The Investigational NOR-SOLIDARITY protocol

Project title
The NOR Solidarity multicenter trial on the efficacy of different anti-viral drugs in SARS-CoV-2 infected patients

Short title: The NOR-SOLIDARITY trial

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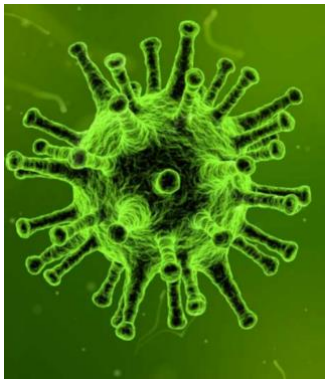

STATEMENT OF COMPLIANCE
This document is a protocol for a clinical research study. The study will be conducted in compliance with all stipulations of this protocol, the conditions of Regional Ethic committee approval and the latest version of the Helsinki Declaration.

This protocol describes a multicenter add-on trial that is part of and based on the global WHO COVID-19 core protocol. The aim of the WHO COVID-19 core protocol is to evaluate and compare four different anti-viral treatment regimens on in-hospital mortality in moderate and severe COVID infected patients. This multicenter add-on trial will be a separate and independent trial but will use the global level randomization and contribute to report endpoints and adverse events to the global trial.

Synopsis of the protocol

Terminology: The novel coronavirus-induced disease first described in 2019 in China is designated COVID-19 (or COVID), and the pathogen itself (an RNA virus) is SARS-coronavirus-2 (SARS-CoV-2). The Norwegian study that is an adapted WHO-study and follows the WHO protocol whilst also analyzing additional factors is referred to as the NOR-SOLIDARITY study. Standard of Care will be referred to as SoC.

Background: In early 2020 there were no approved anti-viral treatments for COVID, and WHO expert groups advised that four re-purposed drugs, Hydroxychloroquine, Remdesivir, Lopinavir with Ritonavir and Interferon (β1a) should be evaluated in an international five-arm randomized trial where the fifth arm is SoC. The NOR-SOLIDARITY study started analyzing the effects of Hydroxychloroquine and Remdesivir initially and may open for a fourth arm.

Notification: Hydroxychloroquine was removed as treatment option by the steering committee on June 8th 2020 due to lack of evidence confirmed both in internal WHO interim analyses and an external report from the Recovery study. Thus, from this date, June 8th 2020, NOR-Solidarity allocate patients only to SoC and SoC+ Remdesivir.

Patient enrolment and randomization: This will be carried out online via a database created for this purpose by the WHO. Adults (age ≥18 years) recently hospitalized, or already in hospital, with definite COVID and, in the view of the responsible doctor, no contra-indication to any of the study drugs will be randomly allocated between

- Local SoC alone,
  OR local SoC plus
- Remdesivir

Data reported before randomization via the WHO database:

- Hospital and randomizing doctor
- Confirmation that informed consent has been obtained
- Patient identifiers, age and sex
- Patient characteristics (yes/no): current smoking, diabetes, heart disease, chronic lung disease, chronic liver disease, asthma, HIV infection, active tuberculosis.
- COVID-19 severity at entry (yes/no): shortness of breath, being given oxygen, already on a ventilator, and, if lungs imaged, major bilateral abnormality (infiltrations/patchy shadowing)
- Whether the study drug is currently NOT AVAILABLE at the hospital.

Inclusion criteria

1. Adult patients, 18 years and older
2. Confirmed SARS-CoV-2 infection by PCR
3. Admitted to the hospital ward or the ICU
4. Subjects (or legally authorized representative) provide informed consent prior to initiation of the study
5. No anticipated transfer within 72 hours to a non-study hospital

Exclusion criteria

1. Severe co-morbidity with life expectancy <3 months according to investigators assessment
2. ASAT/ALAT > 5 times the upper limit of normal
3. Acute co-morbidity within 7 days before inclusion such as myocardial infarction
4. Known intolerance to the study drug
5. Pregnancy or breast feeding
6. Any reason why, in the opinion of the investigators, the patient should not participate

7. Participation in a potentially confounding drug or device trial during the course of the study
8. Already receiving any of the current study drug(s)
9. Patients on concomitant medications, which is part of the list of prohibited medications have to be excluded from the current study.

Prohibited medication:
Haloperidol, carbamazepine, phenytoin, rifampin, phenobarbital, isoniazid, pyrazinamide, nevirapine, ritonavir, sodium valproate/valproic acid

Drug safety: Suspected unexpected serious adverse reactions (SUSARs) that are life-threatening (e.g. anaphylaxis, Stevens-Johnson syndrome, aplastic anemia, or any other life-threatening condition in the opinion of the investigator) must be reported within 24 hours of being diagnosed, without waiting for death or discharge.

Daily blood samples will be taken, including estimated GFR, electrolytes and urea.

Outcomes: The primary outcome is all-cause in hospital mortality compared to standard of care. The major secondary outcomes are duration of hospital stay, time to first receiving ventilation (or intensive care), viral clearance, kidney failure, myocardial failure, co-infections, organ dysfunction, quality of life after 3 months, Inflammatory and anti-inflammatory mediators, markers of extracellular matrix remodeling, markers of endothelial activation and markers of platelet activation.

Data monitoring: A Data and Safety Monitoring Committee will keep the accumulating drug safety results and major outcome results under regular review.
Adaptive design: The WHO may decide to add novel treatment arms while the trial is in progress. Conversely, the WHO may decide to discontinue some treatment arms, especially if the Global Data and Safety Monitoring Committee reports, based on interim analyses, that one of the trial treatments definitely affects mortality.
Data security: Patient information will be encrypted and held securely by the WHO and sponsor. Those analyzing it will use only anonymized data, and no identifiable patient details will appear in publications.

Table of Contents

STATEMENT OF COMPLIANCE

The study will be carried out in accordance with the following, as applicable:
All National and Local Regulations and Guidance applicable at each site The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 (R2) Good Clinical Practice, and the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, National and ethical regulations

The signature below provides the necessary assurance that this study will be conducted according to all stipulations of the protocol including statements regarding confidentiality, and according to local legal and regulatory requirements, and ICH E6(R2) GCP guidelines.

Site Investigator Signature:

Signed: Date:

Name:

Title:

1 Investigators and facilities

1.1 Study locations and principal investigators

Study sites will include hospitals governed by different regional authorities and have one or two principal investigators dependent on the size of the hospital. As of today, 22 different hospital sites are participating. Contact information is to be found in Appendix 6.

