MASTER PROTOCOL

A Multi-centre, Adaptive, Randomized, Double-Blind, Placebo-Controlled Clinical Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Patients

ABOUT THIS PROTOCOL

This is a multi-centre, adaptive, randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of investigational therapeutic agents in combination with standard-of-care for the treatment of hospitalized patients with novel coronavirus disease (COVID-19).

This Master Protocol is largely based on a series of deliberations of the WHO R&D Blueprint Clinical Trials Expert Group. The experts included international clinical trialists, coronavirus experts, regulatory and ethics experts and clinicians, including those treating COVID-19 patients.

Based on those deliberations, experts at the National Institute of Allergy and Infectious Diseases (NIAID) at the US National Institutes of Health developed the full version of the protocol. The version was then further adjusted to facilitate its implementation internationally.

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24 February 2020

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https://apps.who.int/iris/bitstream/handle/10665/330694/WHO-HEO-RDBlueprintCoV-2020-4-eng.pdf
A Multi-centre, Adaptive, Randomized, Double-Blind Placebo-Controlled Clinical Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19
WHY A MASTER PROTOCOL?

Integrating clinical trials of experimental therapeutics as part of the response during infectious disease outbreaks is increasingly recognized as important for determining efficacy of potential therapies.

Using a Master Protocol can speed the implementation of clinical trials. A Master Protocol concept also allows a clinical trial to extend across multiple infectious disease outbreaks and accommodates changing and unpredictable epidemic features and incorporates new investigative team members into the trial over time.

To avoid premature release of data, this Master Protocol specifies that efficacy data from a trial that has not yet been completed due to insufficient enrolment should not be released. A global independent monitoring committee could review results from an interim analysis of study data to make recommendations regarding whether the study should continue or stop for efficacy, futility, or safety, guided by a pre-specified monitoring plan.

A trial carried out under this proposed Master Protocol can continue across outbreak sites until the scientific questions of interest are addressed.

The trial will be conducted in two stages:
1. a Pilot Stage and,
2. a Pivotal Stage.

This Master Protocol includes several important features, including but not limited to:
- Promotes international collaboration, by serving as a template for multiple Sponsors and investigation teams evaluating potential COVID-19 treatments;
- Provides increased confidence that definitive results would be obtained by planning for trial continuation across sites and countries without release of results in settings where an outbreak would wane before the trial study had reliably answered the principal questions it was designed to address;
- Includes design flexibilities, such as those implemented during the PALM RCT in the EVD outbreak in DRC\(^2\), including the addition of other potential candidate therapeutics after the start of the trial and dropping therapies during the trial that are shown to be inferior.

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
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1. PROTOCOL SUMMARY

Synopsis

1.1 Rationale for Proposed Clinical Study

In December 2019, the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknown cause. Coronavirus RNA was quickly identified in some of these patients. This novel coronavirus has been designated SARS-CoV-2, and the disease caused by this virus has been designated COVID-19. Currently there are no approved therapeutic agents available for coronaviruses.

1.2 Study Design

This study is an adaptive, randomized, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of novel therapeutic agents in hospitalized adult patients diagnosed with COVID-19.

The study is a multi-centre trial that will be conducted in up to 50 sites globally with multiple Sponsors.

Conducting a double-blind trial is important, especially if the primary endpoint is not all cause mortality (ACM) but rather one that involves caregiver judgment (such as an ordinal scale for clinical severity).

An important issue is whether it would be feasible to conduct a double-blind trial which involved multiple therapies. One potentially achievable approach to conducting blinded trials involving multiple experimental interventions would be that used by the NIAID-sponsored CPCRA 007 HIV treatment trial, as discussed in Example 5.10 and Figure 5.1 of the Ellenberg S, Fleming T and DeMets DMC textbook Data Monitoring Committees in Clinical Trials: A Practical Perspective (Statistics in Practice) (Second edition).

The study will compare different investigational therapeutic agents to a placebo. There will be interim monitoring to allow early stopping for futility, efficacy, or safety and to introduce new therapies as they become available. If one therapy proves to be superior to others in the trial, this treatment will then become the control arm for comparison(s) with new experimental treatment(s).

Because of the possibility that standards of supportive care may vary between trial centres and may also evolve/improve over time as more is learned about successful management of COVID-19, comparisons of safety and efficacy will be based on data from concurrently randomized participants.
A global independent data and safety monitoring board (DSMB) is proposed to monitor interim data to make recommendations about early study closure or changes to conduct, including adding or removing treatment arms.

Subjects will be assessed daily while hospitalized. Discharged patients will be asked to attend study visits at days 15, and 29. All subjects will undergo a series of efficacy and safety assessments, including laboratory assays. Blood samples and oropharyngeal (OP) swabs will be obtained on days 1; 3, 5, 8, 11 (while hospitalized); and days 15 and 29 (by returning to the clinic or if still hospitalized).

The visits post discharge may not be feasible in some sites. Therefore, follow up visits by phone if physical visit is not feasible, can be considered. Sampling only OP swabs and blood for virological testing may need to be revisited, to include other specimens as pertinent and feasible. As well as testing locally, if feasible, a central laboratory for confirmatory testing is highly desirable. Pharmacokinetics evaluation should be included, if possible, as there is a need to better understand if the drug exposure in humans is adequate (e.g. in ventilated patients or when treatment is co-administered with other antivirals) and to perform exposure-response analyses. It is recognised that if only few samples can be feasibly collected with a heterogenous background of concomitant therapy, such studies might turn out not to be informative.

The proposed primary outcome, the condition of the patient on a 7-point ordinal scale at day 15, will be defined based on blinded review of data from the first 100 subjects. These data will also be used to evaluate the ordinal scale on other days and may collapse parts of the ordinal scale if there are few subjects represented in certain categories.

The pilot study data will be included in the primary analysis of the ‘pivotal’ stage of the trial as long as those using the pilot stage data to make decisions about the design of the pivotal stage do not have access to information from the pilot stage that would be directly or indirectly informative about the efficacy and safety of the experimental regimens being evaluated in the pivotal stage. Principles for endpoint selection will be defined a priori in a separate document.

The pilot study will also evaluate the different constructs of the ordinal scale (different days and different number of categories) by severity (severe vs. mild-moderate). Different primary endpoints may be chosen for patients into the trial with different levels of disease severity. In addition, data from the pilot study will be used to down select and prioritize the secondary endpoints.

After the pilot phase, it could emerge that more profound changes in selection of the primary endpoint than just the day of primary evaluation could be warranted, which would need reflection on how to progress the study and whether a seamless approach, from the pilot to the main trial, would still be appropriate.
In addition, there will need to be further consideration about how the study will progress if one therapy is found to be efficacious and becomes the standard of care for comparison with new therapies, including potential drug-drug interactions.

The initial sample size is calculated to be approximately 400 subjects for a 2-arm trial. If any additional therapeutic arms are added, the sample size will be recalculated.

Randomization will be stratified by:
- Site
- Severity of illness at enrolment:
  - Severe disease: requiring mechanical ventilation or oxygen, a SpO2 ≤ 94% on room air, or tachypnoea (respiratory rate ≥ 24 breaths/min)
  - Mild-moderate disease: SpO2 > 94% and respiratory rate < 24 breaths/min without supplemental oxygen.

1.3 Study Objectives

1.3.1 Primary Objective
The overall objective of the study is to evaluate the clinical efficacy and safety of different investigational therapeutics relative to the control arm in patients hospitalized with COVID-19.
- The choice of the primary outcome measure will be determined by a pilot study of the first 100 subjects.
- Subject clinical status (on a 7-point ordinal scale) at day 15 is the default primary endpoint.

