candidate for this study. If the researcher confirms this, you will be invited to come to the nearest hospital. There, you will receive additional information and an opportunity to ask questions. From the moment you have signed the consent form, the test starts with a blood sample to determine your blood group and detect any antibodies against the corona virus. A number of specific questions are also asked to map your health, as well as your migration background and ethnicity.

Very occasionally we find something during the screening that requires further medical testing. We always inform you about this. Any further research into this, is done by your own GP or specialist. The costs for this are covered by your own health insurance.

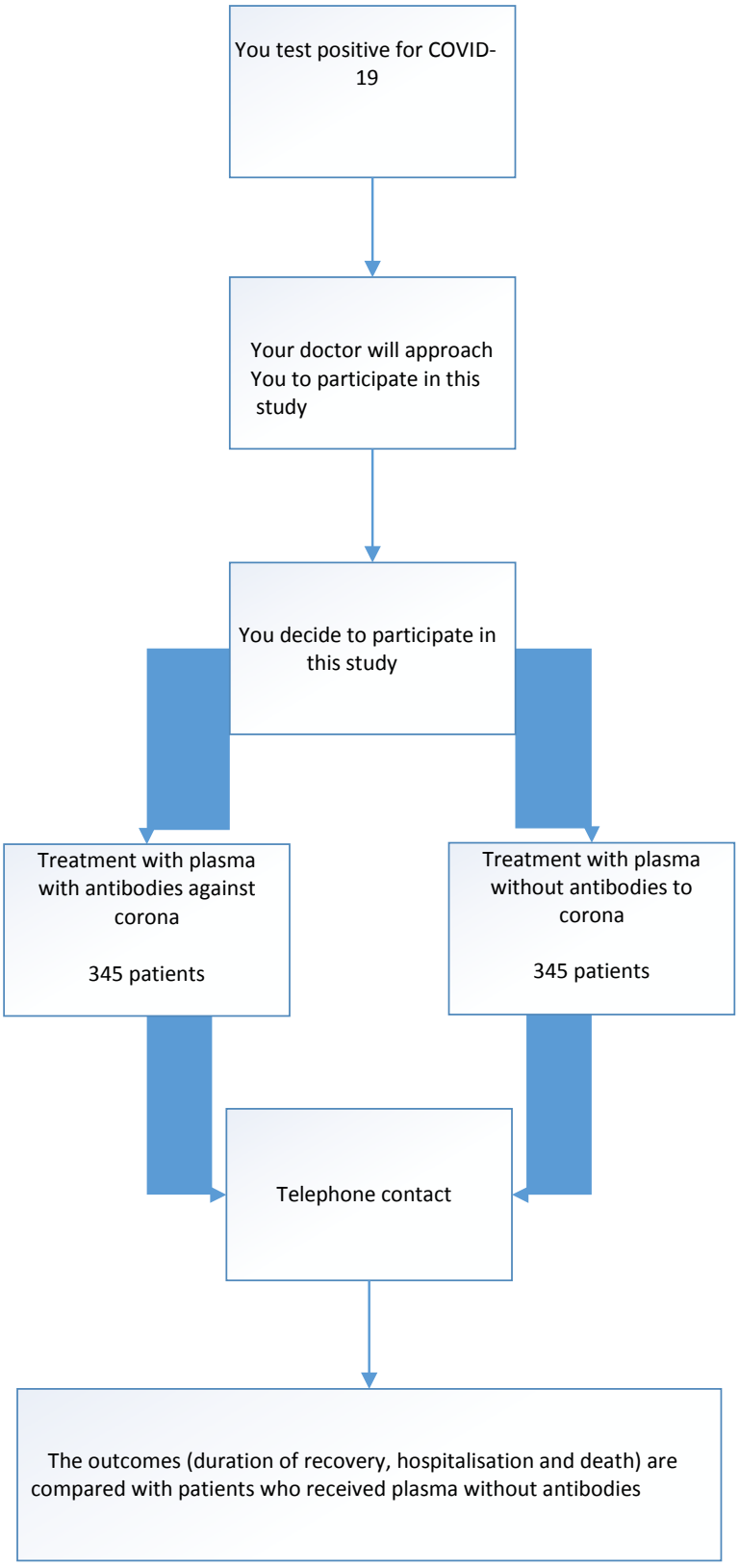
Treatment phase:
If your blood group is known and you also meet the criteria to participate in this study, you will receive the treatment (the plasma, 300 ml) during your visit to the hospital. You can go home after the administration of the plasma.