Northern Norway Regional Health Authority	**PI**
• University Hospital of North Norway, Tromsø (UNN)	Anders Benjamin Kildal Vegard Skogen
• Nordland Hospital, Bodø	Hanne Winge Kvarenes
Central Norway Regional Health Authority	
• St. Olav University Hospital, Trondheim	Pål Klepstad Raisa Hannula
• Levanger Hospital	Nina Vibeche Skei
• Molde Hospital	Birgitte Tholin
• Ålesund Hospital	Dag Arne Lihaug Hoff
Western Norway Regional Health Authority	
• Haukeland University Hospital, Bergen	Bjørn Blomberg Reidar Kvåle
• Haraldsplass Hospital, Bergen	Bård Reiakvam Kittang
• Stavanger University Hospital	Åse Berg
• Fonna Hospital Trust	Lan Ai Kei Le
• Førde Hospital	Pawel Franciszek Mielnik
South-Eastern Norway Regional Health Authority	
• Akershus University Hospital	Olav Dalgård
• Vesfold Hospital, Tønsberg	Asgeir Johannessen
• Telemark Hospital, Skien	Hilde Kristin Skuedal
• Østfold Hospital, Kalnes	Waleed Ghanima
• Kristiansand Hospital	Mette Haugli
• Arendal Hospital	Roy Bjørkholt Olsen
• Drammen Hospital	Lars Heggelund
• Bærum Hospital	Anders Aune Tveita
• Ringerike Hospital	Lars Thoresen
• Kongsberg Hospital	Gernot Ernst
• Oslo University Hospital (OUH)	
○ Ullevål	Anne Margarita Dyrhol Riise Aleksander Rygh Holten
○ Rikshospitalet	Pål Aukrust Andreas Barratt-Due
• Diakonhjemmet Hospital, Oslo	Leif Erik Vinge
• Lovisenberg Hospital, Oslo	Hedda Hoel
• Innlandet Hospital Trust , Lillehammer	Ragnhild Eiken
• Innlandet Hospital Trust , Elverum	Carl Magnus Ystrøm
• Innlandet Hospital Trust , Gjøvik	Even Reinertsen
• Innlandet Hospital Trust , Hamar	Hall Schartum-Hansen

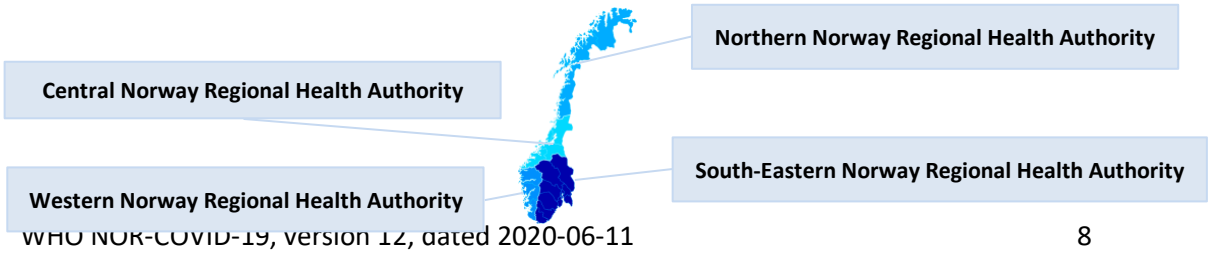

Figure 1: Norway divided into four regional Health Authorities

1.2 Study Management

The Steering and Management Committee will manage and coordinate the study centrally. As of today the steering committee is composed of:

Project leader: Pål Aukrust, MD, PhD, Professor; OUH Rikshospitalet
Andreas Barratt-Due, MD, PhD; OUH Rikshospitalet
Trine Kåsine, MD; OUH Rikshospitalet
Katerina Nezvalova-Henriksen, Cand. Pharm, PhD; OUH Rikshospitalet
Anne Margarita Dyrhol Riise, MD, PhD, Professor; OUH Ullevål
Marius Trøseid, MD, PhD; OUH Rikshospitalet
Inge Christoffer Olsen, Statistician, PhD, OUH Research Support Services.

Locally, the study will be managed and coordinated by a Principal Investigator, with responsibility for data collection and maintenance of study documentation.

1.3 Monitor

The study will be monitored by clinical study monitors located at the University Hospital of North Norway, St Olav's Hospital, Haukeland University Hospital and Oslo University Hospital.

All sites will be visited and/or contacted by phone on a regular basis by the monitor, who will verify that informed consent process, reporting of adverse events and other safety data, adherence to protocol, maintenance of required regulatory documents, facilities and equipment and data completion on the case report forms, including source data verification are up to standard. The details of the monitoring, e.g. the processes, equipment and data to be checked, will be described in a study specific monitoring plan.

2. Background and objectives

2.1 Background Information

Infectious diseases are the single biggest cause of death worldwide. New infectious agents, such as the SARS, MERS and other novel coronavirus as well as influenza viruses, all represent a threat and disease burden to the society and health facilities. Influenza epidemics and pandemics worldwide continue to challenge public health and health care systems. The pandemic in 2009-2010 resulted in 100.000-400.000 deaths, affecting not only elderly individuals and individuals with co-morbidities, but also children and young adults (1). The present pandemic with COVID-19 is expected to result in a high number of critically ill patients in need of hospitalization and respiratory support, and an unknown proportion of patients who inevitably will die. As of today, no specific treatment of COVID-19 has been established. To this end, Remdesivir is the only treatment option that directly inhibits SARS-CoV-2 RNA polymerase and has been shown to inhibit virus replication in vitro. It has also been shown to have protective effects against the familiar coronavirus MERS (2), and notably, both preclinical experiments and case reports suggest that Remdesivir could have beneficial effects in COVID 19 (3, 4). For additional background information about coronaviruses and the Mechanism of action of Remdesivir see sections 1.1.2, 1.2.2, and 3.1.1 of the Remdesivir Investigators Brochure (5). Another promising treatment option is hydroxychloroquine which seems to be effective in limiting the replication of SARS-CoV-2 *in vitro* at least partly by interfering with the pH-dependent endosome-mediated viral entry, and its potential effect in COVID-19 has been suggested by six publications (6). Clinical experience with the use of neuraminidase inhibitors demonstrated that prompt treatment probably represents the most effective strategy for the management of influenza epidemics (7). It is conceivable that a similar early treatment strategy is also necessary in COVID 19 patients and is applicable to other drug therapies, but so far, no data exist to support this assumption.

The WHO COVID 19 core protocol has been designed to prospectively collect clinical data globally, and rapidly evaluate and conclude whether different anti-viral treatment regimens can reduce in-hospital mortality. Along with this, separate and independent add-on trials will use the global level randomization centre and contribute to report endpoints and adverse events as encouraged by the WHO (8).

Notification: Hydroxychloroquine was removed as treatment option by the steering committee on June 8th 2020 due to lack of evidence confirmed both in internal WHO interim analyses and an external report from the Recovery study. Thus, from this date, June 8th 2020, NOR-Solidarity allocate patients only to SoC and SoC+ Remdesivir.

