Protocol Title: Open randomized controlled phase 2 clinical trial for evaluation of safety and efficacy **of COVID-19 convalescent plasma compared to standard care for treatment of COVID-19 disease in elderly patients in care homes.**

Compound: Convalescent plasma donated from healthy convalescent COVID-19 patients with SARS-CoV-2 antibodies

Brief Title: Norwegian COVID-19 convalescent plasma treatment study in elderly patients in care homes.

Study Phase: 2a

Acronym: NORPLASMA CARE

Sponsor Name: Oslo University Hospital, Oslo, Norway

Manufacturer: Blood banks at the following Norwegian hospitals: Oslo University Hospital, Haukeland University Hospital, St. Olav's Hospital

Approval Date:

Coordinating institution Signatory:

John Torgils Vaage	**Date**
Oslo University Hospital	

Medical Monitor: CTU, Forskningsstøtte, Oslo University Hospital

The principal investigator will be responsible for treatment of the participants at the different municipal care homes. The municipality is considered as one site.

Ambulant transfusion team from the coordinating institution will assure transfusions to all participants.

Safety information will be gathered from the care homes.

Contact Details:

Coordinating institution :	**Oslo University Hospital** Address: PO Box 4950 Nydalen, 0424 Oslo Tel: 0278 E-mail:
Coordinating Investigator:	**Børre Fevang** Address: Section of Clinical Immunology and Infectious Diseases, Oslo University Hospital Tel: 47084581 E-mail: borre.fevang@ous-hf.no
Principal Investigator:	**To be determined in each participating municipality** Address: Tel: E-mail:

Innhold

1. Protocol Summary

Overall Design:	**Open, randomized controlled trial**

1.1. Synopsis

Protocol Title: Open randomized controlled phase 2 clinical trial for evaluation of safety and efficacy **of COVID-19 convalescent plasma compared to standard care for treatment of COVID-19 disease in elderly patients in care homes.**

Brief Title: Norwegian COVID-19 convalescent plasma treatment study in elderly patients in care homes.

Rationale: There is currently no approved and accessible treatment for COVID-19. Convalescent plasma from donors may provide a safe and effective treatment to reduce mortality, severity and duration of institutional care for elderly COVID-19 patients in care homes.

Objectives and endpoints

Objectives	Endpoints
Primary	
Assess the effect of convalescent plasma on mortality in COVID-19	Primary endpoint: All-cause mortality within the first 28 days of observation. Secondary endpoints: All-cause mortality within 60 days of observation.
Secondary	
Effect of convalescent plasma on recovery time in patients with active COVID-19 infection	Time from intervention to negative SARS-CoV-2 PCR during a 28 days observation period.
Effect of convalescent plasma on clinical progression of COVID-19 disease	Requirement of oxygen therapy at days 1, 3, 7, 14, 21 and 28 compared to baseline. Change in NEWS score at days 1, 3, 7, 14, 21 and 28 compared to baseline.
Exploratory	
Effect of convalescent plasma on biomarkers in COVID-19	Change in CRP and lymphocyte count at day 1, 3, 7 and 14 after intervention. Time to normalized CRP and lymphocyte count.
Safety of convalescent plasma in COVID-19	Incidence of adverse events.

Brief Summary:	**The objective of this study is to evaluate the safety and efficacy of convalescent plasma treatment in symptomatic elderly COVID-19 patients in Norwegian care homes.** **Approximately 500 eligible participants will randomly allocated to either the intervention (Convalescent plasma and standard care) or control (standard care only) group in a 1:1 ratio. Participants will be followed up over a 60-day observation period.**
Intervention Group and Duration:	**Participants randomized to treatment group will receive convalescent plasma treatment within 2 days after randomization. They will be followed up for 60 days.**
Data Monitoring Committee:	**Yes**
Project leader	**Lise Sofie Haug Nissen-Meyer, Oslo University Hospital**
National coordinating institution:	**Oslo University Hospital**
Study sites:	**Study sites are defined as the care home department of participating municipalities**
Study monitor:	**Clinical trial unit (CTU), Oslo University Hospital**
Study setting:	**Norwegian care homes for elderly patients in participating municipalities**
Inclusion and exclusion criteria	**Inclusion criteria** **1. Age >50 years** **2. SARS-CoV-2 PCR positive in respiratory tract sample within 3 days before inclusion** **3. Onset of symptoms within 7 days before intervention as assessed by the attending clinician,** **4. Voluntary, informed and documented consent by patient or guardian** **Exclusion criteria** **1. Included in any other interventional study for the treatment of COVID-19** **2. Allergic reactions to plasma products** **3. Acute severe co-morbidity**

	4. Estimated life-expectancy <90 days prior to symptomatic COVID-19 as assessed by attending clinician. **5. Other reasons where the attending clinician deems trial participation to be against the best interest of the patient**
Intervention	SARS-CoV-2 convalescent plasma (1 unit; ~200-300 mL) from blood donors who were diagnosed and have recovered from COVID-19 infection, tested and released according to criteria from the Norwegian Health Directorate.
Description of groups	Group 1: Standard of care + convalescent plasma given according to criteria Group 2: Standard of care
Criteria for interruption	There will be one interim analysis for efficacy after half of the patients (n=253) have completed the first 28 days of follow-up. The study will be stopped if the interim analysis demonstrates superiority of the intervention. The steering committee can decide to interrupt the study early if the data monitoring committee recommends discontinuation for safety reasons
Study duration	1. July 2020 – 30. June 2021
Recruitment	To support the recruitment for the study, all COVID-19 RT-PCR confirmed patients who are or will be admitted to nursing homes are reported to the principal investigator. This will initiate the process to engage with the patient and / or relatives to offer participation.
Supportive treatment allowed	Guidelines for the treatment of COVID-19 in nursing homes for this patient group are described by the Norwegian Institute of Public Health and local health authorities. The medical professionals responsible at the nursing home are responsible for providing the health care considered to be professionally required regardless of the purpose of the study.
Participants' timeframe	The events in which study participants are planned to be engaged are described in section "Schedule of activities". Briefly, consent and enrolment will take place within 2 days of notification of the study team for patients fulfilling the case definition for a confirmed COVID-19 patient. Randomization and plasma transfusion will take place immediately after enrolment, by an ambulant transfusion team. Blood samples will be taken at day 0, 1, 3, 7 and 14 in the study period. Oropharynx samples will be taken at day 0, 1, 3, 7, 14, 21 and 28 in the study period.