1.3.2 Secondary Objectives
Evaluate clinical efficacy of different investigational therapeutics as compared to the control arm as assessed by:

Clinical Severity

Ordinal scale:
- Time to an improvement of one category from admission on an ordinal scale.
- Subject clinical status on an ordinal scale at days 3, 5, 8, 11, and 29.
- Mean change in the ranking on an ordinal scale from baseline to days 3, 5, 8, 11, 15 and 29 from baseline.

National Early Warning Score (NEWS):
A Multi-centre, Adaptive, Randomized, Double-Blind Placebo-Controlled Clinical Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19

- The time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first.
- Change from baseline to days 3, 5, 8, 11, 15, and 29 in NEWS.

Oxygenation:
- Oxygenation free days in the first 28 days (to day 29).
- Incidence and duration of new oxygen use during the trial.

Mechanical Ventilation:
- Ventilator free days in the first 28 days (to day 29).
- Incidence and duration of new mechanical ventilation use during the trial.

Hospitalization
- Duration of hospitalization (days).

Mortality
- 15-day mortality.
- 28-day mortality.

Evaluate the safety of the intervention through 28 days of follow-up as compared to the control arm as assessed by:

- Cumulative incidence of serious adverse events (SAEs)
- Cumulative incidence of Grade 3 and 4 adverse events (AEs).
- Discontinuation or temporary suspension of infusions (for any reason).
- Changes in white cell count, haemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, and AST over time.

1.3.3 Exploratory Objective

Evaluate the virologic efficacy of different investigational therapeutics as compared to the control arm as assessed by:

- Percent of subjects with SARS-CoV-2 detectable in OP sample at days 3, 5, 8, 11, 15, and 29.
- Quantitative SARS-CoV-2 virus in OP sample at days 3, 5, 8, 11, 15, and 29.
- Development of resistance of SARS-CoV-2 in OP sample at days 3, 5, 8, 11, 15, and 29.
- Quantitative SARS-CoV-2 virus in blood at days 3, 5, 8, and 11.
1.4 Study Endpoints

One important component in determining the benefits and harms of medical interventions is the use of well-defined and reliable outcome assessments as endpoints in clinical trials. Improving endpoints can better define patient benefits, allowing more accurate assessment of drug efficacy and more informed benefit-vs-risk decisions; another potential plus is facilitating efficient trial design. Talbot GH et al Clinical Infectious Diseases, Volume 62, Issue 5, 1 March 2016, Pages 603–607.

To enable confirmatory analyses beyond those for the primary endpoint, given issues of multiplicity, it would be preferable to have at most 4 secondary endpoints and for other endpoints to be included with the exploratory endpoints.

To assist in achieving that goal, it usually would be preferable to focus on clinical efficacy measures when defining the primary and secondary endpoints.

1.4.1 Primary Endpoint

Clinical status of subject at day 15 (on a 7-point ordinal scale):
1. Not hospitalized, no limitations on activities
2. Not hospitalized, limitation on activities;
3. Hospitalized, not requiring supplemental oxygen;
4. Hospitalized, requiring supplemental oxygen;
5. Hospitalized, on non-invasive ventilation or high flow oxygen devices;
6. Hospitalized, on invasive mechanical ventilation or ECMO;
7. Death.

1.4.2 Secondary Endpoints

- Status on an ordinal scale assessed daily while hospitalized and on days 15 and 29.
- NEWS assessed daily while hospitalized and on days 15 and 29.
- Duration of supplemental oxygen (if applicable).
- Duration of mechanical ventilation (if applicable).
- Duration of hospitalization.
- Date and cause of death (if applicable).
- Grade 3 and 4 adverse events
- SAEs.
- White cell count, haemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, and AST on days 1; 3, 5, 8, 11 (while hospitalized); and Day 15 and 29 (if able to return to clinic or still hospitalized).
1.4.3 Exploratory Endpoint

- Qualitative and quantitative PCR for SARS-CoV-2 in OP swab on days 1; 3, 5, 8, 11 (while hospitalized); and days 15 and 29 (if able to return to clinic or still hospitalized).
- Qualitative and quantitative PCR for SARS-CoV-2 in blood on days 1; 3, 5, 8, 11 (while hospitalized).

1.5 Inclusion criteria

1. Subject (or legally authorized representative) provides written informed consent prior to initiation of any study procedures.
2. Understands and agrees to comply with planned study procedures.
3. Agrees to the collection of OP swabs and venous blood per protocol.
4. Male or non-pregnant female adult ≥18 years of age at time of enrolment.
5. Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other commercial or public health assay in any specimen < 72 hours prior to randomization.
6. Illness of any duration, and at least one of the following:
   - Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), or
   - Clinical assessment (evidence of rales/crackles on exam) AND SpO2 ≤ 94% on room air, or
   - Requiring mechanical ventilation and/or supplemental oxygen.
7. Women of childbearing potential must agree to use at least one primary form of contraception for the duration of the study (acceptable methods will be determined by the site).

1.6 Exclusion criteria

1. ALT/AST > 5 times the upper limit of normal.
2. Stage 4 severe chronic kidney disease or requiring dialysis (i.e. eGFR < 30)
3. Pregnancy or breast feeding.
4. Anticipated transfer to another hospital which is not a study site within 72 hours.
5. Allergy to any study medication

1.7 Study Phase

Phase 2
1.8 Study Population

Hospitalized adult (≥18 years old) patients with COVID-19.

1.9 Sites

Site selection will be determined as information becomes available about the epidemiology of COVID-19, and sites will be activated based on the number of local/regional cases and the willingness of local investigators to participate in the study.

Multiple sites will be IRB approved, but activation will be dependent on the incidence of COVID-19 at the site.

Preferably, potential sites should be proactively approached, and this should not be delayed until cases are confirmed. This will avoid unnecessary delays.

1.10 Study intervention:

The study is designed to evaluate multiple interventions.

WHO has convened an independent panel of experts to deliberate on potential therapeutic candidates that could be further evaluated in the current COVID-19 epidemic. This review will be conducted regularly as relevant data become available.

The intention is to assess the evidence available for potential candidate therapies with regards to safety and efficacy and recommend those that should be advanced for clinical care through a compassionate protocol and/or evaluated in a clinical trial.

Based on the evidence available on January 27, 2020 on the different therapeutic options, Remdesivir was considered the most promising candidate therapy based on its broad antiviral activity, the in vitro and in-vivo data available for coronaviruses and the extensive clinical safety database (in particular from the Ebola virus disease clinical trial (and MEURI) in eastern Congo). Further, studies in mouse models using Remdesivir showed superior efficacy over Kaletra + IFNbeta.

Among the repurposed drugs, the investigation of the antiretroviral medicine (HIV protease inhibitors), lopinavir/ritonavir, either alone or in combination with IFNbeta1b, was considered a suitable second option for rapid implementation in clinical trials. Preclinical data available and limited clinical experience in the context of MERS, would suggest that it could provide some degree of clinical benefit and would be worth investigating, particularly in severe cases.

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4 [https://www.who.int/blueprint/priority-diseases/key-action/Table_of_therapeutics_Appendix_17022020.pdf?ua=1](https://www.who.int/blueprint/priority-diseases/key-action/Table_of_therapeutics_Appendix_17022020.pdf?ua=1)
Initially, this protocol proposes a trial with 2 arms, and Remdesivir is used as an example of an active product, but, as noted above, other candidate therapeutics may be considered:

- Subjects will be randomized to receive either active product or placebo. Remdesivir will be administered as a 200 mg intravenous loading dose on day 1, followed by a 100 mg once-daily intravenous maintenance dose for the duration of the hospitalization up to a 10 days total course.
- A matching placebo will be given at an equal volume at the same schedule.