The only way to prove that plasma from cured COVID-19 patients can be an effective treatment is to give half of the patients 300 ml plasma with antibodies (treatment) against COVID-19 by drawing lots and the other half 300 ml of plasma that does not contain antibodies against COVID-19 (placebo). Only in this way can it be investigated whether the treatment with plasma that contains the antibodies does indeed promote recovery.

Neither you nor your treating doctor will know whether you will be given plasma with or without antibodies. After the study, or if this would be of importance for your health, you can check whether you have received the treatment (plasma with antibodies) or the placebo (plasma without antibodies).

Follow-up phase

You will in any case be monitored until day 28 after the examination. One week, two weeks and four weeks after the administration of plasma, you will be contacted by telephone to check whether you still have symptoms.


You test positive for COVID-19
Your doctor will approach You to participate in this study
You decide to participate in this study
Treatment with plasma with antibodies against corona
345 patients
Treatment with plasma without antibodies to corona
345 patients
Day 1
Telephone contact
Day 7, 14, 28
The outcomes (duration of recovery, hospitalisation and death) are compared with patients who received plasma without antibodies

The additional studies you can participate in, if you wish:

If you choose to participate in (one of) the additional studies listed below, you will be called or invited to come to the hospital several times after the plasma has been administered. These are the 4 studies in which you can participate:

- (**Only for patients that are at least 70 years old). Research into daily functioning and quality of life after COVID-19 infection in patients 70 years of age or older**. To find out how daily functioning is affected after experiencing COVID-19, we will ask a number of additional questions by telephone, 1, 3 and 6 months after the plasma was administered.
- **Research into how quickly the virus disappears after administration of plasma and into antibodies against COVID-19 infection in the blood**. To study how the antibodies against COVID-19 develop, one tube of blood is taken on days 1, 3, 7, 14 and 28 to measure the number of antibodies against COVID-19 in the blood. It is also tested whether the virus is still detectable in the nose and throat at that time. The blood test and the throat and nose swab will take place in the hospital and you can bring an informal caregiver to your appointment.
- **Research into the long-term resistance (immunity) to COVID-19**.To examine how resistance to COVID-19 has developed, blood is drawn on the first day, after 14 days, after 28 days, after 3 months, after 6 months and after 1 year to see how your immune system has developed. These are 6 tubes of blood per blood draw moment. The blood test takes place in hospital and you can bring an informal caregiver to your appointment.
- **Long-term lung damage examination**. To examine how frequently there is permanent lung damage after experiencing COVID-19, a measurement is made 3 months after the start of the study on how well the lungs have recovered. We measure the recovery of the lungs by using a lung function test consisting of blowing in and out several times in a measuring device. In addition, a scan (a so-called low dose CT scan) of the lungs will also be made. You will also be asked to complete some questionnaires. The blood test takes place in the hospital and you can bring an informal caregiver to your appointment.

5 What is expected of you

For the research to run smoothly, it is important that you follow the study instructions:

- Keep to the appointments for telephone contacts.
- If you participate in 1 of the additional studies, you also follow the instructions in that regard.
- It is important that you contact your GP or the hospital researcher, whose contact details can be found in Appendix A to this letter:
    - If you are admitted to a hospital.
    - If you no longer want to participate in the study.
    - If your contact details change.