1.2. Schedule of Activities (SoA)

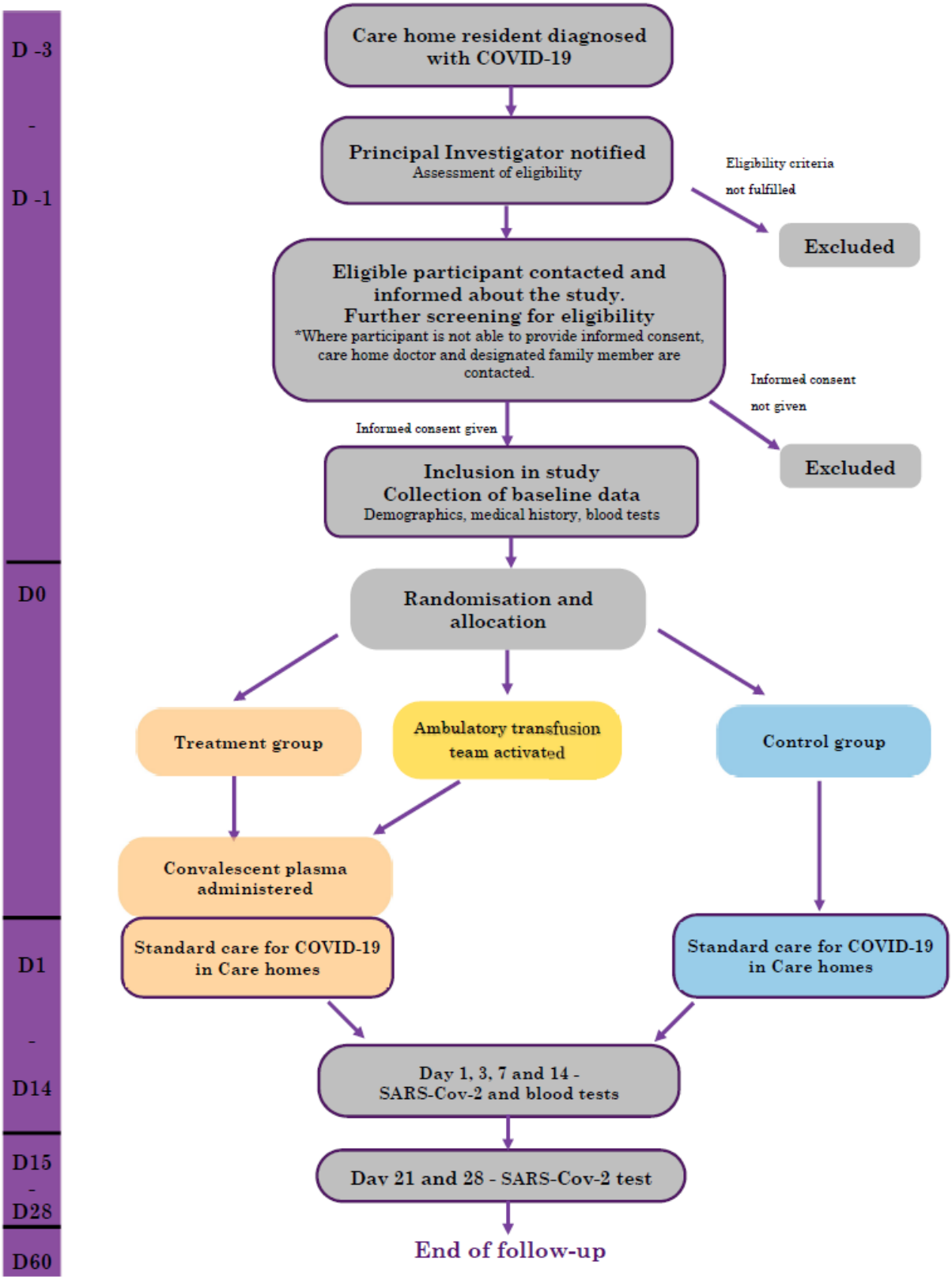
Activities are scheduled as presented in table and flow-chart below.

Procedure	Screening (up to intervention day)	Intervention (day 0)	Observation Period (day 1-60)						
		0	1	3	7	14	21	28	60
Informed consent	X								
Inclusion and exclusion criteria	X								
Randomization	X								
Demography	X								
Height and weight	X								
Medical status and co-morbidities	X								
Current medication	X								
Blood samples*		X	X	X	X	X			
Oropharynx samples**		X	X	X	X	X	X	X	
Clinical assessment***		X	X	X	X	X	X	X	
Mortality registration								X	X
Study intervention (plasma transfusion)		X							
AE and SAE review									X

* Blood: Hemoglobin, thrombocytes, leukocytes with differential count, CRP, anti-Spike IgG.

**Oropharynx: RTPCR SARS-CoV-2.

*** Registration of oxygen therapy at all care homes, NEWS score where implemented in the care home routines.


D -3
-
D -1
D0
D1
-
D14
D15
-
D28
D60
Care home resident diagnosed with COVID-19
Principal Investigator notified
Assessment of eligibility
Eligibility criteria not fulfilled
Excluded
Eligible participant contacted and informed about the study.
Further screening for eligibility
*Where participant is not able to provide informed consent, care home doctor and designated family member are contacted.
Informed consent not given
Excluded
Informed consent given
Inclusion in study
Collection of baseline data
Demographics, medical history, blood tests
Randomisation and allocation
Treatment group
Ambulatory transfusion team activated
Control group
Convalescent plasma administered
Standard care for COVID-19 in Care homes
Standard care for COVID-19 in Care homes
Day 1, 3, 7 and 14 - SARS-Cov-2 and blood tests
Dav 21 and 28 - SARS-Cov-2 test
End of follow-up