The study will randomize participants 1:1 to placebo or investigational product.

If additional arms are added to or dropped from the trial, randomization will proceed with an equal probability of assignment to each of the remaining arms. As new interventions are added, the protocol will be amended and reviewed by IRBs/IECs and applicable regulatory agencies before implementation.

The current protocol lays out the general principles of how the multi-intervention trial would be implemented. This will be provided in more detail in a subsequent version of the Master Protocol.

### 1.11 Study Duration

The study will last for up to 3 years.

#### 1.11.1 Participant Duration

An individual subject will complete the study in about 29 days, from screening at day -1 or 1 to follow-up on day 29 ±3 days.

#### 1.11.2 Safety

- Given the severity of illness in COVID-19, there are no pre-specified study stopping rules for safety. The protocol team will review blinded AE / SAE data every 2 weeks. If there are a concerning number of unexpected AEs, the DSMB will be asked to review unblinded safety data in an ad hoc meeting.
- The DSMB will review safety data after every 50 subjects are entered into the trial and ad hoc reviews will be undertaken if there are other specific safety concerns. The study will not stop enrolment awaiting these DSMB reviews, though the DSMB may recommend temporary or permanent cessation of enrolment based on their safety reviews.
**1.12 Schedule of Assessments**

### Table 1. Schedule of Assessments

<table>
<thead>
<tr>
<th>Time</th>
<th>Screen</th>
<th>Baseline</th>
<th>Daily until hospital discharge</th>
<th>15±2</th>
<th>29±3</th>
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<tr>
<td>Day +/- Window</td>
<td>−1 or 1</td>
<td>1</td>
<td>Day until hospital discharge</td>
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<td>Assesments/Procedures</td>
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<td>Informed consent</td>
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<td>Demographics &amp; Medical History</td>
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<td>Review SARS-CoV-2 results</td>
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<td>Randomization</td>
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<td>Administration of Remdesvir</td>
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<td><strong>STUDY PROCEDURES</strong></td>
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<td>Vital signs including SpO₂</td>
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<td>Daily until discharge</td>
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<td>Daily until discharge</td>
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<tr>
<td>Safety haematology, chemistry and liver tests²</td>
<td>X³</td>
<td>X⁴</td>
<td>Day 3, 5, 8, 11 (all ± 1 day) if hospitalized</td>
<td></td>
<td></td>
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<tr>
<td>Pregnancy test for females of childbearing potential</td>
<td>X³</td>
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<td><strong>RESEARCH LABORATORY</strong></td>
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<tr>
<td>Blood for serum</td>
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<td>Day 3, 5, 8, 11 (all ± 1 day) if hospitalized</td>
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<td>X</td>
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<tr>
<td>Blood for PCR SARS-CoV-2</td>
<td>X³</td>
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<td>Day 3, 5, 8, 11 (all ± 1 day) if hospitalized</td>
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<tr>
<td>Oropharyngeal swab</td>
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<td>Day 3, 5, 8, 11 (all ± 1 day) if hospitalized</td>
<td>X</td>
<td>X</td>
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</tbody>
</table>

**Notes:**
1. Refer to Section 9.1 of the protocol for details of clinical data to be collected. This includes ordinal score, NEWS, oxygen requirement, Mechanical ventilator requirement, etc.
2. White cell count, haemoglobin, platelets, creatinine, glucose, total bilirubin, ALT/SGPT, AST/SGOT.
3. Laboratory tests performed in the 48 hours prior to enrolment will be accepted for determination of eligibility.
4. Any laboratory tests performed as part of routine clinical care within the specified visit window can be used for safety laboratory testing.
5. Baseline assessments should be performed prior to study drug administration.
6. In person visits are preferred but recognizing quarantine and other factors may limit the subject’s ability to return to the clinic. In this case, these visits may be conducted by phone.
1.13 Study Schema

**Key:**
- Periods for comparison of Placebo vs Remdesivir
- Periods for comparison of Placebo vs Drug Y

† Potential drug shortage
‡ Trial plans will vary in the event of a shortage. Initiation of a 3rd arm is one option.

Sample size per arm:
- Pilot phase
- Interim monitoring as described in protocol

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2. INTRODUCTION

2.1 Study Rationale

COVID-19 is a respiratory disease caused by a novel coronavirus (SARS-CoV-2) and causes substantial morbidity and mortality. There is currently no vaccine to prevent Covid-19 or infection with SARS-CoV-2 or therapeutic agent to treat COVID-19. This clinical trial is designed to evaluate potential therapeutics for the treatment of adult patients hospitalized with COVID-19.

2.2 Background

2.2.1 Purpose of Study

Coronavirus (CoVs) are positive-sense single stranded enveloped RNA viruses, many of which are commonly found in humans and cause mild symptoms. Over the past two decades, emerging pathogenic CoVs capable of causing life-threatening disease in humans and animals have been identified, namely severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle Eastern respiratory syndrome coronavirus (MERS-CoV).

In December 2019, the Wuhan Municipal Health Committee (Wuhan, China) identified an outbreak of viral pneumonia cases of unknown cause. Coronavirus RNA was quickly identified in some of these patients. This novel coronavirus has been abbreviated as SARS-CoV-2 and has 89% nucleotide identity with bat SARS-like-CoVZXC21 and 82% with that of human SARS-CoV (1). Most of the infections outside China have been travel-associated cases in those who had recently visited Wuhan City and are thought to have acquired the virus through contact with infected animals or contact with infected people.

This novel coronavirus has been designated SARS-CoV-2, and the disease caused by this virus has been designated COVID-19.

Outbreak forecasting and mathematical modelling suggest that these numbers will continue to rise (2).

Global efforts to evaluate novel antivirals and therapeutic strategies to treat COVID-19 have intensified. There is an urgent public health need for rapid development of novel interventions.
2.2.2 Potential therapeutics

WHO has convened an independent panel of experts to deliberate on potential therapeutic candidates that could be evaluated in the current COVID-19 epidemic. This review will be conducted regularly as more data become available. The intention is to assess the evidence available for these candidates with regards to safety and efficacy and recommend those that should be advanced for clinical care through a compassionate protocol and/or evaluated in a clinical trial.

Based on the evidence available on January 27, 2020, of the different therapeutic options, Remdesivir was considered the most promising candidate based on the broad antiviral spectrum, the in vitro and in-vivo data available for its use against coronaviruses and the extensive clinical safety database (in particular coming from the Ebola virus disease clinical trial and MEURI in eastern Congo). Further, studies in mice using Remdesevird showed superior efficacy over Kaletra + IFNbeta. Among the repurposed drugs, the investigation of the antiretroviral medicine (HIV protease inhibitors), lopinavir/ritonavir, either alone or in combination with IFNbeta1b, was considered a suitable second option for rapid implementation in clinical trials. Preclinical data available and limited clinical experience in the context of MERS, suggests that it could provide some degree of clinical benefit and would be worth investigating, particularly in severe cases.