2.1.1 Clinical trial rationale

The rationale for the study is to test whether available anti-viral drugs with the potential to inhibit SARS-CoV-2 (at this moment only Remdesivir) have any clinical effect on COVID-19 infected patients.

Knowledge from this study will hopefully contribute to the clarification of whether Remdesivir is beneficial or not and if early Remdesivir intervention is needed to have any beneficial effects. This is important knowledge and highly relevant for future treatment of COVID-19 infected patients.

Data from the study will also provide increasing knowledge of the pathogenesis of severe COVID-19 infection and in particular, which molecular pathways and biomarkers that characterize those patients that need ICU management and those that could be managed at the hospital ward.

2.2 Target audience

Departments of Infectious Diseases and ICUs at hospitals in Norway treating COVID-19 infected patients are invited to participate in this study and contribute with data to a centralized database. We encourage all centres to contribute to this effort. In all cases, a proportionate case report form (a web-based electronic "eCRF") will be completed.

2.3 Study design

The NOR-SOLIDARITY study is an adaptive, randomized, open clinical multicentre trial to evaluate the safety and efficacy of possible therapeutic agents in hospitalized adult patients diagnosed with COVID-19. See the WHO COVID-19 core protocol (Appendix 1) for the core trial design. This multicentre add-on trial will follow the WHO core protocol version 10 dated 22.03.2020 but will add additional secondary and exploratory endpoints.

Adults (age ≥18 years) recently hospitalized, or already in hospital, with definite COVID and, in the view of the responsible doctor, no contra-indication to any of the study drugs will be randomly allocated between

- Local standard of care alone,
  OR local standard of care plus
- Remdesivir (one intravenous loading dose, then daily infusions for altogether 10 days)

The primary objective of the trial is to investigate the effect of Remdesivir on all-cause in-hospital mortality compared to standard of care.

Patients will be followed daily during hospitalization, after 28 days by telephone/sms and then by an outpatient clinical visit after 3 months.

In the core protocol follow-up data are only collected at discharge. In this protocol subjects will additionally be assessed for efficacy and safety both during hospitalization and after hospitalization.

In addition to the global independent data and safety monitoring board (DSMB) as described in the core protocol, a national DSMB will monitor the safety and risk-benefit of the trial interventions in the Norwegian population.

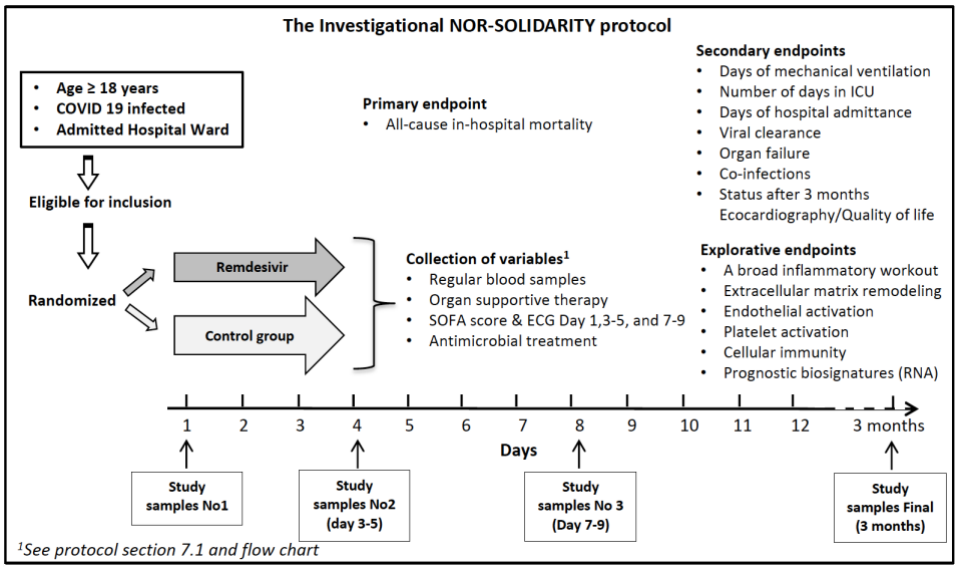

Figure 2: The Investigational NOR-SOLIDARITY protocol

3 Objectives and endpoints

Objectives	Endpoints (Outcome measures)
Primary (in line with WHO core protocol)	
To investigate the effect of Remdesivir on all-cause in-hospital mortality compared to standard care.	All-cause in-hospital mortality
Secondary (in line with WHO core protocol)	
Assess the effect of Remdesivir on hospital duration, receipt of ventilation or intensive care, and to identify any serious adverse reactions.	During hospitalization • Receipt of mechanical ventilation • Time to first receiving and duration of mechanical ventilation • Receipt of intensive care • Duration of intensive care • Occurrence of Suspected Unexpected Serious Adverse Reactions (SUSARs)
Secondary (as addition to the WHO core protocol)	
Assess the effect of Remdesivir on 28 days mortality, viral clearance, kidney and myocardial failure, co-infections, organ dysfunction and health-related Quality of Life.	**Assessed during hospitalization** • Viral clearance as assessed by SARS-CoV-2 PCR in oropharyngeal specimens during hospitalization • Occurrence of kidney failure (eGFR <40 mL/min) • Occurrence of myocardial involvement assessed by biochemical markers as well as echocardiography measuring left ventricular ejection fraction within the first week • Occurrence of co-infections (super infections with bacteria, fungi and other virus) **Assessed after 28 days** • Overall survival • Patient reported respiratory health status by CAT (Chronic Obstructive Pulmonary Disease (COPD) assessment Test) score **Assessed after 3 months** • Occurrence of systolic and diastolic cardiac dysfunction and level of remodelling assessed by echocardiography and biochemical markers • Occurrence of pulmonary dysfunction and level of fibrosis assessed by spirometry and thoracic CT scan • Health related quality of life assessed by the RAND 36-item Short Form Health Survey (SF-36) item scores and the 5-dimension EuroQol (EQ-5D) questionnaires index value.
Exploratory (as addition to the WHO protocol)	

Assess the effect of Remdesivir on biomarkers and its safety.	Biomarkers during hospitalization and after 3 months • Inflammatory and anti-inflammatory mediators as assessed in serum and plasma • Markers of extracellular matrix remodelling • Markers of endothelial activation • Markers of platelet activation • Cellular immunity • Prognostic biosignatures (RNA) • Gut microbiota assessed by rectal swab • Pharmacokinetics during hospitalization • Adverse events during hospitalization

4 Study population

4.1 Inclusion criteria (as described in WHO COVID 19 core protocol)

1. Adult patients, 18 years and above
2. Confirmed SARS-CoV-2 infection by PCR
3. Admitted to the hospital ward or the ICU
4. Subjects (or legally authorized representative) provide informed consent prior to initiation of the study
5. No anticipated transfer within 72 hours to a non-study hospital