2. Introduction

Since the first confirmed case in Norway on Feb 26th 2020 the number of cases rapidly increased over a one months' period. Currently, (May 26th) there are 8364 cases of confirmed infected, 235 deaths. Although currently under control scenarios prepared by the Norwegian Institute of Public Health indicates a risk of a second wave of cases in the coming months, exceeding the capacity to treat patients. The ability to provide satisfactory treatment to at-risk groups will then be severely impaired, and high mortality can be expected. Health workers may also be exposed to a high risk of infection. Infection prevention measures in the population have been effective, but on return to normalcy of school closures, kindergartens and businesses the number of cases is expected to increase further. The duration of a second wave of the epidemic is unknown and may last for 6-8 months, perhaps longer, depending on the effectiveness and overall societal acceptability of continuing physical distance measures. The physical distancing interventions have severe effects on health and finance, but it will likely be in effect in some degree until effective treatment or vaccines are available. However, availability of vaccines and new anti-viral drugs will be very restricted due to the universal desire to source these, and it is uncertain whether Norway when will be able to source these at a scale aligned with the estimated demand.

2.1. Study Rationale

Convalescent plasma in the treatment of infections was used during the H1N1 influenza pandemic of 1918-20 (McGuire&Redden 1918, Luke et al 2006). In the pre-antibiotics area convalescent plasma was also used to treat bacterial disease (Casadevall&Scharff 1995). Data from clinical trials using convalescent plasma during the SARS-CoV-1 epidemic demonstrated clinical improvements in the patients if transfused early. Two studies from 2020 that included 10 (Duan et al PNAS 2020) and 5 (Shen et al JAMA 2020) cases who were given SARS-CoV-2 convalescent plasma documented clinical improvements along several parameters. A matched control study in US patients showed benefit in non-intubated patients (Sean et al, 2020). The first randomized clinical study in China was terminated due to lack of effect in late stages (Li et al, 2020), but also reported potential benefits (Casadevall, Joyner & Pirofski, 2020). There are also reports of more anecdotal character. In the absence of any documented efficient drugs or vaccines it is highly rational to perform a clinical trial of the safety and efficacy of SARS-CoV-2 convalescent plasma. COVID-19 associated mortality is highest in patients older than 65 years. A randomized clinical trial in this risk group using convalescent plasma early after CoV-2 diagnosis will yield the highest probability of demonstrating an effect.

2.2. Background

Originating in Wuhan Province of China in late 2019, a new coronavirus named SARS-CoV-2 has spread throughout much of the world. The virus, which causes respiratory infection and in some a serious respiratory illness, was declared a pandemic by WHO in March. As of ultimo May 2020, the number of detected infected is approaching 5,5 million worldwide, and more than 350,000 people have died. In addition, the numbers of actual infected are underestimated as adequate testing in large parts of the world is impossible and a substantial number of cases are

asymptomatic. In Norway, drastic measures have achieved a controlled spread of virus, and we are currently able to treat the number of patients within the total hospital care capacity, including intensive care units. However, it must be assumed that the spread of infection will continue and that a significant number of patients will die before vaccines become available. Although most people experience mild infection, serious illness and high mortality has been observed especially among the elderly, individuals with comorbidities such as cardiovascular disease, diabetes and obesity.

As per end of May 2020, about 90% of the 235 deaths reported in Norway due to COVID-19 had occurred between patients aged 70 years or more, and 60% of all deaths occurred among patients admitted to institutions outside hospitals. Within outbreaks in care homes in Norway, case fatality rates of 15 to 50% have been reported in 2020. Patients in care homes are not prioritized for any advanced supportive medical treatment for COVID-19, and mechanical ventilation is not an option in these institutions.

The WHO has provided strategic guidelines (WHO Roadmap) for prioritization of which treatment alternatives should be systematically tested, and included convalescence plasma an alternative to consider. Norwegian hospitals are already part of the WHO Solidarity treatment trial to evaluate the safety and efficacy of antiviral treatments. Based on the potential to provide an effective COVID-19 treatment with reliably local supply until a safe and effective vaccine is available, Norwegian blood banks led by the Norwegian Health Directorate have converged on a national project for the collection and testing of convalescence plasma.

At several leading centers in the world different variants of clinical trials are now underway to clarify the efficacy and safety of treatment with convalescence plasma. Several countries' health authorities (among others in the USA, Italy and Sweden) also allow use outside study settings, conditional to the reporting of data before and after transfusion to enable later efficacy evaluation (https://ccpp19.org/).

In Norway, plasma is being prepared in accordance with guidance from the European Blood Alliance (EBA) (https://ec.europa.eu/health/blood_tissues_organs/COVID-19). The Norwegian Directorate for Health has issued guidelines for the Norwegian blood banks to ensure adherence with the EBA guidance.

2.3. Benefit/Risk Assessment

Convalescent plasma has not yet been shown to be safe and effective as a treatment for COVID-19. A pre-publication study on safety in 5000 patients indicates that convalescent plasma treatment is safe, even to critically ill COVID-19 patients (Joyner et al 2020).

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Risks commonly associated with transfusion	Low frequency, but higher risk for transfusion associated complications among elderly	Preparation of plasma according to EU guidelines for COVID-19

Allergic reaction Viral infection Plasma may not be effective Based on studies in animals with vaccines against SARS-CoV-2. there is a theoretical risk of antibody dependent disease enhancement (ADE) associated with antibodies against the S protein (deAlwis et al 2020)	Antibody titer criterion for critical level of functional antibodies	Eligibility criteria for patients

2.3.2. Benefit Assessment

Convalescent plasma is not proven to provide any benefit for treatment of COVID-19. Potential benefit of receiving convalescent plasma during the study duration is to reduce the mortality, severity of disease and/or shorten the time of treatment for COVID-19 patients.