Example using Remdesivir

Remdesivir (GS-5734) is a broad-spectrum nucleotide prodrug that inhibits RNA-dependent RNA polymerase activity among a diverse group of RNA viruses including filoviruses (e.g. Ebola, Sudan, Marburg), paramyxoviruses (e.g. RSV, Nipah, Hendra) and pathogenic coronaviruses (3-5). Multiple nonhuman primate studies have demonstrated the therapeutic efficacy of Remdesivir against Ebola virus, supporting the development of Phase 2 clinical trials in Africa (4-6). Studies in human airway epithelial cell assays demonstrated that Remdesivir inhibits replication of coronaviruses, including MERS-CoV (7). In mouse infection models, Remdesivir had therapeutic efficacy against Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV) (7,8). In vitro studies with mouse hepatitis virus (murine coronavirus) found that Remdesivir inhibits coronavirus replication through interference with the viral polymerase, despite the presence of a viral proofreading exoribonuclease, and coronaviruses that were partially resistant to inhibition by Remdesivir, were still sensitive to higher concentrations of Remdesivir, and fitness was impaired in the resistant viruses as compared to wild-type MERS-CoV (9). In a recent non-human primate study, therapeutic Remdesivir treatment initiated 12 hours post inoculation with MERS-CoV provided clinical benefit with a reduction in clinical signs, reduced virus replication in the lungs, and decreased presence and severity of lung lesions (10,11). These nonclinical in vitro and in vivo data suggest that Remdesivir might be useful for the treatment of COVID-19 for which no medical countermeasures are currently approved and support testing the efficacy of Remdesivir treatment among hospitalized adults with COVID-19 (12).

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6 https://www.who.int/blueprint/priority-diseases/key-action/Table_of_therapeutics_Appendix_17022020.pdf?ua=1
2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

For each new therapeutic agent under investigation, findings from the preclinical and clinical studies will be briefly described in this section and a summary of the findings described in the IB will be in an appendix.

**Example using Remdesivir**

The potential risks of participating in this trial are those associated with having blood drawn, the intravenous (IV) catheterization, possible reactions to Remdesivir and breach of confidentiality. Drawing blood may cause transient discomfort and fainting. Fainting is usually transient and managed by having the subject lie down and elevate his/her legs. Bruising at the blood collection sites may occur but can be prevented or lessened by applying pressure to the blood draw site for a few minutes after the blood is taken. Intravenous catheterization may cause insertion site pain, phlebitis, haematoma formation, and infusate extravasation; less frequent but significant complications include bloodstream and local infections. The use of aseptic (sterile) technique will make infection at the site where blood will be drawn or at catheter site less likely.

2.3.2 Potential Risks

**Example using Remdesivir**

Remdesivir is a relatively safe investigational therapeutic agent. A few subjects may experience constipation, heartburn, itching, unusual feelings in the ear, dizziness, loss of appetite, nausea, vomiting, shaking of the leg and arm, headache, loose stool, or upset stomach. These adverse events are temporary, lasting only a few days, and none are serious. In clinical studies, transient elevations in ALT and AST have been observed with single doses of Remdesivir up to 225 mg and multiple once daily doses of Remdesivir 150 mg for up to 14 days, with mild, reversible PT prolongation in some subjects but without any clinically significant change in INR or other evidence of hepatic effects. The mechanism of these elevations is currently unknown. Patients with underlying chronic liver disease, as evidenced by a screening ALT or AST >5 times the upper limit of normal, will not be eligible for study enrolment. For subjects enrolled in the study, regular laboratory assessments should 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. In nonclinical animal studies, toxicity studies found dose-dependent and reversible kidney injury and dysfunction. No clinical evidence of nephrotoxicity has been observed with single doses of Remdesivir up to 225 mg or multiple once daily doses of Remdesivir 150 mg for up to 14 days. A 150-mg dose of the solution and lyophilized formulations of Remdesivir contains 9 and 4.5 g, respectively, of SBECID, for which the maximum daily recommended dose (based on an EMA safety review) is approx. 250 mg/kg. Because SBECID is renally cleared, subjects with moderate or severe renal impairment may have SBECID exposures greater than those with less severe renal impairment or normal renal function. Patients with underlying renal disease as evidenced by a creatinine clearance < 30 ml/min will not be eligible for study enrolment. Remdesivir should not be used with other drugs that have significant hepatotoxicity. This includes other antivirals such as
Lopinavir/ritonavir. Although there have been no clinical studies, it is anticipated there would be additive hepatotoxicity.

2.3.3 Risks to Privacy

Subjects will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see the subject’s PHI. All study records will be kept in a locked file cabinet or maintained in a locked room at the participating clinical site. Electronic files will be password protected.

Only people who are involved in the conduct, oversight, monitoring, or auditing of this trial will be allowed access to the PHI that is collected.

Any publications from this trial will not use information that will identify subjects by name. Organizations that may inspect and/or copy research records maintained at the participating site for quality assurance and data analysis include groups such as the IRB, Sponsor and the pertinent regulatory authorities.

2.3.4 Known Potential Benefits

The candidate therapeutic(s) being evaluated may or may not improve clinical outcome of an individual adult subject with COVID-19 who participates in this trial. However, there is potential benefit to society from their participation in this study resulting from insights gained about the therapeutic agents under study as well as the natural history of the disease. While there may not be benefits for an individual subject, there may be benefits to society if a safe, efficacious therapeutic agent can be identified during this global COVID-19 outbreak.

2.3.4 Assessment of Potential Risks and Benefits

Example using Remdesivir

Remdesivir is generally a well-tolerated medication. There are significant liver toxicities that have been observed in prior studies. These have been self-limited and resolved after cessation of the medication. There is the potential for renal toxicities as observed in pre-clinical data. By excluding those with significant underlying liver and renal disease, and appropriate monitoring during the study, the risk to subjects can be minimized.
3. OBJECTIVES AND ENDPOINTS

The overall objective of the study is to evaluate the clinical efficacy and safety of different investigational therapeutics relative to the control arm among hospitalized adult patients who have COVID-19.

<table>
<thead>
<tr>
<th>OBJECTIVES</th>
<th>ENDPOINTS (OUTCOME MEASURES)</th>
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<tbody>
<tr>
<td>Primary</td>
<td></td>
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<tr>
<td>1. The overall objective of the study is to evaluate the clinical efficacy of different investigational therapeutics relative to the control arm in adult patients hospitalized with COVID-19.</td>
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<tr>
<td>• The primary endpoint will be determined by a pilot study of the first 100 subjects.</td>
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<tr>
<td>• Subject clinical status (on a 7-point ordinal scale) at day 15 is the default primary endpoint.</td>
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<tr>
<td></td>
<td>1. Not hospitalized, no limitations on activities</td>
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<td></td>
<td>2. Not hospitalized, limitation on activities;</td>
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<td></td>
<td>3. Hospitalized, not requiring supplemental oxygen;</td>
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<td></td>
<td>4. Hospitalized, requiring supplemental oxygen;</td>
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<td></td>
<td>5. Hospitalized, on non-invasive ventilation or high flow oxygen devices;</td>
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<td>6. Hospitalized, on invasive mechanical ventilation or ECMO;</td>
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<tr>
<td></td>
<td>7. Death.</td>
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Secondary

1. Evaluate the clinical efficacy of different investigational therapeutics as compared to the control arm as assessed by:

**Clinical Severity**

- Ordinal scale:
  - Time to an improvement of one category from admission using an ordinal scale.
  - Subject clinical status using ordinal scale at days 3, 5, 8, 11, and 29.
  - Mean change in the ordinal scale from baseline to days 3, 5, 8, 11, 15 and 29 from baseline.

- National Early Warning Score (NEWS):
  - The time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first.
  - Change from baseline to days 3, 5, 8, 11, 15, and 29 in NEWS

- Oxygenation:
  - Oxygenation free days in the first 28 days (to day 29).
  - Incidence and duration of new oxygen use during the study

- Ordinal outcome assessed daily while hospitalized and on day 15.