4.2 Exclusion criteria

1. Severe co-morbidity with life expectancy <3 months according to investigators assessment
2. ASAT/ALAT > 5 times the upper limit of normal
3. Acute co-morbidity within 7 days before inclusion such as myocardial infarction
4. Known intolerance and hypersensitivity to any of the components of the available study drug.
5. Pregnancy or breast feeding
6. Any reason why, in the opinion of the investigators, the patient should not participate
7. Participation in a potentially confounding drug or device trial during the course of the study
8. Already receiving any of the study drugs
9. Patients on concomitant medications, which are part of the list of prohibited medications, have to be excluded from the current study **(see point 4.3).**

4.3 Prohibited concomitant medication in relation to Remdesivir

Carbamazepine, phenytoin, rifampin, isoniazid, pyrazinamide, nevirapine, ritonavir, sodium valproate/valproic acid

4.4 Baseline characteristics

According to the CRF a description of the included patients co-morbidity, ongoing treatment and performance status (Frailty score) will be required. Severe disease is defined as patients which need ICU management and mild/moderate disease is defined as people which can be treated at the hospital ward.

A pregnancy test will be performed in all women of childbearing potential. For the purpose of this document, a woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy

5 Study products and study drug regimes

See core protocol (Appendix 1 and SOP-4 to SOP-7b). Note that this protocol currently only includes Remdesivir as study drug.

5.1 Remdesivir

The lyophilized formulation of Remdesivir is a preservative-free, white to off-white or yellow, lyophilized solid containing 100 mg of Remdesivir to be reconstituted with 19 ml sterile water for injection and diluted with IV infusion fluids prior to IV infusion. It is supplied as a sterile product in a single-use, 50 mL, Type 1 clear glass vial. Following reconstitution, each vial contains 5 mg/ ml concentrated Remdesivir solution with sufficient volume to allow withdrawal of 20 ml (100 mg of Remdesivir). In addition to the active ingredient, the lyophilized formulation of Remdesivir contains the following inactive ingredients: water for injection, SBECD (sulfobutylether cyclodextrin), hydrochloric acid, and/or sodium hydroxide. Hydrochloric acid and/or sodium hydroxide are used to adjust the formulation to a final pH of 3.0 to 4.0 following reconstitution.

Remdesivir will be delivered by WHO when available. Remdesivir will be given intravenously with a loading dose of 200 mg at inclusion, day 1. Thereafter the patient will receive a daily intravenous maintenance dose of 100 mg from day 2 to day 10.

The total volume of administration can be 250 mL or 500 mL of Normal Saline. The infusion can be administered over a period of between 30 minutes and 2 hours.

5.2 Medical side effects and management of Remdesivir

In clinical studies, no evidence of nephrotoxicity has been observed with doses of Remdesivir up to 225 mg or multiple doses of 150 mg for up to 14 days. However, for subjects with an $eGFR_{CG}$ decrease of ≥ 50%, permanent discontinuation of Remdesivir treatment should be considered. Subjects should then be followed as clinically indicated until $eGFR_{CG}$ returns to baseline or is otherwise explained, whichever occurs first.

It is recommended that regular laboratory assessments be performed in subjects receiving Remdesivir in order to monitor hepatic function. Any observed liver function-related laboratory abnormalities or possibly related AEs should be treated appropriately and followed to resolution. Special attention to liver function-related laboratory abnormalities has to be paid when drugs with a hepatotoxic potential are administered together with Remdesivir. The Investigator has to consider carefully whether the administration of those drugs is deemed necessary and is in the best interest of the patients. Remdesivir is pro-drug that is metabolized to its active drug through P450 3A4 (CYP-3A4) and other medications that influence the activity of this enzyme should be avoided. Remdesivir is contraindicated in patients who develop resistance to any of the components of the study drug. Treatment has to be stopped when development of resistance is being suspected. Please refer to section 6 “Guidance to the Investigator” of the Investigators Brochure (IB) for Remdesivir for further information concerning the treatment with and safety precautions required for treatment with Remdesivir (5).

Except for the intervention with Remdesivir all medical management will be provided according to standard of care at the treating site. The Research intervention with Remdesivir may potentially induce adverse effects most likely to be hypotension (9)

Specific attentions to this potentially related side effect will therefore be followed closely.

5.2.1 Remdesivir and renal function
Particular attention will be paid to patients included in the Remdesivir arm. Daily blood samples will be taken, including eGFR, electrolytes and urea.

5.2.2 Remdesivir and prohibited concomitant medication
When the patient is randomized to treatment with Remdesivir the following list of medication must not be given concomitantly: Isoniazid, rifampin, pyrazinamide, nevirapine, ritonavir, phenytoin, carbamazepine, sodium valproate/valproic acid

5.3 General information on intervention drugs
No clinical drug-drug interaction studies have been conducted with Remdesivir. Although Remdesivir is a substrate for CYP2C8, CYP2D6, and CYP3A4 in vitro, co-administration with inhibitors of these CYP isoforms is unlikely to markedly increase Remdesivir levels, as its metabolism is likely to be predominantly mediated by hydrolase activity. While hepatocyte donor-dependent induction of mRNA levels of CYP1A2 and CYP2B6 was observed, Remdesivir showed no induction of CYP3A4 mRNA or CYP3A4/5 activity. The nucleoside metabolite GS-441524 and the intermediate metabolite GS-704277 showed no induction of CYP enzymes. Consistently, no potential for induction of enzymes or transporters via PXR or AhR was detected in reporter cell lines. Remdesivir is a substrate for OATP1B1 and P-gp. However, the impact of these transporters on Remdesivir disposition is likely minimized by the parenteral route of administration. Remdesivir is an inhibitor of OATP1B1, OATP1B3, BSEP, MRP4, and NTCP in vitro, but its potential to be the perpetrator of clinically significant drug-drug interactions is limited by its rapid clearance. The major systemic metabolites of Remdesivir, GS-704277 and GS-441524, are not inhibitors of human BSEP, MRP2, MRP4, or NTCP transporters (IC50 > 100 μM). If unanticipated drug-drug interactions are observed, the short-term course of Remdesivir treatment may allow for temporary dose modification of other interacting drugs. The drugs that may influence the metabolism of Remdesivir to a clinically significant level include dexamethasone, haloperidol, carbamazepine, phenytoin, rifampin and phenobarbital.

Information about the administration, preparation, doses, storage and handling, disposition of unused product and the maintenance of inventory logs is provided in the Pharmacy manuals for Remdesivir (SOP-4).