Participation in this study will hopefully lead to the determination of the safety and efficacy of convalescent plasma for treatment of COVID-19, and hence can inform the health authorities' decision to recommend plasma treatment for wider use. This can potentially save lives and reduce the need for infection prevention control measures targeted on reducing transmission to ultimately prevent the most vulnerable groups at risk for contracting COVID-19 disease

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with COVID-19 convalescent plasma are justified by the anticipated benefits that may be afforded to participants with COVID-19.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
Assess the effect of convalescent plasma on mortality in COVID-19	Primary endpoint: All-cause mortality within the first 28 days of observation. Secondary endpoints: All-cause mortality within 60 days of observation.
Secondary	
Effect of convalescent plasma on recovery time in patients with active COVID-19 infection	Time from intervention to negative SARS-CoV-2 PCR during a 28 day observation period
Effect of convalescent plasma on clinical progression of COVID-19 disease	Requirement of oxygen therapy at days 1, 3, 7, 14, 21 and 28 compared to baseline Change in NEWS score at days 1, 3, 7, 14 , 21 and 28 compared to baseline
Exploratory	
Effect of convalescent plasma on biomarkers in COVID-19	Change in CRP and lymphocyte count at day 1, 3, 7 and 14 in the study period. Time to normalized CRP and lymphocyte count
Safety of convalescent plasma in COVID-19	Incidence of adverse events

4. Study Design

4.1. Overall design

The *Norwegian convalescent plasma in COVID-19 study* is an unblinded randomized controlled trial investigating the effects of convalescent plasma on the clinical course of disease in patients with active COVID-19.

Patients referred to or staying at nursing homes with newly diagnosed symptomatic COVID-19 infection and a positive SARS-CoV-2 PCR in a respiratory tract sample will be randomized 1:1 to be given:

-Local standard supportive treatment alone

OR

-Local standard supportive treatment AND a single dose of COVID-19 convalescent plasma transfusion

Participants will be followed up on-site for up to 28 days by clinical assessments, respiratory tract sampling for SARS-CoV-2 PCR and biochemical testing at a pre-specified schedule. Participants will be followed up remotely for up to 60 days after intervention to assess mortality.

4.2. Scientific rationale for study design

Innate and adaptive immune responses play a central role in combating viral infections like COVID-19. The innate immune system represents an immediate and first frontline that sets the stage for a more advanced and specific adaptive immune response that typically arises some days later. This adaptive immune response includes the production of increasingly specific antibodies in the form of immunoglobulins M and G (IgM and IgG, respectively) directed towards the invading culprit. These immunoglobulins thus represent an end product and the pinnacle of the immunological response, capable of destroying the invading microbe both directly and indirectly. Immunoglobulins are furthermore a central part of immunological memory, i.e. the ability of the immune system to “remember” an invading pathogen and mount a swift and powerful response to a second challenge. Administering specific antibodies to an individual with no immunological memory to the pathogen – either in the form of vaccines (like hepatitis A, hepatitis B) or therapeutically (like Varicella, Rabies, hepatitis B) - mimics this memory and gives the patient a well-documented advantage in fighting off the infection. The injected antibodies give the adaptive immune system a head-on start even as it starts to produce its own antibodies.

Immunoglobulins constitute a major part of human plasma, and plasma will therefore include specific antibodies towards a wide range of pathogens, including both bacteria and virus. The composition and relative abundance of this antibody repertoire will vary between individuals, but a major feature will be relatively high levels of antibodies towards recently encountered microbes and infections. The use of serum or plasma from recently immunized individuals (or horses) that contain high levels of relevant antibodies to treat newly infected individuals have a long tradition in human medicine but few studies have actually tested the effect in a rigorous manner.

COVID-19 disease elicits varying degree of both innate and adaptive immune response in infected patients. Preliminary reports suggests there is an initial delay of innate antiviral mechanisms leaving the SARS-CoV-2 virus with an extended replicative phase of typically 3-5 days before the patient's immune system reacts properly and the patient enters a symptomatic stage that can include fever, cough, dyspnea, rhinorrhea, diarrhea, nausea and abdominal pain. The adaptive immune response to SARS-CoV-2 is poorly understood with a striking variability in the production of specific antibodies that seem related to the degree of symptomatic disease, while the nature of adaptive cellular responses is characterized by a pan-T cell depletion. Specific SARS-CoV-2 antibodies have been detected as early as the first week after debut of symptoms in moderately and severely ill patients with the prevalence of seropositivity gradually increasing to 100 % after 3 weeks.

Recent case reports or case series from China, with the inherent bias of small sample size and open, non-controlled clinical trials, indicated no major safety issues. It was not possible to elucidate any effect of plasma on the course of disease, due to concomitant therapy with other drug interventions (Duan et al 2020, Shen et al 2020). A matched control study in US patients showed benefit in non-intubated patients (Sean et al, 2020). The first randomized clinical study in China was terminated due to lack of effect in late stages (Li et al, 2020), but potential benefits were also reported (Casadevall, Joyner & Pirofski, 2020).

There is however a strong scientific rationale for testing the efficacy of convalescent plasma in treatment of COVID-19 patients, and this study is designed to maximize the effect of the plasma by including patients in an early stage of the disease.

4.3 Justification for dose

The suggested dosing of SARS-CoV-2 convalescent plasma for transfusion is 1 unit; ~200-350 mL. This is based on the volume of available plasma drawn from donors in one unit, and from a prior study of SARS-CoV-1 patients in 2005 showing clinical benefit at median 291 mL plasma administered per patient.

4.4 End of study definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if he/she has completed all procedures of the study including the last visit.

5. Study Population

The target population for this study is individuals above the age of 50 in early stages of COVID-19 disease. Participants will be recruited from municipal healthcare institutions that admit and care for symptomatic COVID-19 patients in need of medical care but not referred to hospitals.

In Norway, around 15% of the population is aged 67 years or more. In 2018, around 32200 persons were living in care homes for the elderly on long term basis, and an additional 9000 persons on time-limited stays.

Data on COVID-19 in Norway showed that at end of April 2020, among the total 204 deaths in the population reported, 60% were among patients in institutions outside hospitals, and 89% of the total 204 deaths were persons aged 70 years or more (FHI.no).

The population in care homes has a high proportion of dementia and co-morbidities, which both are significant factors to take into account in the study implementation and outcome analysis. In particular, the presence of dementia represents a challenge for the consent to participate which will need to be handled by the patient′s guardian if such is appointed, acting in the best interest of the patient.