6 Possible side effects and discomfort

The administration of plasma can have side effects. If you participate in this study, you will have plasma administered with or without antibodies against the coronavirus. Over the past 6 months, a great deal of experience has been gained worldwide with the administration of plasma. Although it has not yet been proven to be an effective treatment, it has been found that the treatment very rarely leads to serious side effects. An American study in which 5000 patients were administered plasma found that 25 patients (0.5%) suffered from a serious adverse reaction. In an earlier study in the Netherlands, we also administered plasma to a total of approximately 50 COVID-19 patients. No life-threatening side effects were seen in any of these patients. We therefore estimate the risk of serious side effects to be extremely small. Appendix D contains a list of the most common side

effects of plasma.

Measurements:
A number of additional actions and inconveniences are associated with the additional examinations:

- Participants in the study for the elderly aged 70 or older will be asked additional questions via a telephone interview.
- Participants in the study into the disappearance of the virus will be repeatedly tested with a cotton swab in their nose and throat to see if the virus is still present and additional blood samples will be collected. This can feel uncomfortable and slightly painful. There may also be a bruise after the injection. Forty ml of blood is taken over 4 weeks (10 ml at a time).
- In participants in the study about long-term resistance: a blood vessel is pierced to take some blood. Puncturing a blood vessel can feel uncomfortable and slightly painful. There may also be a bruise after the injection. Depending on the additional examination in which you participate, 354 ml of blood will be taken, spread over a year (so 54 ml of blood will be taken at 6 different times). By way of comparison: 500 ml of blood is taken from the blood bank each time someone donates blood.
- Participants in the study on lung damage will have a lung function test 3 months after the start of the study. There will also be a scan (CT) of the lungs, and you will be asked to complete a questionnaire.

Radioactive exposure
If you participate in the examination into lung damage by the coronavirus, you will be exposed to X-rays with a low-dose CT during the scanning of the lung. During this low-dose CT, you will be exposed to an amount of radiation of 2 mSV. This is comparable to the amount of radiation to which an adult is exposed in 12 months as a result of natural radiation.
Very occasionally we find something during the study that requires further medical testing. We always inform you about this. Any further research into this, is done by your own GP or specialist. The costs for this are covered by your own health insurance.

7 Possible benefits and disadvantages

It is important that you carefully consider the possible advantages and disadvantages before deciding to participate or not.

Possible benefits:

- Treatment of the coronavirus with plasma with antibodies on top of the standard treatment can potentially lead to a faster cure and/or prevent hospitalization and/or improve the chance of survival. This is not yet certain and that is why we are conducting this study.

Disadvantages of participating in the study can be:

- Possible additional side effects from the administration of plasma.
- Both groups, the group receiving the treatment (plasma with antibodies) but also the control group (plasma without antibodies, placebo) must come to the hospital for a day for plasma administration.

Participation in the additional examinations means, depending on what you are going to participate in, additional blood tests, additional nose-throat swab, additional breathalyser and lung scan and additional questionnaires that you must complete.

8 If you do not want to participate or want to discontinue with the study

You decide as to whether you want to participate in the study. Participation is entirely voluntary. If you do not want to participate, you will be treated for your infection in the usual way; according to the guideline and based on what your doctor considers right at the time.

If you do participate, you can always change your mind and discontinue, even during the study. This also applies to the various additional studies during this study. You will then be treated as usual for your infection again. You do not have to state why you are discontinuing. However, you must immediately report this to the researcher. The data collected up to that point will be used in this study. If you want to, the collected blood or other body material can be destroyed.

9 End of the study

Your participation in the study will stop if:

- All visits as described under point 4 have passed.
- You opted to discontinue.
- The entire study has come to an end.
- The researcher thinks it's better for you to discontinue.
- The researcher, the government or the reviewing medical ethics review committee decides to discontinue with the study. In that case, the researcher will inform you.

The entire study is over when all participants have finished their participation. After processing all the data, the researcher can inform you about the outcome of the entire study.