6 Drug discontinuation and patient withdrawal
As described in the core protocol (Appendix 1):
At all times the patient's medical team remains solely responsible for decisions about that patient's care and safety. Hence, study drug administration must be stopped if the team suspects any serious unexpected drug-related reaction that is life-threatening. The study will be stopped in case of occurrence of AEs unknown to date in respect to their nature, severity, and duration that may negatively affect the benefit/risk of the trial.

Patients are free to withdraw from study treatment at any time, but could still remain in the study, with in-hospital outcome reported to the study at death or discharge.

Patients are also free to withdraw from the whole study at any time without any consequence and would continue to be offered the local standard of care (but not be reported on). When patients cannot withdraw from study treatment or the whole study themselves, due to their current health status, an appropriate patient representative can withdraw them on their behalf

7 Study assessments and procedures

The WHO core protocol assesses all-cause-in-hospital-mortality. In addition the following will be assessed for this national add-on protocol (see flow chart).

7.1 Clinical variables

Collecting of daily clinical data will start when the patient is included in the study and be continued until the patient is discharged or dies. The following data will be collected (See, flow-chart for detailed description)

- Regular blood samples
- Respiratory support
- Other organ supportive support therapy (e.g., circulatory, kidney)
- SOFA score at admittance and day 3-5, 7-9
- Blood pressure, heart rate, respiratory rate, oxygen tension and temperature (for patients at hospital ward/not ICU)
- Echocardiography within the first week and after 3 months
- Co-infections
- Antimicrobial treatment in addition to the study drug
- Chest X-ray or CT scan during hospitalization and CT scan after 3 months
- Pulmonary functional test at 3 months
- Rectal swab sample at 3 months

Samples required for clinical management will at all times have priority over samples taken for research tests. Aliquots or samples for research purposes should never compromise the quality or quantity of samples required for medical management. Wherever practical, taking research samples should be timed to coincide with clinical sampling.

7.2 Case report form and patient numbers

There will be two electronic web-based case report forms (eCRFs) for data entering. The core data collection and randomization will be done in the WHO eCRF (see Appendix 1 for details), while national-specific data according to this protocol will be collected in a separate eCRF. The patient study number issued from the WHO eCRF will be registered in the national eCRF for validity.

The local study site will keep a person-identifiable code secured at a separate place, available only for the primary local investigators. The study samples taken at baseline, day 1, day 3-5, day 7-9, thereafter weekly or when discharged from hospital/ICU, will be assigned a corresponding number to that of the patient as well as a number indicating sample order; (Sample taken day 1= sample 1, taken day 3-5= sample 2, taken 7-9 = 3 and so on).

7.3 Risks to participants

7.3.1 Remdesivir

Risks associated with Remdesivir treatment are expected to be hypotension (9), transient elevation in transaminases and transiently increased respiratory rate (personal communication with the manufacture).

7.3.2 General risk considerations

The patients included in this study will be severely ill, possibly in need of organ supportive care, and the implementation of a new drug in this situation may induce unknown effects that may aggravate organ dysfunction. Thus, Remdesivir must be provided under special vigilance. On the other hand patients with COVID-19 infection at ICU will have a high mortality rate and without any

established anti-viral therapy, the potential beneficial effects of this promising anti-viral agent will in our opinion outweigh the potential adverse effects of drugs in this severely ill patient group.

Blood sampling: This represents an insignificant inconvenience for the included patients. Blood samples will be taken at baseline (day 1) and day 3-5, and will constitute a minimal blood loss and no harm for the patients.

7.4 Benefits to participants

7.4.1 Remdesivir
We anticipate that intravenous administration of this drug will be particularly beneficial for patients admitted to ICU.

7.5 Specimens and laboratory analysis
Routine medical biochemistry data will be collected daily at each centre and analyzed by the local laboratory.

Samples for SARS-CoV-2 PCR analyses will be analysed in oropharyngeal specimens at admission and every third day.

In addition, blood study samples will be taken at inclusion of the study (baseline) and at day 4 (3-5) and day 8 (7-9), thereafter weekly and at three months. At each time point it will be taken: (i) EDTA, 12 mL and (ii) Serum 8 mL. Additionally, some study sites will take whole blood EDTA samples (5 mLs) and blood for isolation of peripheral blood mononuclear cells (PBMC; 16 mLs) three times during the study. It might be difficult for all participating centers to collect these samples therefore lack of collection will not be considered as a protocol deviation.

Samples will be processed and centrifuged within 1 hour and stored at -80°C (PBMC in -80 °C or in liquid nitrogen) before analysed collectively at Research Institute of Internal Medicine, and Department of Immunology, Oslo University Hospital. We recognize that -80°C storage is not available at all sites. In this case it will be possible to store the samples temporarily at -20°C for 1 month before transfer to the Research Institute if Internal Medicine and Department of Immunology, Oslo. For preparation of plasma and serum, see also appendix A5.

Strict Biosafety procedures and international regulations will be applied with regard to the collection, storage, transfer and laboratory handling of research samples. Appropriate processing and storage of samples will be carefully reviewed when different hospitals and study sites decide to adhere to the study.

Research Institute of Internal Medicine at Oslo University hospital has extensive experience in analysing relevant markers in a large number of samples using multiplex technology, enzyme immune assays on a robot platform and proteomics.

8 Data management
International data management will be performed by the WHO (see Appendix 1), while national data management will be performed at Oslo University Hospital. Patients' identities will be protected and their information held securely. Only anonymized data will be stored at the web databases, whereas the participant list will be stored separately, secured, at the different local study sites.

It is important that data generated now are not destroyed unnecessarily, since they will be of considerable potential value to future generations faced with similar outbreaks of infectious disease. Electronic data and electronic copies of paper documents will be stored for at least 15 years.

9 Safety monitoring and reporting

The PI is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) and a serious adverse event (SAE). The sponsor is responsible for assessing whether a SAE is defined as SUSAR as well as for reporting of all SUSARs to the national competent authority. Each patient will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious. Safety analyses will include tabulation of the type and frequency of adverse events. Any serious adverse events will be reported with comprehensive narratives. Any value of safety laboratory parameters outside the expected ranges will be identified. The methods for collection of safety data are described below.

9.1 Adverse Events and Serious Adverse Events

9.1.1 Definition of Adverse Event (AE)

AE means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases, it should be recorded as an AE.

Given the nature of severity of the underlying illness, subjects will have many symptoms and abnormalities in vitals and laboratory. All Grade 3 AEs will be captured as AEs in this trial and will be considered as notable events. For Remdesivir, additional information on AE grade 1 or 2 occurring while administration or within the first hour will be reported in the eCRF in a separate form; *Remdesivir, mild adverse reaction (grade 1 &2)*.