5.1. Inclusion criteria

1. Age >50 years
2. SARS-CoV-2 PCR positive in respiratory tract sample within 3 days before intervention
3. Onset of symptoms within 7 days before intervention as assessed by the attending clinician
4. Volunteered, informed and documented consent by patient or guardian.

5.2. Exclusion criteria

1. Included in any other RCT
2. Allergic reactions to plasma products
3. Acute severe co-morbidity
4. Estimated life-expectancy <90 days prior to COVID-19 as assessed by the attending clinician.
5. Other reasons where the attending clinician deems trial participation to be against the best interest of the patient

5.3. Study Intervention and Concomitant Therapy

Convalescent plasma will be collected from volunteer non-paid donors who recovered from a CoV-2 infection. Collection volume will be split to therapeutic units of 200-300 ml. Previous medical therapy will be continued with no interruption.

6. Study Intervention Administered

ARM Name	COVID-19 convalescent plasma
Intervention Name	ISBT E9735 CONVALESCENT PLASMA|CPD/XX/<=-18C|COVID-19 ISBT E9736 Apheresis CONVALESCENT PLASMA|CPD/XX/<=-18C|COVID-19 ISBT E9754 Apheresis CONVALESCENT PLASMA|ACD-A/XX/<=-18C|1st container|COVID-19 ISBT E9755 Apheresis CONVALESCENT PLASMA|ACD-A/XX/<=-18C|2nd container|COVID-19 ISBT E9756 Apheresis CONVALESCENT PLASMA|ACD-A/XX/<=-18C|3rd container|COVID-19 ISBT E9757 Apheresis CONVALESCENT PLASMA|ACD-A/XX/<=-18C|4th container|COVID-19
Type	Biologic
Dose Formulation	200-300 ml
Unit Dose Strength(s)	High titer, defined as virus neutralization assay titer >1:160 or equivalent in accordance with EBA (to be confirmed)
Dosage Level(s)	1 dose at inclusion
Route of Administration	I.V. transfusion
Use	Clinical indication
IMP and NIMP	Investigational Medicinal product (IMP)
Sourcing	COVID-19 convalescent plasma from voluntary non-paid donors at the following Norwegian blood banks: Oslo University Hospital, Haukeland University Hospital, St. Olav's Hospital
Packaging and Labeling	Following local SOP for plasma-labeling, using the correct ISBT code

6.1. Preparation/Handling/Storage/Accountability

The study intervention will be manufactured at collaborative blood bank units according to specified procedures. Briefly, potential donors of convalescent plasma will be evaluated at the blood-bank according to local SOP for plasma donors, regulated by "Blodforskriften". Male donors with previous transfusion history and all female donors will be screened for HLA I and HLA II antibodies. As a rule, plasma will be collected by apheresis in volumes of 600-850ml

dependent on body weight, and later split into therapeutic units of 200-350 ml before freezing according to local SOP. Plasma derived from a full-blood donation may also be used.

At the coordinating institution

1. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the ambulatory team.
3. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. Administration will follow SOP for transfusion. Blood pressure, pulse, respiratory frequency and temperature will be taken at pre-specified time-points (before transfusion, at the end of transfusion, 15 minutes after transfusion and 1 hour after transfusion.
4. Authorized site staff must monitor participants closely for 1 hour after study intervention for signs of adverse events. SAEs (Section 8.3) and other serious events (Section 8.3.5) will be reported immediately to the Medical Monitor, and an adverse events form will be recorded at the end of the study participation.
5. The coordinating investigator is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

6.2. Measures to Minimize Bias: Randomization and Blinding

Sequence: A randomization sequence will be generated in a computer program and associated with predefined rows of unique patient identification numbers and inserted into the electronic data capture system (EDCS). After the participant has consented the ambulatory team will be informed and will randomize the participant using the EDCS.

Implementation; The randomization list will be produced by the CTU at OUH.

Blinding: This is an open-label, randomized controlled trial with a plasma arm administered as a transfusion, and all participants and staff will thus know the intervention to which the patient is allocated.

6.3. Study Intervention Compliance

When participants are dosed at the nursing homes, they will receive study intervention directly from the ambulatory team. The date and time of each dose administered in the nursing home will be recorded in the source documents and recorded. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.4. Dose Modification

All participants will be evaluated before inclusion and should be eligible for receiving the maximum volume of 300ml plasma. In case of adverse events, transfusion will be terminated, possibly resulting in a dose reduction. The actual dose of the study intervention will then be recorded and these participants will be excluded from the PPS.

6.5. Treatment of Overdose

Overdosing with plasma is not relevant. TACO or excess/perturbed fluid-balance will be considered under adverse events.

6.6. Concomitant Therapy

Any medication or vaccine that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

No medication is contraindicated.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

In this study there is only one intervention performed (plasma transfusion) directly after the informed consent has been obtained.

7.2. Participant Discontinuation/Withdrawal from the Study

In cases when the patient withdraws his/her consent:

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

7.3. Lost to Follow up

In this study, the majority of the patients will remain at the nursing home for the whole duration of the study. Some patients will, however, leave the nursing home for home based isolation at a point in time when the SARS-CoV-2 PCR is still positive. In such cases a home based visit will be performed by site personnel, to obtain the final measures according to the SoA.

A participant will be considered lost to follow-up if unable to be contacted by the study site. Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant.

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study. Where possible, telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods should be attempted. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including

those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up.

- Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. Study Assessments and Procedures

8.1. Efficacy assessments

The efficacy of convalescent plasma on the primary endpoint of all-cause mortality at day 28 will be recorded from the Norwegian death registry.

The efficacy of convalescent plasma on the secondary endpoint of all-cause mortality at day 60 will be recorded from the Norwegian death registry.

The efficacy of convalescent plasma on the secondary endpoint of recovery time will be assessed by repeated respiratory tract sampling for SARS-CoV-2 PCR analyses at day 1, 3, 7, 14 and 28. The site for sampling as well as the actual sampling technique will be standardized, underscoring the importance of a uniform procedure for all participating centers. Samples will be analyzed at the participating local microbial laboratories adhering to national guidelines for this testing. All samples for a single patient will be tested at the same laboratory to reduce inter-institutional variability. Samples will furthermore be stored for analyses at a core laboratory after the end of the study.