10 Use and storage of your data and body material

For this study, your personal data and body material (blood and virus test material) will be collected, used, and stored. This pertains to data such as your name, year of birth and data about your health. The collection use and storage of your data and your body material is necessary to be able to answer the questions asked in this study and to facilitate publishing of the results. We ask your consent for using your data and body material.

Confidentiality and storage of your data and body material

To protect your privacy, your data and your bodily material are encoded. Your name and other data that can directly identify you are omitted. Data can only be traced back to you with the key to the code. The key to the code remains safely stored in the hospital where you are being treated. Only the researcher in the hospital where you are being treated and employees of the hospital, who assist the researcher in conducting the study, know which code you have. The data and blood samples that are sent to the sponsor and any other parties involved in the study (e.g., Sanquin) only contain the code, but not your name or other data with which you can be identified. The data cannot be traced back to you in reports and publications about the study either. If you also participate in the study for patients aged 70 or older, your contact details (name and telephone number) will be shared with the research team of the Leiden University Medical Centre because they will go through the questionnaires with you by telephone. If you do not want to do so, you cannot participate in this study.

Access your data for verification

Some people can access all of your data in the hospital where you are being treated. Also, to the data that has not been encoded. This is necessary to facilitate checking whether the study has

been carried out properly and reliably. Persons who can inspect your data are: A quality controller (monitor) who works for the sponsor of the research, the committee that monitors the safety of the research and national supervisory authorities, for example the Healthcare and Youth Inspectorate in the Netherlands. They keep your information secret. We ask you to consent to this access.

Storage period for the data and body tissue

Your data must be stored for 15 years in the hospital where you are being treated and for 25 years with the researcher at the Erasmus MC. Your body material is not destroyed immediately after use. It is sent, encoded, to Erasmus MC and stored there so that it can be used in future studies, for example, into the usefulness for new tests to better detect a corona infection.

Storage and use of data and body tissue for other research

Your data and body material may also be important for other scientific research in the field of coronaviruses after this study has been completed. To this end, your body material will be stored at Erasmus MC for 25 years. You can indicate on the consent form as to whether you consent to this.

Withdrawing your consent

You can always withdraw your consent for the use of your personal data and body material. This applies to this study as well as to the storage and use for future research. The study data collected until you withdraw your consent will still be used in the study because a reliable representation of the results of this study necessitates this.

More information about your rights when processing data

For general information about your rights when processing your personal data, you can consult the website of the Dutch Data Protection Authority.

If you have any questions about your rights, please contact the person responsible for processing your personal data. For this study, this is Erasmus MC. See **Appendix A** for contact details.

If you have any questions or complaints about the processing of your personal data, we recommend that you first contact the study site (the hospital where you were treated). You can also contact the Data Protection Officer of the hospital where you are being treated, see **Appendix A**, or the Dutch Data Protection Authority.

Registration of the study

Information about this study is also included in 1 or more websites in which current medical scientific research is listed. It does not include any data that can be traced back to you. After the study, the website can display a summary of the results of this study. You can find this research with the search term CoV- Early on www.clinicaltrials.gov.

11 Insurance for participating patients in this study

Insurance has been taken out for everyone who participates in this study. The insurance covers damage caused as a result of this study. Not all damage is covered. In Appendix B you will find more information about the insurance and the exceptions. It also states to whom you can report damage.

12 Inform your GP

Your GP will be informed about participation in this study.

13 No compensation for participation

The administration of plasma and any additional examinations will cost you nothing. The sections of the treatment in this study that belong to standard care are declared with your health insurance, as would have been the case otherwise. You will not be paid for participating in this study except for reimbursement of travel costs when needed. If you participate in one of the sub-studies and you have to come to hospital for this, you will receive reimbursement for the (additional) travel costs.

14 Do you have questions?

If you have any questions, please contact the researcher. For independent advice about participating in this study, you can contact an independent doctor. He knows a lot about this study but has nothing to do with this study.