9.1.2 Definition of Serious Adverse Event (SAE)

An SAE is defined as “An AE or suspected adverse reaction is considered serious if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death,
- a life-threatening AE,
- prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- or a congenital anomaly/birth defect.
- important medical events

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

"Life-threatening" refers to an AE that at occurrence represents an immediate risk of death to a subject. An event that may cause death if it occurs in a more severe form is not considered life-threatening. Similarly, a hospital admission for an elective procedure is not considered a SAE. All SAEs, as with any AE, will be assessed for severity and relationship to study intervention. All SAEs will be recorded on the appropriate SAE CRF. All SAEs will be followed through resolution or stabilization by a licensed study physician.

9.1.3 Suspected Unexpected Serious Adverse Reactions (SUSAR)

A SUSAR is any SAE where a causal relationship with the study product is at least reasonably possible but is not listed in the Investigator Brochure (IB), and/or Summary of Product Characteristics (SmPC). In the case of Remdesivir medication, particular focus will be directed towards renal function.

9.1.4 Classification of an Adverse Event

The determination of seriousness, severity, and causality will be made by an on-site investigator who is qualified (licensed) to diagnose AE information, provide a medical evaluation of AEs, and classify AEs based upon medical judgment.

9.1.5 Severity of Adverse Events

AEs will be graded according to the following definitions:

- Mild (Grade 1): Events that are usually transient and may require only minimal or no treatment or therapeutic intervention and generally do not interfere with the subject's usual activities of daily living.
- Moderate (Grade 2): Events that are usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.
- Severe (Grade 3): Events interrupt usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating.
- Life-threatening (Grade 4): Urgent intervention indicated.

AEs characterized as intermittent require documentation of onset and duration of each episode. The start and stop Duration of each reported AE will be recorded on the appropriate CRF. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity.

9.1.6 Relationship to Study Intervention

For each reported adverse reaction, the SPONSOR must assess the relationship of the event to the study product using the following guideline:

- Related – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- Not Related – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

9.1.7 Time Period and Frequency for Event Assessment and Follow-Up

For this study, all Grade 3 and 4 AEs, Grade 1 and 2 AEs for Remdesivir occurring while administration or within the first hour and all SAEs occurring from the time the informed consent is signed through three months follow-up will be documented, recorded, and reported.

9.1.8 Investigators Reporting of AEs

Information on all grade 3 AEs should be recorded on the appropriate CRF. All clearly related signs, symptoms, and results of diagnostic procedures performed because of an AE should be grouped together and recorded as a single diagnosis. If the AE is a laboratory abnormality that is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than the individual laboratory abnormality. Each AE will also be described in terms of duration (start and stop date), severity, association with the study product, action(s) taken, and outcome. Guidelines regarding reporting and limits will be provided to all participating centers.

9.1.9 Serious Adverse Event Reporting

Investigators Reporting of SAEs

Any AE grade 4 that meets a protocol-defined criterion as a SAE must be submitted immediately (within 24 hours of site awareness) in the eCRF. The designated Medical Monitor will review and assess the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct. The Medical Monitor will be available 24/7 on a designated mobile number.

Regulatory Reporting of safety data

All Suspected Unexpected Adverse Reactions (SUSAR) have to be reported, within the legal timeframe, by the sponsor to the National Competent Authority of the Member State concerned. The timelines for expedited initial reporting (day 0) starts as soon as the information containing the minimum reporting criteria has been received by the sponsor. For fatal and life-threatening SUSARs the sponsor should report at least the minimum information as soon as possible and in any case no later than seven days after being made aware of the case. SUSAR which are not fatal and not life-threatening are to be reported within 15 calendar days. If significant new information on an already reported case is received by the sponsor, this information should be reported as a follow-up report within 8 days after being made aware of the relevant complementary information.

In addition, any serious unexpected adverse reaction that is life-threatening (e.g. anaphylaxis, Stevens-Johnson syndrome, aplastic anaemia, or any other life-threatening condition in the opinion of the investigator) must be reported through the WHO study website within 24 hours (SOP 9).

Once a year throughout the clinical trial, the sponsor should submit to the national competent authority and the Ethics Committee of the Member States, an annual safety report.

9.2 Procedures in Case of Emergency

The investigator is responsible for assuring that there are procedures and expertise available to cope with emergencies during the study. The study is not blinded and code breaking procedures is therefore unnecessary.

9.3 Safety Committee

There will be two Data and Safety Monitoring Committees (DSMC), one global and one national. The global is detailed in the core protocol (Appendix 1) while the national DSMC will monitor the safety and evaluate the risk-benefit of the study interventions in the Norwegian patients. The national DSMC will consist of two clinicians and one statistician.

9.4 Protocol deviations

A protocol deviation handling plan will describe reporting procedures for important protocol deviations. Substantial overdosing should be reported within 24 hours in the WHO study website. As the protocol leaves the local doctor fully responsible for all decisions about patient care, including the possibility of discontinuing study medication if this is considered appropriate, the

only possible major protocol deviation would be substantial over-dosing with a study drug. If this happens, it should be reported within 24 hours on the study website. The DSMC chair will then decide whether this constitutes a sufficiently major protocol deviation for it to need to be forwarded promptly to the relevant national coordinator and to any relevant ethics committee

10 Statistical methods and data analysis

10.1 Determination of Sample Size

Recruitment will continue until the global core trial is concluded (Appendix 1). Assuming 5% all-cause in-hospital mortality in the standard of care arm and that 2% absolute risk difference is regarded a clinically meaningful difference, 2377 patients in each arm are required to conclude with benefit on a 2.5% two-sided significance level with 90% power. This calculation adjusts for multiple testing using Bonferroni correction. If even more proof is needed, 3412 patients in each arm are needed to conclude with benefit on a 1% two-sided significance level with 95% power. We will not be able to reach these numbers in this trial alone but will rely on the combined analyses of all participating trials in the global consortium.

In this trial we will therefore aim to show a difference in receipt of intensive care. Currently in Norway there are 70 patients in intensive care out of 268 (26%). With a minimum clinically important difference of 10% our goal is to randomize 406 patients in each group to be 90% certain to conclude with benefit on the 2.5% two-sided level.

10.2 Randomization

10.2.1 Allocation- sequence generation

Eligible patients will be allocated in an equal ratio, using a computer randomization procedure. The allocation sequence will be prepared by an independent statistician appointed by the international steering group. The randomization procedure will accommodate availability of each treatment such that a patient cannot be allocated to an unavailable treatment. There will be no stratification of the allocation sequence, only simple randomization.

10.2.2 Allocation- procedure to randomize a patient

Eligible patients will be entered into the www.who.int/COVIDcore database including patient baseline details and available treatment arms at the study site. Patients will then be randomized to one of the available arms. The allocation will be registered in the patient's journal and in the eCRF system (Viedoc). This is an open-label study and no steps to conceal allocation are necessary. The study statistician will be blinded to the randomization allocation for the writing of the national statistical analysis plan (SAP). The authorisations bound to role of the study statistician in the eCRF when reading or downloading data will ensure that the statistician won't see the treatment allocation until database lock.