8.2. Safety assessments

The safety of convalescent plasma will be assessed through standard clinical observation during and after transfusion of the product. Any event will be registered on the adverse event form and in the case of a severe adverse event the principal investigator will be contacted.

In standard clinical practice patients are observed for 1 hour after infusion of plasma products, and the majority of adverse reactions will occur within this timeframe. However, a delayed adverse event can present and will be registered accordingly.

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs), and safety reporting

The general definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Appendix 3. Serious adverse events of special interest are described in Appendix 4: “Definitions of transfusion reactions”.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and qualified staff at the nursing homes are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs.

The study site will record AEs and SAEs is in the adverse events form as a part of the CRF. Both intensity and causality (related to transfusion/study intervention) of the event should be evaluated (Appendix 3).

8.3.1. Frequency for Collecting AE and SAE Information

All SAEs will be collected from the start of intervention until the end of the study period (day 60). Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions, not as AEs.

All SAEs will be recorded and reported to the medical monitor immediately and under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it.

8.3.5. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

The following disease-related events (DREs) are common in participants with COVID-19 and can be serious/life threatening:

- Fever and/or chills
- Need for increased oxygenation or ventilation support
- Persistent pain or pressure in the chest
- New-onset confusion
- Multiple organ dysfunction or failure

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of an SAE. These DREs will be followed by the medical monitor and recorded by the site designee for later evaluation by the Data Monitoring Committee (DMC).

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an AE/SAE (instead of a DRE):

The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

The investigator considers that there is a reasonable possibility that the event was related to study intervention.

8.3.6. Adverse Events of Special Interest

Adverse events of special interest (AESI) are defined as transfusion reactions as specified in Appendix 4, and will be registered in the Norwegian Directorate of Health's system for Hemovigilance monitoring.

8.4. Biomarkers and immunological assessments

Collection of biological samples for research is also part of this study. Samples will be collected in the general COVID-19 (SARS-CoV-2) Biobank at Oslo university hospital (REK:135924). The following samples for biomarker research will be collected from all participants in this study as specified in the SoA and Appendix 2:

- Oropharynx samples will be tested for presence of SARS-CoV-2 RNA to evaluate their association with the observed clinical responses to convalescent plasma.
- Blood samples will be tested for hemoglobin, thrombocytes, leukocytes with differential count and CRP. These samples will be tested by the sponsor or sponsor's designee.
- Serum samples will be tested for antibodies to SARS-CoV-2 Spike protein. These samples will be tested by the sponsor or sponsor's designee. Other analyses may be performed to further characterize the antibody profile after transfusion.
- Other samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to SARS-CoV-2, pathogenesis and protection mechanisms.
- Samples may be stored for a maximum of 5 years following the last participant’s last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to coronaviruses.

9. Statistical Considerations

9.1. Statistical Hypotheses

This study is designed to detect a 40% reduction in mortality with treatment of COVID-19 with convalescent plasma among the study population, under the assumption that the mortality in the standard care group is 30%.

The primary null hypothesis is that there is no difference in mortality between standard care and standard care + treatment with convalescent plasma.

The primary alternative hypothesis is that there is a difference in mortality between standard care and standard + treatment with convalescent plasma.

9.2. Sample Size Determination

In countries with at least 100 deaths in total and data are available, the proportion of COVID-related deaths among care home residents ranged from 19% in Hungary to 62% in Canada; for Norway this was 61%.

The case fatality rate among COVID-19 patients in institutions outside hospitals is inconsistently reported across multiple Western countries, including Norway (https://ltcCOVID.org).

In a study from Wuhan, China with 201 COVID-19 patients the CFR was 21.9% among a population with median age 51 years (IQR 43-60)(Wu et al 2020). Others have reported CFR among COVID-19 patients aged 80 years or above in Hubei, China at 39.0% (95% KI: 31.1-48.9%) and at 89.0% (95%KI: 56.2-99.6%) in North Italy (Hauser et al 2020)

Estimates for reduction in mortality among patients receiving convalescent plasma for treatment of COVID-19 have not been found. We therefore consider several different scenarios below (Table 1 and 2).

The sample size-calculations are based on a primary outcome of time to death, to be analyzed by a Cox regression model.

We consider this to be the most realistic scenario:: To achieve 80% power to detect a difference between 30% mortality in the standard care group and 18% mortality in the convalescent plasma group (a relative reduction in mortality of 40%, which corresponds to a hazard ratio of approximately 0.60), N = 502 patients need to be recruited and 121 deaths need to be observed during the follow-up period.

There will be one interim analysis of efficacy (on the primary outcome) after half the patients have completed the first 28 days of follow-up. We will use a O'Brien and Fleming group sequential design (Wassmer&Brannath, 2016), where the interim analysis will be performed with a significance level of α=0.0052, and the final analysis (after all patients have completed the

study) will be performed with a significance level of α=0.048, thus maintaining an overall significance level of 5%. The inflation factor with this design is 1.008, raising the total number of patients to N = 502*1.008 = 506. The interim analysis will be carried out on 253 patients.

Table 1: Sample size (and number of events) to achieve 80% power with a 5% significance level

	Relative reduction of mortality in the convalescent plasma group			
Mortality in the standard care group	**20% #events = 631**	**30% #events=247**	**40% #events=121**	**50% #events=66**
20%	N = 3503	N = 1452	N = 752	N = 436
30%	N = 2336	N = 968	N = 502	N = 291
40%	N = 1752	N = 726	N = 376	N = 218
50%	N = 1402	N = 581	N = 301	N = 175

Table 2: Corresponding mortality rates in the convalescent plasma group

	Relative reduction of mortality in the convalescent plasma group			
Mortality in the standard care group	**20%**	**30%**	**40%**	**50%**
20%	16%	14%	12%	10%
30%	24%	21%	18%	15%
40%	32%	28%	24%	20%
50%	40%	35%	30%	25%

9.3. Statistical Analyses

A statistical analysis plan (SAP) will be finalized prior to database lock. The SAP will include detailed descriptions of the statistical analyses of the primary and all secondary endpoints. This section briefly describes the primary analysis and some general statistical methods and considerations..