If you have any complaints about the study, you can discuss this with the researcher or with your attending physician. If you prefer not to do this, you can contact the complaints committee at your hospital. All information can be found in **Appendix A**: Contact details.

15 Signing of the consent form

When you have had sufficient reflection time, you will be asked to decide whether you want to participate in this study. If you consent, we will ask you to confirm it in writing on the accompanying consent form. By giving your written consent, you indicate that you have understood the information and that you agree to participate in the study. Both you and the researcher will receive a signed version of this consent form.

Thank you for reading this information. We trust that this will allow you to make an informed decision about your participation.

16 Appendices to this information

A: Contact details
B Information about the insurance C Consent form
D Summary of the side effects of a plasma infusion
E Schedule contact times

Appendix A Contact details

More information

You can get more information about the study from the researcher at your hospital:

<Name of the researcher>
<Department>
<Hospital>
<Tel.>

Independent doctor

As an independent doctor, you can

consult: Dr J.L. Nouwen
Internal Medicine, Infectious Diseases Department,
Erasmus MC Doctor Molewaterplein 40, 3015 GD,
Rotterdam
Tel: 010 7033510

The data protection officer

The data protection officer at Erasmus MC can be
reached at:
Functionaris.gegevensbescherming@erasmusmc.nl
Tel. 010 703 49 86

The data protection officer at your hospital can be reached at:
<E-mail address>
<Tel.>

Complaints

You can submit a complaint to:
<Complaints committee at the name of hospital>
<Contactable via telephone number during office hours>

Appendix B Information about the insurance

Insurance has been taken out by Erasmus MC for everyone participating in this study. The insurance covers damage due to participation in the study. This applies to damage manifesting during the study or within four years of the end of your participation in the study. You must notify the insurance company about the damage within those four years.

The insurance does not cover all damages. The damages that are not covered are listed briefly at the end of this text.This is set out in the Medical Research (Human Subjects) Compulsory Insurance Decree. This decree can be found in the Law Bank of the government (https://wetten.overheid.nl). If you have any questions, please contact the insurer directly.

The insurer of this study is:	
Name:	CNA nsurance Company imited
Address:	Polaris avenue 140 2134 JX Hoofddorp
Telephone number:	021 – 3036004
E-mai:l	Esther.vanherk@cnahardy.com
Policy number:	HCCD0416C / 10220695
Contact person:	Esther van Herk

The insurance provides cover for

- per test subject € 650.000
- for the entire study € 5.000.000
- per insurance year € 7.500.000

The insurance does **not** cover the following damage:

- damage because of a risk about which you have been informed in the written information. This does not apply if the risk is more serious than anticipated or if the risk was highly unlikely;
- damage to your health that would also have occurred if you had not taken part in the study;
- damage because of not (fully) following directions or instructions;
- damage to your descendants as a result of a negative effect of the study on you or your descendants;
- damage caused by an existing treatment method when researching existing treatment methods

Appendix C: Consent form from a test subject

Official title: *Convalescent plasma therapy from recovered patients to treat COVID-19 early in SARS- CoV-2 disease. (CoV-Early study)*

- I have read the information letter. I could also ask questions. My questions have been sufficiently answered. I had enough time to decide whether to participate or not.
- I know that participation is voluntary. I also know that I can decide at any time not to participate or to discontinue with the study. I do not have to provide a reason for that.
- I consent to my GP being informed that I am participating in this study.
- I consent to the collection and use of data, blood tests, and nose-throat swabs in the manner and for the purposes stated in the information letter.
- I know some people may have access to all of my data for the verification of the study. Those people are listed in this information letter. I give permission for such access by these persons.
- I give permission that my data may be kept for 15 years after the end of the study in the hospital and 25 years with the client.
- I consent to be informed of the findings of the screening if they are relevant to my health.
- I want to participate in this study

I do □ **CONSENT** □ **DO NOT CONSENT**
that my encoded data and the body material that was collected during this study will be kept for 25 years and that it can be used for future research in the field of coronaviruses.