10.2.3 Blinding and emergency unblinding

This is an open-label study. However, the staff at the central laboratory at OUS as well as the statistician responsible for analysis of the data will be blinded to the treatment allocation for the writing of the SAP.

10.3 Population for Analysis

The following populations will be considered for the analyses:

- Intention to treat (ITT) population: All randomized participants will be included in the main ITT analyses, regardless of protocol adherence.
- Per-protocol population (PP): Includes all patients in the ITT population having completed the study treatment without major protocol violations and good adherence to the IMP.

Criteria for inclusion in the PP population will be specified in the SAP and the final criteria will be defined prior to database lock

- Safety population: Includes all subjects with any safety information after baseline. Patients randomized to Remdesivir without receiving any amount of the treatment will be excluded from the safety population.
- Total population: All enrolled participants independent of study arm will be used for additional analyses in the total population.

The primary population is the ITT population.

10.4 Planned analyses

The planned analyses will be detailed in separate statistical analysis plans. There will be two plans, one for the global analyses and one for the analyses of the patients included according to this protocol.

The statistical analyses are planned when the global trial is stopped for either efficacy or futility of the included treatments or when we have reached our recruitment goal of at least 406 patients per arm.

Prior to each statistical analysis, the data in the data base will be exported and the exported data will be locked for further altering of data. A SAP will provide details on the planned statistical analyses. The SAP will be finalized, signed and dated prior to analysis. There will be no efficacy interim analyses according to this protocol.

10.5 Statistical Analysis

10.5.1 Primary analysis

The primary analysis will be identical to the primary analysis according to the WHO core protocol and corresponding statistical analysis plan, restricted to the population included in this add-on trial. The primary analyses assess any effects of treatment allocation on all-cause in-hospital mortality, compared to standard of care, analyzing separately people who already had severe disease at entry (admitted directly to intensive care) and those who did not.

10.5.2 Secondary analyses

Between group comparisons will be performed for the primary variable on the per-protocol population in addition to secondary efficacy endpoints on both efficacy populations (ITT and PP populations).

The between-group comparisons for secondary variables will be tested as for the primary variable where applicable and additional analyses will be performed based on the following methods (but not limited to):

- Continuous secondary variables will be subject to repeated measures mixed models or appropriate non-parametric alternatives
- Binary response variables will be analysed using logistic regression (possibly adjusting for within-subject dependencies by generalized estimating equations or mixed models) or chi-square/Mantel-Haenszel tests
- Time-to-event variables will be analysed using the Kaplan-Meier method and comparisons between the two groups will be performed using the log rank test, Cox regression analyses or appropriate parametric models such as the gamma or Weibull model.

Unless otherwise specified, all statistical hypotheses will be tested as the primary variable, i.e. with an assessment of superiority of the estimated difference between the groups. All efficacy analyses will be presented with the results from the hypothesis testing (by p-value) in addition to estimates and 95% confidence limits of the treatment effect.

10.5.3 Safety analyses

Safety endpoints include death through three months, SAEs, discontinuation of study infusions, and severe AEs. These events will be analysed univariately and as a composite endpoint. Time-to-event methods will be used for death and the composite endpoint. Each AE will be counted once for a given participant and graded by severity and relationship to COVID-19 or study intervention. AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be presented by system organ class, duration (in days), start- and stop-date. Adverse events leading to premature discontinuation from the study intervention and serious treatment-emergent AEs should be presented either in a table or a listing.

10.5.4 Descriptive statistics

Descriptive statistics will be presented with number and percentages for categorical variables, and means, standard deviation, and range for continuous variables. In case of clearly skewed continuous variables, they will be presented with median, interquartile range (25^{th} and 75^{th} percentiles) and range. Demographics and baseline characteristics will be presented with descriptive statistics without any hypothesis testing.

10.5.5 Missing data

If missing data is regarded as having a significant effect on the conclusions of the trial, sensitivity analyses with different methods for handling missing data will be included. Such methods may include complete case analyses, last observation carried forward, worst case/best case imputation and multiple imputation techniques.

11 Ethical considerations

This study will be conducted in compliance with the principles set out in the Declaration of Helsinki. Where applicable, the principles of Good Clinical Practice (ICH 1996) and other applicable regulations and guidelines will be used to guide procedures and considerations. This protocol will be reviewed and approved by the regional ethical committee and by The Norwegian Medicines Agency (using the EudraCT form) before patients are enrolled in the study.

After approval the study will immediately be registered in ClinicalTrials.gov.

This study is conducted during a disease outbreak. This is a challenging research situation because this falls in the area between clinical care, public health and clinical research (WHO Ethical Review in Disease Outbreak Expert Meeting 2009). Normally research activities are defined by anything conducted outside standard clinical care. The patients included in this study will be treated according to normal practice at the different hospitals, which follow international guidelines in relation to sepsis and ARDS (10, 11).

11.1 Informed Consent

Recruitment of critically ill patients who are not able to consent is a ubiquitous problem in acute and critical care research and there is a clear legal framework under which these patients may be recruited to research studies. In all cases, efforts will be made to obtain informed consent from patients early in the course of illness, before critical illness interferes with their capacity to make decisions and to confirm consent at the earliest point in recovery. Consent forms will be provided in Norwegian or in English if required. If the patient consents in participating in this add-on study he or she automatically consents in participating in the WHO global study.

In this peculiar situation with COVID 19 infected patients, the signed form may itself be a source of infection. To overcome this, a third person (health worker, nurse or physician) will be present while the patient is informed, and independently evaluate and confirm whether the patient is consent competent and voluntary says yes/no to join the study. This will thereafter be

documented in the patient's medical record. Thus, a written consent is not required as long as we ensure and document that the patient has been thoroughly informed and voluntary consents to participate.

Due to the patient condition, it is likely that he/she is not capable to sign an informed consent form. Thus, when the patient lacks the capacity to consent to participation, an appropriate representative will be approached. A pdf-file of the consent form will be sent to the patient's representative for reading, who will thereafter be contacted by phone. A third person (health worker, nurse or physician) will join this conversation, and independently evaluate and confirm whether the representative on behalf of the patient, provides an informed consent and voluntary says yes/no to join the study. This will thereafter be documented in the patient's medical record. Staff trained in consent procedures that protect the rights of the patient, and adhere to the ethical principles within the Declaration of Helsinki will be used. Staff will explain the details of the study to the participant or representative and allow them time to discuss and ask questions. The staff will review the informed consent form with the person giving consent and endeavor to ensure understanding of the contents, including study procedures, risks, benefits, the right to withdraw and alternatives to participation. Patient autonomy to withdraw from the study at any time will be respected.