9.3.1. Randomization

Eligible patients with will be randomized in a 1:1 ratio to the intervention vs. control groups, i.e. standard care + convalescent plasma treatment vs. standard care alone. The randomization procedure will be performed electronically through the eCRF (Viedoc). The randomization list will be stratified according to study site (hospital or care home). Block randomization will be used, with block sizes of 4 and 6, in random order.

9.3.2. Analyses Sets

The statistical analyses will be performed on the Full Analysis Set (FAS), which will contain all patients with sufficient data to allow inclusion in the analyses, as randomized. The FAS analyses thereby comply with the intention to treat principle.

A secondary analysis of the primary outcome will be performed on a Per Protocol Set (PPS), where patients who did not receive the entire plasma treatment are excluded.

The FAS and the PPS will be described in detail in the SAP.

9.3.3. Primary Analysis

The primary endpoint is COVID-19 related mortality during the first 28 days of follow-up. The imary endpoint will be analyzed with a Cox regression model, with plasma treatment (yes/no) and study site (stratification factor in the randomization) as covariates. A hazard ratio of plasma treatment with a 95% confidence interval will be estimated, and a test of a hazard ratio equal to one will be performed.

The survival curves for the two groups (intervention vs. control) will be estimated and plotted with the Kaplan-Meier estimator and the equality of the survival curves will be tested with the log-rank test.

The primary analysis will be performed on the FAS. A secondary analysis will be performed on the PPS.

9.3.4. Secondary Analyses

Secondary endpoints will be analyzed in a similar manner as the primary endpoint, with Cox regression models and Kaplan-Meier survival curve estimation – or other suitable statistical methods – as detailed in the SAP, to be completed before database lock.

9.4. Safety Analyses

The Data Monitoring Committee (DMC) will review all safety data, including adverse events, after inclusion of 20%, 50% and 70% of patients. After each meeting, the DMC will make a recommendation of either continuation or discontinuation of the study to the steering committee. The DMC may also comment on the safety and overall conduct of the study. The responsibility

of continuing or discontinuing the study lies with the steering committee. The DMC charter will contain the details of the responsibilities of the DMC.

9.5. Interim Analyses

The DMC will perform an interim analysis of effect after half of the patients (n=253) have completed the first 28 days of follow-up and data on mortality are available for all these patients. The efficacy analysis will be performed on the primary outcome with a significance level of α=0.0052 (see Section 9.2). If the analysis demonstrates an effect of the intervention, the study will be stopped early. Details will be presented in the DMC charter.

9.6. Data Monitoring Committee (DMC)

A Data Monitoring Committee (DMC), consisting of a leader (clinician), a statistician, and at least one more participant, will meet after inclusion of 20%, 50% and 70% of patients to assess the safety and overall conduct of the study. The members of the DMC will be independent of the study group and not otherwise involved in the study. A DMC charter will detail the responsibilities of the DMC, to be made available before the first DMC meeting.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, documents describing the quality of the convalescent plasma product and other relevant documents (e.g., advertisements) will be submitted to the Regional Ethical Committee (REC) by the investigator and reviewed and approved by REC before the study is initiated.
- Any amendments to the protocol will require REC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require REC approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to REC in accordance with the requirements, policies, and procedures established by REC.
  - Notifying REC of SAEs or other significant safety findings as required by REC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the REC and all other applicable local regulations

10.1.2. Informed Consent Process

- The principal investigator or a delegated contact person at the care home will explain the nature of the study to the participant or their guardian and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their guardian will be required to sign a statement of informed consent that meets the requirements of REC and ICH guidelines.
- The study medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent

was obtained. The person obtaining the informed consent (e.g. investigator or delegated person) must also sign the ICF.

- A copy of the ICF must be provided to the participant or their guardian.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or delegated person will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

A separate informed consent form (REK135924) will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research.

10.1.3. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with Norwegian data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate REC members, and by inspectors from regulatory authorities.

10.1.4. Committees Structure

Data Monitoring Committee

- Participant safety will be continuously monitored by the Sponsors designated Data Monitoring Committee (DMC).
- In addition, an early aggregated safety data review will be performed, the goal of which is to allow for a cautious, stepwise approach to [intervention] administration. An initial safety review for this study is planned for the first 50 participants/ 20 % of participants who are dosed and have provided safety data for 14 days after administration of convalescent plasma.
- All safety data collected will be summarized and reviewed by the DMC for agreement of next steps.
- In particular, data will be reviewed by the Sponsor for identification of the following events that would potentially contribute to a requirement to stop or pause the study.
    - Any deaths, regardless of causality
    - Any SAE
    - Any AESI (see table in Appendix 4)

- If a pausing rule is met, a decision will be made, based on the review, as to whether enrollment in the study will be allowed to resume.
- Safety data will also be included in the Norwegian Health Directorate's system for Hemovigilance monitoring (https://www.helsedirektoratet.no/rapporter/overvaking-av-blod-i-norge)

10.1.5. Dissemination of Clinical Study Data

Submission of results of the clinical study will be accelerated to the extent possible to inform the guidance on use of convalescent plasma in Norway. This will include but is not limited to description of primary and secondary study endpoints. Access to these data will be allowed for third parties following an independent assessment of the scientific merit of a rigorously defined research question. If the outcome is negative or the study is terminated, this will also be reported to the REC.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in a specific SOP or Study Manual.
- The investigator must permit study-related monitoring, audits, | review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy, methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 5 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be

explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- Definition of what constitutes source data:
  - Data from Recruitment, Screening and Informed consent process
  - CRF
  - Data on participant samples
  - Databases collating the information collected during the study process
  - Analysis process documents and end reports
- The principal investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.8. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the REK or local health authorities, the sponsor's procedures, or GCP guidelines

- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the REC, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.9. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in this table are the recommended panel of routine testing to be offered in nursing homes. These are only required at the request of the doctor in charge at the care home (NOKLUS).