I □ **WANT TO** □ **DO NOT WANT TO** participate
in the study of patients 70 years and older looking at daily functioning after a COVID-19 infection. To this end, I will be called a number of times to evaluate my health and functioning by telephone.

I □ **WANT TO** □ **DO NOT WANT TO** participate
In the study that looks at the speed at which the virus disappears from the body and the number of antibodies that are detectable in the blood in the first 4 weeks after the administration of plasma. To this end, a blood and a nose-throat smear will be taken on days 1, 3, 7, 14 and 28.

I □ **WANT TO** □ **DO NOT WANT TO** participate
in the study that looks at developing long-term resistance to COVID-19 infection in which blood is drawn after 3, 6 and 12 months to examine the immune system.

I □ **WANT TO** □ **DO NOT WANT TO** participate
in the study looking at the long-term effects of COVID-19 infection on lung function through questionnaires, lung function tests and CT scan.
(tick your choice above)

Name of the test subject:

Signature: Date: / / _

I declare that I have fully informed this subject about the study referred to. If information becomes known during the study that could influence the subject's consent, I will inform him/her in good time.

Name of researcher (or his representative):

Signature: Date: / / _

Additional information is provided by (if

applicable): Name:

Position:

Signature: Date: / / _

Appendix D summary of the side effects of a plasma infusion

The side effects of plasma transfusion are comparable to the side effects of a blood transfusion. The side effects for plasma are described below.

Side effects reported during plasma treatment are in order of occurrence

Common (1-10%): hives, itching.

Sometimes (0,1-1%): allergic reaction (anaphylactic reaction). Nausea, vomiting. Increased sensitivity to touch. Low blood oxygen level. Fever.

Uncommon (0,01-0,1%): hypersensitivity.

Extremely uncommon (< 0,01%): anaphylactic reaction (incl. shock). Cardiac arrest, tachycardia, arrhythmia. Circulatory collapse, embolism, hypertension, hypotension, flushing. Pulmonary haemorrhage, pulmonary oedema, bronchospasm, shortness of breath (dyspnoea), respiratory failure. Restlessness, anxiety, agitation. Haemolytic anemia. Increased tendency to bleed (haemorrhagic diathesis). Dizziness, paraesthesia. Abdominal pain. Backache. (Erythematous) rash, hyperhidrosis. Chest pain, chills, malaise. Application site reactions (including oedema). Transfusion-related circulatory overload, haemolytic transfusion reaction. Signs of citrate intoxication such as fatigue, paraesthesia, tremor, hypocalcaemia, and cardiovascular effects may occur; especially with high infusion rates, liver function disorders or plasma exchange transfusions. Positive antibody test decreased oxygen saturation.

Appendix E Schedule contact times

Study schedule contact times

	Screening Day 1	Baseline Day 1	Day 3	Day 7	Day 14	Day 28	Day 90 (optional)
Blood sample for blood group testing and an antibodies test as well as a nose-throat smear for SARS-CoV-2 test	X						X (optional)
Plasma administration		X					
Measurement of the blood oxygen level		X					
Telephone contact				X	X	X	

Study schedule contact times sub-examinations

	Screening Day 1	Baseline Day 1	Day 3	Day 7	Day 14	Day 28	Month 3	Month 6	Month 12
Blood sample for the level of the height antibodies (1 tube) + nose-throat swab		x	x	x	x	x			
Blood collection for immune tests (7 tubes)		x			x	x	x	x	x
Questionnaire for daily functioning > 70 years		x				x	x	x	
Lung function test, questionnaire, and CT of the lung							x + CT	See *	See *

* Only if the pulmonologist considers this necessary because there is permanent lung damage, you will be asked to undergo another lung examination 6 and 12 months after the start of the study.