We are sensitive to the fact that some patients or their representatives may feel under an unusually strong moral obligation to participate given the nature of this research and the wide, and often inaccurate, publicity surrounding emerging infections. In view of this, we have tried to make both the potential benefits and limitations of this explorative investigational study clear in the information sheet. In the informed consent form we also stress that participation is entirely voluntary and there is no penalty of any kind for declining to join the study. Balance between public health and research. Patients with emerging infections are commonly the subject of public health investigations. The work proposed here is research and will be clearly presented as such. There is no primary gain to the patient from participating. In designing and describing this research we are clear that, in accordance with the guiding principles of Good Clinical Practice, the needs and autonomy of the individual are paramount and the potential benefits to wider society do not take precedence.

11.2 Confidentiality

Clinical staff will conduct this study and those involved in the study will ensure that each study participant's privacy and confidentiality is maintained. Participants will not be identified in any published reports of this study. All records will be kept confidential to the extent provided by international and local law. All laboratory specimens, evaluation forms, reports, study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party. Paper and electronic medical records may be accessed during the study to confirm, verify or complete clinical information provided in the case report form. Site files will at all times be accessible only to clinical and research staff. Consent will be sought for investigators to access patient data.

Participation in international collaboration involving sharing of data from the NOR-SOLIDARITY trial and merging of NOR-SOLIDARITY data with other (similar) studies will be based on fully de-identified data.

12 Scientific and peer review

The results of the study will be published in a peer-reviewed internationally recognized journal. We are aware that there may be too few patients enrolled in the study, thus our national study

may not be able to answer the objectives of the protocol. However, the principal investigators will keep close collaboration with WHO (WHO adaptive master protocol on Clinical Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Patients) making it likely that the results can be incorporated in a multinational study. This will secure that the data from this study will be used in a bigger setting and contribute to increased knowledge.

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Appendix

A1 The WHO COVID-19 core protocol, version 10

This is attached as a separate document

A2 WHO Standard Operating Procedures and appendix, version 10

This attached as a separate document

A3 Sofa Score

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score[a]

	Score				
System	0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

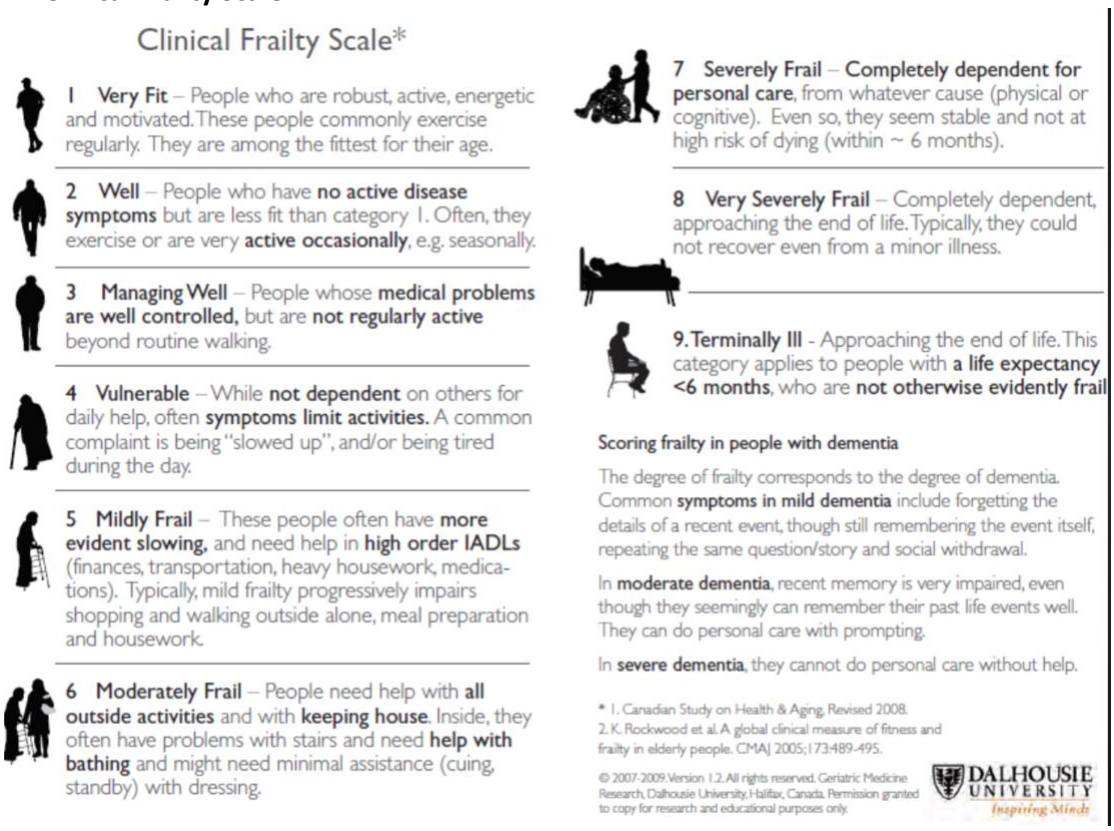
Abbreviations: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

A4 Clinical Frailty Scale



Clinical Frailty Scale*

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 **Managing Well** – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **Severely Frail** – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.
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A5 Preparation of plasma and serum (study samples)

EDTA-plasma (12 mL blood): Collect EDTA-blood into two tubes. Immediately after sampling, mix blood by inverting the tube three times. Place the tube on crushed ice (optional) and centrifuge as soon as possible (within 30 minutes, latest within 60 minutes) at 3000*g* for 15 minutes. Isolate plasma (leave the 0.5 cm closest to the cell layer) into NUNC-tubes. Freeze immediately -70°C/or -80°C.

Serum (8mL blood): Collect the blood in one red topped tube. Leave it undisturbed at the bench, approximately 30 minutes until coagulation. Then centrifuge at 2000*g* for 10 minutes. Isolate serum (leave the 0.5 cm closest to the cell layer) into NUNC-tubes. Freeze immediately -70°C/or -80°C.

Labeling: Every nunc tubes have to be named according to study site number, patient number and sample number as described in the biobank procedure.

A6 Participating hospitals and contact information

Hospital	Contact person	E-mail
	Helse Vest	
Haukeland	Bjorn Blomberg	bjorn.blomberg@uib.no
Haukeland	Kvåle, Reidar	reidar.kvale@helse-bergen.no
Haraldsplass	Bård Reiakvam Kittang	Bard.Kittang@uib.no
Stavanger	Åse Berg	ase.berg@sus.no
Fonna	Lan Ai Kieu Le	lan.ai.kieu.le@helse-fonna.no
Førde	Pawel Franciszek Mielnik	pawel.franciszek.mielnik@helse-forde.no
	Helse Midt	
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A7 Flow chart