- NEWS assessed daily while hospitalized and on day 15

- Duration of supplemental oxygen (if applicable)
<table>
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<tr>
<th>OBJECTIVES</th>
<th>ENDPOINTS (OUTCOME MEASURES)</th>
</tr>
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| o Mechanical Ventilation:  
  ▪ Ventilator free days in the first 28 days (to day 29).  
  ▪ Incidence and duration of new mechanical ventilation use during the study. | • Duration of mechanical ventilation (if applicable) |
| • Hospitalization  
  o Duration of hospitalization (days). | • Duration of hospitalization |
| • Mortality  
  o 28-day mortality | • Date and cause of death (if applicable) |
| 2. Evaluate the safety of the intervention through 28 days of follow-up as compared to the control arm as assessed by:  
  • Cumulative incidence of serious adverse events (SAEs) through 29 days of follow-up.  
  • Cumulative incidence of Grade 3 and 4 AEs.  
  • Discontinuation temporary suspension of infusions (for any reason)  
  • Changes in white cell count, haemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, and AST over time. | • SAEs  
  • Severe adverse events  
  • White cell count, haemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, and AST on days 1; 3, 5, 8, 11 (while hospitalized); and Day 15 and 29 (if able to return to clinic or still hospitalized). |
| Exploratory |  
Evaluate the virologic efficacy of different investigational therapeutics as compared to the control arm as assessed by:  
  • Percent of subjects with SARS-CoV-2 detectable in OP sample at day 3, 5, 8, 11, 15, and 29.  
  • Quantitative SARS-CoV-2 virus in OP sample at day 3, 5, 8, 11, 15, and 29.  
  • Development of resistance of SARS-CoV-2 in OP sample at day 3, 5, 8, 11, 15, and 29.  
  • Quantitative SARS-CoV-2 virus in blood at day 3, 5, 8, and 11 | • Qualitative and quantitative PCR for SARS-CoV-2 in OP swab on Days 1; 3, 5, 8, 11 (while hospitalized); and Day 15 and 29 (if able to return to clinic or still hospitalized).  
  • Qualitative and quantitative PCR for SARS-CoV-2 in blood on Days 1; 3, 5, 8, 11 (while hospitalized). |
4. STUDY DESIGN

4.1 Overall Design

This study is an adaptive, randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of novel therapeutic agents in hospitalized adult patients diagnosed with COVID-19. The study is a multicentre trial that will be conducted in up to 50 sites globally. The study will be a series of 2-arm comparisons between different investigational therapeutic agents and a placebo. There will be interim monitoring to introduce new arms and allow early stopping for futility, efficacy, or safety. If one therapy proves to be efficacious, this treatment will then become the control arm for comparison(s) with new experimental treatment(s). Because of the possibility that background standards of supportive care may vary between centres and evolve/improve over time as more is learned about successful management of COVID-19, comparisons of safety and efficacy will be based on data from concurrently randomized participants. An independent data and safety monitoring board (DSMB) will actively monitor interim data to make recommendations about early study closure or changes to study arms.

Randomization will be stratified by:
- Site
- Severity of illness at enrolment:
  - Severe disease: requiring mechanical ventilation or oxygen, a SpO2 ≤ 94% or tachypnoea (respiratory rate ≥ 24 breaths/min)
  - Mild-moderate disease: SpO2 > 94% and respiratory rate < 24 breaths/min without supplemental oxygen.

Notwithstanding that the number of strata should kept to the minimum and the ones selected of major importance, the time of onset of symptoms should be considered for stratification - or at least, collection of these data is essential for proper subgroup analyses, and in consideration of the pilot data it might be one key factor to consider as to whether there should be stratification on this variable.

Subjects will be assessed daily while hospitalized. Follow-up is for approximately 29 days. Discharged patients will be asked to attend study visits at Days 15, and 29. All subjects will undergo a series of efficacy, safety, and laboratory assessments. Blood samples and oropharyngeal (OP) swabs will be obtained on days 1, 3, 5, 8, 11 (while hospitalized); and days 15 and 29 (if able to return to clinic or still hospitalized).

The proposed primary outcome, assessed on a 7-point ordinal scale at day 15, will be defined based on blinded review of data from the first 100 subjects. The pilot study data will be used to evaluate the ordinal scale on other days and parts of the ordinal scale may be collapsed if there are few subjects represented in certain categories. As long as the primary endpoint remains the ordinal scale, the pilot study data will be included in the primary analysis. Principles for endpoint selection will be defined a priori in a separate document.
The pilot study will also evaluate different aspects of the ordinal scale (different days and different number of categories) by severity (severe vs. mild-moderate). Different primary endpoints may be chosen for different severity populations. In addition, data from the pilot study will be used to determine the choice of the secondary endpoints, and to down select and prioritize the secondary endpoints.

### 4.2 Scientific Rationale for Study Design

At present, there is no specific antiviral therapy for coronavirus infections.

Few treatment studies have been conducted because most human coronavirus strains cause self-limited disease and care is supportive.

After the severe acute respiratory syndrome (SARS) coronavirus was identified in 2002 and caused a large global outbreak, there was an increased interest in the development of specific therapeutic agents. SARS CoV case-patients were treated with corticosteroids, type 1 IFN agents, convalescent plasma, ribavirin, and lopinavir or ritonavir, and, except for ribavirin, many of these agents have in vitro pre-clinical data that support their efficacy (13-28). Since the SARS outbreak, new therapeutic agents targeting viral entry proteins, proteases, polymerases, and methyltransferases have been tested, however, none of them has been shown to be efficacious in clinical trials (29-31).

This study utilizes an adaptive design that maximizes efficiency in identifying a safe and efficacious therapeutic agent for COVID-19 during the current outbreak. Some investigational products may be in limited supply and this study design enables continuation of the study even if a product becomes unavailable. In addition, the adaptive design allows for the evaluation of new therapeutic agents as they are identified. As the study will be a multicentre, multinational randomized controlled study, it will be possible to acquire rigorous data about the safety and efficacy of investigational therapeutic agents for COVID-19 that will lead to generalizable evidence.

Randomization is essential for establishing efficacy of these new therapeutic agents. Also, collecting clinical and virologic data on enrolled patients using a standardized timeline and collection instruments should provide valuable information about the clinical course of and morbidities associated with severe COVID-19 in a diverse group of hospitalized adult patients.

### 4.3 Justification for Dose

**Example Remdesivir**
The dose of Remdesivir used in this study will be the same dose that was has been used in the human Ebola clinical trials.
5. STUDY POPULATION

Approximately 400 male and non-pregnant female adults ≥18 years of age with COVID-19 who meet all eligibility criteria will be enrolled at up to 50 clinical trial sites globally.

Children are proposed to be excluded but the inclusion of adolescents could be considered.

The estimated time from screening (day -1 or day 1) to end of study for an individual subject is approximately 29 days.

Information regarding this trial may be provided to potential subjects who have previously participated in other trials conducted at the sites and to medical care providers who have cases of COVID-19 admitted to their hospital or in the referral area. Other forms and/or mechanisms of recruitment may also be used. The IRB will approve the recruitment process and all materials prior to use.

Subject Inclusion and Exclusion Criteria must be confirmed by a study clinician named on the delegation log.

5.1 Inclusion Criteria

In order to be eligible to participate in this study, a patient must meet all of the following criteria:

1. Subject (or legally authorized representative) provides written informed consent prior to initiation of any study procedures.
2. Understands and agrees to comply with planned study procedures.
3. Agrees to the collection of OP swabs and venous blood per protocol.
4. Male or non-pregnant female adult ≥18 years of age at time of enrolment.
5. Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other commercial or public health assay in any specimen < 72 hours prior to randomization.
6. Illness of any duration, and at least one of the following:
   2.3.3 Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), OR
   2.3.4 Clinical assessment (evidence of rales/crackles on exam) AND SpO2 ≤ 94% on room air, OR
   2.3.5 Requiring mechanical ventilation and/or supplemental oxygen.
7. Women of childbearing potential must agree to use at least one primary form of contraception for the duration of the study (acceptable methods will be determined by the site).