	Laboratory test	Response time	Distribution
Basic tests	Hemoglobin, CRP	Few hours	All care homes
	Glucose	<0.5 hours	All care homes
	Thrombocytes, Leukocytes with differential count (shipped to external laboratory)	2-3 days	All care homes
Extended repertoire	INR, fecal blood test	2-3 hours	Some care homes
	Creatinin, sodium, potassium, calcium, thrombocytes, leukocytes with differential count, D-dimer (in-house laboratory)	2-3 hours	Few care homes

- These tests are of relevance for
  - Study inclusion/exclusion
  - Monitoring of study endpoints
  - AE monitoring
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (haematology, clinical chemistry, or urine analysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

10.3.2. Definition of SAE

An SAE is defined as any serious adverse event that
a. Results in death
b. Is life-threatening
c. Requires inpatient hospitalization or prolongation of existing hospitalization
d. Results in persistent or significant disability/incapacity

e. Is a suspected transmission of any infectious agent

10.3.3. Recording and Follow-up of AE and/or SAE

Assessment of Intensity
Grade 1 (Non-Severe): The recipient may have required medical intervention (e.g. symptomatic treatment) but lack of such would not result in permanent damage or impairment of a body function. **Grade 2 (Severe):** The recipient required in-patient hospitalization or prolongation of hospitalization directly attributable to the event; and/or the adverse event resulted in persistent or significant disability or incapacity; or the adverse event necessitated medical or surgical intervention to preclude permanent damage or impairment of a body function. **Grade 3 (Life-threatening):** The recipient required major intervention following the transfusion (vasopressors, intubation, transfer to intensive care) to prevent death **Grade 4 (Death)** The recipient died following an adverse event

Assessment of Causality (related to transfusion/study intervention)
Definite (certain): when there is conclusive evidence beyond reasonable doubt that the adverse event can be attributed to the transfusion **Probable (likely**): when the evidence is clearly in favor of attributing the adverse event to the transfusion **Possible:** when the evidence is indeterminate for attributing the adverse event to the transfusion or an alternate cause **Unlikely (doubtful**): when the evidence is clearly in favor of attributing the adverse event to causes other than the transfusion

Excluded: when there is conclusive evidence beyond reasonable doubt that the adverse event can be attributed to causes other than the transfusion

10.4. Appendix 4: Definitions of SAE of special interest (transfusion reactions)

Transfusion reactions
Immunological: • Transfusion-related acute lung injury (TRALI) • Acute hemolytic transfusion reaction (AHTR) • Anaphylactic reaction • Other
Non- immunological: • Transfusion transmitted infection (bacteria, virus, parasites) • Transfusion associated circulatory overload (TACO) • Hypotensive transfusion reaction • Other

Transfusion reactions-Definitions
TRALI (Transfusion associated acute lung injury) In patients with no evidence of acute lung injury (ALI) prior to transfusion, TRALI is diagnosed if a new ALI is present (all five criteria should be met): • Acute onset • Hypoxemia o $Pa0_2 / Fi0_2 < 300$ mm Hg or o Oxygen saturation is < 90% on room air or o Other clinical evidence Bilateral infiltrates on frontal chest radiograph No evidence of left atrial hypertension (i.e. circulatory overload)

No temporal relationship to an alternative risk factor for ALI,

during or within 6 hours of completion of transfusion.

Hemolytic transfusion reaction

A hemolytic transfusion reaction is one in which symptoms and clinical or laboratory signs of increased red cell destruction are produced by transfusion. Hemolysis can occur intravascularly or extravascularly and can be immediate (acute) or delayed.

Acute hemolytic transfusion reaction (AHTR)

An AHTR has its onset within 24 hours of a transfusion. Clinical or laboratory features of hemolysis are present.

Common signs of AHTR are:

- Fever
- Chills/rigors
- Facial flushing
- Chest pain
- Abdominal pain
- Back/flank pain
- Nausea/vomiting
- Diarrhea
- Hypotension
- Pallor
- Jaundice
- Oligoanuria
- Diffuse bleeding
- Dark urine
- Common laboratory features are:
- Hemoglobinemia
- Hemoglobinuria
- Decreased serum haptoglobin
- Unconjugated hyperbilirubinemia
- Increased LDH an AST levels
- Decreased hemoglobin levels

Not all clinical or laboratory features are present in cases of AHTR.

Blood group serology usually shows abnormal results but absence of immunological findings does not exclude AHTR. AHTR may also be due to erythrocyte auto-antibodies in the recipient or to non immunological factors like mechanical factors inducing hemolysis (malfunction of a pump, of a blood warmer, use of hypotonic solutions, etc.).

Anaphylactic reaction

An allergic reaction can involve respiratory and/or cardiovascular systems and present as an anaphylactic reaction.

There is anaphylaxis when, in addition to mucocutaneous systems there is airway compromise or severe hypotension requiring vasopressor treatment (or associated symptoms like hypotonia, syncope). The respiratory signs and symptoms may be laryngeal (tightness in the throat, dysphagia, dysphonia, hoarseness, stridor) or pulmonary (dyspnea, cough, wheezing/bronchospasm, hypoxemia).

Such a reaction usually occurs during or very shortly after transfusion.

Transfusion transmitted infection (bacteria, virus, parasites)

Confirmed by microbiological analyses

Transfusion associated circulatory overload (TACO)

TACO is characterized by any 4 of the following:

- Acute respiratory distress
- Tachycardia
- Increased blood pressure
- Acute or worsening pulmonary edema on frontal chest radiograph
- Evidence of positive fluid balance

Occurring within 6 hours of completion of transfusion. An elevated BNP is supportive of TACO.

Hypotensive transfusion reaction

This reaction is characterized by hypotension defined as a drop in systolic blood pressure of ≥h30 mm Hg occurring during or within one hour of completing transfusion **and** a systolic blood pressure ≤ 80 mm Hg. Most reactions do occur very rapidly after the start of the transfusion (within minutes). This reaction responds rapidly to cessation of transfusion and supportive treatment. This type of reaction appears to occur more frequently in patients on ACE inhibitors. Hypotension is usually the sole manifestation but facial flushing and gastrointestinal symptoms may occur.

All other categories of adverse reactions presenting with hypotension, especially allergic reactions, must be excluded. The underlying condition of the patient must also be evaluated as a possible explanation for the hypotension.

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