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. ALT/AST > 5 times the upper limit of normal.
2. Stage 4 severe chronic kidney disease or requiring dialysis (i.e., eGFR < 30)
3. Pregnant or breast feeding.
4. Anticipated transfer to another hospital which is not a study site within 72 hours.
5. Allergy to any study medication

5.2.1 Exclusion of Specific Populations

Children are proposed to be excluded but adolescents could be considered. A risk benefit analysis for each specific candidate therapeutic

**Example using Remdesivir**

Children and adolescents will not be included in this trial. The drug has only been used in a small number of paediatric patients. Initial information about the epidemiology of COVID-19 indicates that the overwhelming burden of severe disease occurs among older adults especially those with comorbidities. Given significant gaps in knowledge in children, and a low incidence of severe morbidity/mortality, the risk/benefits do not warrant inclusion of this population into this trial at this time.

In nonclinical reproductive toxicity studies, Remdesivir demonstrated no adverse effect on embryofoetal development when administered to pregnant animals. Embryonic toxicity was seen when Remdesivir was initiated in female animals prior to mating and conception, but only at a systematically toxic dose. Because the effects on the foetus are not fully known, pregnant women will not be eligible for the trial.

5.2.2 Inclusion of Vulnerable Participants

Not Applicable

5.3 Lifestyle Considerations

During this study, subjects are asked to:

- Refrain from drinking alcohol for 14 days after they begin receiving Remdesivir.
- Avoid taking paracetamol (acetaminophen) for 14 days after they begin receiving Remdesivir.
- Avoid getting pregnant during the study from day 1 through day 29 if female subject.

5.4 Screen Failures
After the screening evaluations have been completed, the investigator or designee is to review the inclusion/exclusion criteria and determine the subject’s eligibility for the study.

Only the reason for ineligibility will be collected on screen failures. Subjects who are found to be ineligible will be told the reason for ineligibility.

Individuals who do not meet the criteria for participation in this study (screen failure) because of an abnormal laboratory finding may be rescreened once.

5.5 Strategies for Recruitment and Retention

5.5.4 Recruitment
It is anticipated that patients with COVID-19 will present to participating hospitals, and that no other efforts to recruit potential subjects are needed. Recruitment efforts may also include dissemination of information about this trial to other medical professionals / hospitals.

Patients that are confirmed to have SARS-CoV-2 will be assessed for eligibility.

Screening will begin with a brief discussion with study staff. Some will be excluded based on demographic data and medical history i.e. pregnant, < 18 years of age, renal failure, etc. Information about the study will be presented to potential subjects (or legally authorized representative) and questions will be asked to determine potential eligibility. Screening procedures can begin only after informed consent is obtained.

5.5.5 Retention
Participating subjects will be reminded of subsequent visits.

5.5.6 Compensation Plan for Subjects
Compensation, if any, will be determined locally and in accordance with local IRB requirements, and subject to local IRB approval.

5.5.7 Costs
There is no cost to subjects for the research tests, procedures/evaluations and study product while taking part in this trial. Procedures and treatment for clinical care including costs associated with hospital stay may be billed to the subject, subject’s insurance or third party, if and as appropriate.
6. STUDY PRODUCT

6.1 Study Product(s) and Administration

6.1.1 Investigational Therapeutic and matching placebo

Study Product Description

**Example Remdesivir**
Remdesivir is a single diastereomer monophosphoramidate prodrug designed for the intracellular delivery of a modified adenine nucleoside analog GS-441524. In addition to the active ingredient, the lyophilized formulation of Remdesivir contains the following inactive ingredients: water for injection, sulfobutylether β-cyclodextrin sodium (SBECO), and hydrochloric acid and/or sodium hydroxide.

The supplied matching placebo lyophilized formulation is identical in physical appearance to the active lyophilized formulation and contains the same inactive ingredients.

**Dosing and Administration**
Subjects will be randomized to receive either active product or placebo. Initially, the trial will have 2 arms. Subjects will be randomized to receive either active product or placebo.

Remdesivir will be administered as a 200 mg intravenous loading dose on Day 1, followed by a 100 mg once-daily intravenous maintenance dose for the duration of the hospitalization up to a 10 days total course.

A matching placebo will be given at an equal volume using the same schedule.

See the protocol-specific Manual of Procedures (MOP) Appendices for detailed information on the preparation, labelling, storage, and administration of Remdesivir and placebo. Drug preparation will be performed by the participating site’s research pharmacist on the same day of administration to the subject. Missed doses are not made up.

**Dose Escalation**
Not Applicable

**Dose Modifications**
There are no clinical safety or pharmacokinetic data available for Remdesivir in patients with renal and/or hepatic impairment. Given the benefit-to-risk ratio in patients with COVID-19, these subjects are excluded from the study.

If the estimated creatinine clearance decreases by more than ≥ 50% from baseline, the study infusion should not be given. The infusion may be resumed when the estimated creatinine clearance returns to baseline.

If the liver function tests (ALT and/or AST) increase to > 3 times upper limits of normal, the dose of Remdesivir should be held. Dosing may be resumed when the ALT and/or AST returns to baseline. Dosing may be given later the same day. If a day’s dosing is missed, the dosing is not made up.

If any of the following occur, the dose of Remdesivir should be stopped and should not be restarted:
- ALT ≥3 × upper limits of normal and bilirubin ≥2 × upper limits of normal,
- ALT and/or AST increases to > 5 times upper limits of normal

6.1.2 Preparation/Handling/Storage/Accountability

Acquisition and Accountability

Therapeutic agents will be shipped to the site either directly from participating companies, from the sponsor, or from other regional or local drug repositories. All other supplies will be provided by the site.

Accountability

The site PI is responsible for study product distribution and disposition and has ultimate responsibility for study product accountability. The site PI may delegate to the participating site’s research pharmacist responsibility for study product accountability.

The participating site’s research pharmacist will be responsible for maintaining complete records and documentation of study product receipt, accountability, dispensation, storage conditions, and final disposition of the study product(s). Time of study drug administration to the subject will be recorded on the appropriate data collection form (CRF).

All study product(s), whether administered or not, must be documented on the appropriate study product accountability record or dispensing log. The sponsor’s
monitoring staff will verify the participating site’s study product accountability records and dispensing logs per the site monitoring plan. Refer to the protocol-specific MOP for details on storing active and placebo medications.

**Destruction**

After the study treatment period has ended or as appropriate over the course of the study after study product accountability has been performed, disposition of unused and used active and placebo vials should occur as noted:

Unused and Used active and placebo vials:

- Should be returned to the sponsor or destroyed on-site following applicable site procedures or by the site’s selected destruction vendor. Following the site’s procedure for the destruction of hazardous material or study product destruction policy/standard operating procedure (SOP) when destroying used and unused items.
- A certificate of destruction should be provided to the sponsor and retained in the Pharmacy Binder once completed.

### 6.1.3 Formulation, Appearance, Packaging, and Labelling

**Example Remdesivir**

The lyophilized formulation of Remdesivir is a preservative-free, white to off-white or yellow, lyophilized solid containing 150 mg of Remdesivir to be reconstituted with 29 mL of sterile water for injection and diluted into IV infusion fluids prior to IV infusion. Following reconstitution, each vial contains a 5 mg/mL Remdesivir concentrated solution with sufficient volume to allow withdrawal of 30 mL (150 mg of Remdesivir). It is supplied as a sterile product in a single-use, 50 mL Type 1 clear glass vial. In addition to the active ingredient, the lyophilized formulation of Remdesivir contains the following inactive ingredients: water for injection, SBECD, 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.

**Placebo to match**

The supplied matching placebo lyophilized formulation is identical in physical appearance to the active lyophilized formulation and contains the same inactive ingredients.

**Example Remdesivir**

The lyophilized formulation of matching placebo is filled in a 50-mL glass vial closed with a rubber stopper and aluminium seal with a plastic flip-off cap. Each single-use vial contains sufficient volume to allow withdrawal of 30 mL of Remdesivir 5 mg/mL concentrate or placebo following reconstitution.
Each of the study products will be labelled according to manufacturer specifications and include the statement “Caution: New Drug Limited by Regulatory Authority to Investigational Use.”

### 6.1.4 Product Storage and Stability

**Example Remdesivir**
Ambient vials of the lyophilized formulation of Remdesivir should be stored below 30°C. The lyophilized formulation needs to be reconstituted and then diluted into IV infusion fluids before use. After reconstitution, the total storage time before administration (including any time before or after dilution) should not exceed 4 hours at room temperature or 24 hours at refrigerated temperature (2°C to 8°C). See MOP for additional information.

**Placebo to match**
Vials of the lyophilized formulation of matching placebo should be stored below 30°C. The lyophilized formulation needs to be reconstituted and then diluted into IV infusion fluids before use. After reconstitution, the total storage time before administration (including any time before or after dilution) should not exceed 4 hours at room temperature or 24 hours at refrigerated temperature (2°C to 8°C).

### 6.1.5 Preparation

Refer to the protocol-specific MOP for details about preparation.

Measures that minimize drug contact with the body should always be considered during handling, preparation, and disposal procedures.
7. Measures to Minimize Bias: Randomization and Blinding

The study will randomize participants 1:1 to placebo or investigational product. If additional arms are added to or dropped from the trial, randomization will proceed with an equal probability of assignment to each of the remaining arms. Randomization will be stratified by:

- Site
- Severity of illness at enrolment:
  - Severe disease: requiring mechanical ventilation or oxygen, a SpO2 ≤ 94% on room air, or tachypnoea (respiratory rate ≥ 24 breaths/min)
  - Mild-moderate disease: SpO2 > 94% and respiratory rate < 24 breaths/min without supplemental oxygen.

The randomization procedure will be described in an SOP, which will define procedures for blinding.

7.1 Study Intervention Compliance

Each dose of study product will be administered by a member of the clinical research team, that is qualified and licensed to administer the study product. Administration and date, time, and location of injection will be entered into the case report form (CRF).

7.2 Concomitant Therapy

Therapy prior to enrolment with antivirals including lopinavir/ritonavir (Kaletra) or other therapeutic agents (e.g. corticosteroids) are permitted. However, these may be discontinued on enrolment.

If the local standard of care per written policies or guidelines (i.e., not just an individual clinician decision) includes lopinavir/ritonavir (Kaletra) or other agents, then continuing these during the study is permitted, but may require additional safety monitoring by the site.

Additionally, there should be plans on how the concomitant drugs are stopped for transaminase elevations, and prior to the thresholds for Remdesivir dose modification above (Section 0).

Otherwise, there should not be concomitant use of lopinavir/ritonavir (Kaletra) and Remdesivir due to lack of evidence on additive or synergistic effects and potential for an increased risk of transaminase elevations.
The current wording, “is permitted,” seems proper, given the interest in understanding relative efficacy and relative safety of randomized interventions in real world settings.

On the other hand, even if background interventions would be supported by local guidelines, stronger wording such as “is required” would be problematic if the relative efficacy and safety of such background interventions had not been reliably established.

Concomitant medications in a hospitalized population change daily and are difficult to collect and attribute to success and failure of therapy and impact on safety. Therefore, only select concomitant medications will be recorded in this trial. The list of medications will be assessed only from 7 days prior to enrolment to day 11 and will be detailed in the MOP.

7.1 Rescue Medicine
Not Applicable

7.2 Non-Research Standard of Care
Not Applicable
8. STUDY INTERVENTION DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

8.1 Halting Criteria and Discontinuation of Study Intervention

8.1.1 Individual Infusion Halting

For an individual subject, an individual infusion must be stopped if they have a suspected drug-related event of hypersensitivity (Grade 2 or higher) during the infusion. Subjects who have an IV infusion stopped for a safety related issue will not continue with dosing. See 8.1.1 Individual Infusion Halting for information about dose modifications due to laboratory abnormalities.

8.1.2 Study Halting for Safety

Given severity of illness in COVID-19, there are no pre-specified stopping rules. Instead there will be close oversight by the protocol team and frequent DSMB reviews for safety. Treatment should be stopped if a patient is found to be pregnant after randomization.

8.1.3 Withdrawal from Randomized Treatment or from the Study

Patients are free to withdraw from participation in the study at any time upon request, without any consequence. Patients should be listed as having withdrawn consent only when they no longer wish to participate in the study and no longer authorize the Investigators to make efforts to continue to obtain their outcome data. Every effort should be made to encourage patients to remain in the study for the duration of their planned outcome assessments. Patients should be educated on the continued scientific importance of their data, even if they discontinue study drug. In the case of a patients becoming lost to follow-up, attempts to contact the patient should be made and documented in the patient’s medical records.

8.1.4 Discontinuation of Study Drug

A patient in this clinical study may discontinue study drug for any of the following reasons:

- Patient requests to discontinue study drug
- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol
• Any serious adverse event (SAE), clinically significant adverse event, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the patient
• Patient fails to comply with protocol requirements or study-related procedures

Unless the patient withdraws consent, those who discontinue study drug early should remain in the study for further acquisition of endpoint measurements. The reason for patient discontinuation of study drug should be documented in the case report form.

8.1.5 Withdrawal of Patients from the Study
A patient may be removed from the study for the following reasons post initial dosing; however, whenever possible the patient should be followed for safety evaluations per protocol:
• Patient withdraws consent or requests discontinuation from the study for any reason
• Death of the patient
• Termination of the study
• Lost to follow-up.

Patients who withdraw from this study or are lost to follow-up after signing the informed consent form (ICF) and administration of the study product, will not be replaced. The reason for patient discontinuation from the study will be recorded on the appropriate case report form.

8.1.6 Lost to Follow-Up
A subject will be considered lost to follow-up if he or she fails to appear for a follow-up assessment and cannot be contacted with good effort. These efforts will be documented in the subject’s record.
9. STUDY ASSESSMENTS AND PROCEDURES

9.1 Screening and Efficacy Assessments

9.1.1 Screening Procedures

After the informed consent, some or all of the following assessments are performed to determine eligibility requirements as specified in the inclusion and exclusion criteria:

- Confirm the positive SARS-CoV-2 test result.
- Focused medical history, including the following information:
  - Day of onset of COVID-19 symptoms
  - History of chronic medical conditions related to inclusion and exclusion criteria
  - Medication allergies
  - Review medications and therapies for this current illness and record on the appropriate CRF.
- Counsel subjects to use adequate birth control methods required during the trial to avoid pregnancy.
- Obtain weight
- Review recent radiographic imaging (x-ray or CT scan)
- Targeted physical exam focused on lung auscultation
- \( \text{SpO2} \)
- Obtain blood for screening laboratory evaluations if not done in the preceding 48 hours:
  - ALT
  - AST
  - Cr (and calculate creatinine clearance)
  - Urine or serum pregnancy test (in women of childbearing potential)

Clinical screening laboratory evaluations will be performed locally by the site laboratory. The overall eligibility of the subject to participate in the study will be assessed once all screening values are available. The screening process can be suspended prior to complete assessment at any time if exclusions are identified by the study team. Study subjects who qualify will be immediately randomized.

The volume of venous blood to be collected is presented in Table 3.
9.1.2 Efficacy Assessments

For all baseline assessments and follow-up visits, refer to SOA for procedure to be done, and details below for each assessment.

Measures of clinical support

At each study day while hospitalized, the following measure of clinical support should be assessed:

- Hospitalization
- Oxygen requirement
- Non-invasive mechanical ventilation (via mask)
- Mechanical ventilator requirement (via endotracheal tube or tracheostomy tube)
- ECMO requirement

Ordinal Scale

The ordinal scale is an assessment of the clinical status at the first assessment of a given study day. Each day, the worse score for the previous day will be recorded. i.e. on day 3, day 2 score is obtained and recorded as day 2. The scale is as follows:

1. Not hospitalized, no limitations on activities
2. Not hospitalized, limitation on activities;
3. Hospitalized, not requiring supplemental oxygen;
4. Hospitalized, requiring supplemental oxygen;
5. Hospitalized, on non-invasive ventilation or high flow oxygen devices;
6. Hospitalized, on invasive mechanical ventilation or ECMO;
7. Death.

NEW Score

The NEW score has demonstrated an ability to discriminate patients at risk of poor outcomes. (Smith, 2016). This score is based on 7 clinical parameters. The NEW Score is being used as an efficacy measure.

This should be evaluated at the first assessment of a given study day. These parameters can be obtained from the hospital chart using the last measurement prior to the time of assessment. This is recorded for the day obtained. i.e. on Day 3, Day 3 score is obtained and recorded as Day 3.
Table 2: NEW Score

<table>
<thead>
<tr>
<th>PHYSIOLOGICAL PARAMETERS</th>
<th>3</th>
<th>2</th>
<th>1</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiration Rate</td>
<td>≤8</td>
<td>9 - 11</td>
<td>12 - 20</td>
<td>21 - 24</td>
<td>≥25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen Saturations</td>
<td>≤91</td>
<td>92 - 93</td>
<td>94 - 95</td>
<td>≥96</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Supplemental Oxygen</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td>≤35.0</td>
<td>35.1 - 36.0</td>
<td>36.1 - 38.0</td>
<td>38.1 - 39.0</td>
<td>≥39.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>≤90</td>
<td>91 - 100</td>
<td>101 - 110</td>
<td>111 - 210</td>
<td>≥220</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Rate</td>
<td>≤40</td>
<td>41 - 50</td>
<td>51 - 90</td>
<td>91 - 110</td>
<td>111 - 130</td>
<td>≥131</td>
<td></td>
</tr>
<tr>
<td>Level of Consciousness</td>
<td>A</td>
<td>V, P, or U</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Level of consciousness = alert (A), and arousable only to voice (V) or pain (P), and unresponsive (U).

9.1.3 Exploratory assessments

Viral Shedding

OP swabs will be collected on days 1; 3, 5, 8, 11 (while hospitalized); and Day 15 and 29 (if able to return to clinic or still hospitalized) and stored as outlined in the MOP. These assays are not developed yet, and the ability to test samples at one central lab is not clear. Therefore, while viral shedding is thought to be an important endpoint, considering the limitations above it is listed as an exploratory endpoint.

If virology assays can be set up with enough numbers of specimens tested, this data will be submitted as part of the Clinical Study Report. This may be submitted separately, as a supplemental Clinical Study Report.

Alternative Ordinal Scales

Given the limited structured clinical data available for COVID-19, the best construct of ordinal scale is not known. Additional data may be used to construct different ordinal scales to test their utility in a treatment study. These are hypothesis generating and will not be submitted as part of a final Clinical Study Report.
9.3 Safety and Other Assessments

Study procedures are specified in the SOA. A study physician licensed to make medical diagnoses and listed will be responsible for all trial-related medical decisions.

- **Physical examination:** A symptom-directed (targeted) physical examination will be performed to evaluate for any possible adverse event. No physical exam is needed for routine visits.

- **Clinical laboratory evaluations:**
  - Fasting is not required before collection of laboratory samples.
  - Blood will be collected at the time points indicated in the SOA. Clinical laboratory parameters include WBC, Hgb, PLT, Cr, glucose, total bilirubin, AST, ALT.
  - This testing will be performed at each clinical trial site in real time.

### Table 3: Venepuncture Volumes

<table>
<thead>
<tr>
<th>Day +/- Window</th>
<th>Screen</th>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day +/- Window</td>
<td>Screen</td>
<td>Baseline</td>
</tr>
<tr>
<td>Day +/- Window</td>
<td>Screen</td>
<td>Baseline</td>
</tr>
<tr>
<td>Day +/- Window</td>
<td>Screen</td>
<td>Baseline</td>
</tr>
<tr>
<td>Day +/- Window</td>
<td>Screen</td>
<td>Baseline</td>
</tr>
<tr>
<td>Day +/- Window</td>
<td>Screen</td>
<td>Baseline</td>
</tr>
<tr>
<td>Day +/- Window</td>
<td>Screen</td>
<td>Baseline</td>
</tr>
<tr>
<td>Safety haematology, chemistry and liver tests²¹</td>
<td>X 6mL</td>
<td>X 6mL</td>
</tr>
<tr>
<td>Blood for Serum</td>
<td>X 24mL</td>
<td>X 24mL</td>
</tr>
<tr>
<td>Plasma (includes PCR)</td>
<td>X 8mL</td>
<td>X 8mL</td>
</tr>
<tr>
<td>Total volume</td>
<td>38ml</td>
<td>38ml</td>
</tr>
<tr>
<td>Total all study days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

9.3.1 Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

If a physiologic parameter, e.g., vital signs, or laboratory value is outside of the protocol-specified range, then the measurement may be repeated once if, in the judgment of the investigator, the abnormality is the result of an acute, short-term, rapidly reversible condition or was an error. A physiologic parameter may also be repeated if there is a technical problem with the measurement caused by malfunctioning, or an inappropriate measuring device (i.e., inappropriate-sized BP cuff).
9.4  Adverse Events and Serious Adverse Events

9.4.1 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 unfavourable 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 and 4 AEs will be captured as AEs in this trial.

9.4.2 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,
- inpatient hospitalization or 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 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.”

“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 (for IND studies, a physician listed on the Form FDA 1572 as the site PI or Sub-Investigator).

All SAEs will be reviewed and evaluated and will be sent to the SMC (for periodic review), and the IRB/IEC.

9.4.3 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), Package Insert, and/or Summary of Product Characteristics.

9.4.4 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. This includes but is not limited to physicians, physician assistants, and nurse practitioners.

Severity of Adverse Events

All AEs and SAEs will be assessed for severity, according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events, version 2.1 (July 2017).

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **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.

• Severe (Grade 4): Events that are potentially life threatening.

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.

Relationship to Study Intervention
For each reported adverse reaction, the PI or designee 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 aetiology has been established.

9.4.5 Time Period and Frequency for Event Assessment and Follow-Up
For this study, all Grade 3 and 4 AEs and all SAEs occurring from the time the informed consent is signed through the Day 29 (end of study) visit will be documented, recorded, and reported.

Investigators Reporting of AEs
Information on all 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.
9.4.6 Serious Adverse Event Reporting

Investigators Reporting of SAEs

Any AE that meets a protocol-defined criterion as a SAE must be submitted immediately (within 24 hours of site awareness) on an SAE form to the designated Pharmacovigilance Group, at the following address:

Insert name and contact details of pharmacovigilance focal point

Other supporting documentation of the event may be requested by the designated Pharmacovigilance Group and should be provided as soon as possible. The designated Medical Monitor will review and assess the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct.

At any time after completion of the study, if the site PI or appropriate sub-investigator becomes aware of an SAE, the site PI or appropriate sub-investigator will report the event to the designated Pharmacovigilance Group.

Regulatory Reporting of SAEs

Following notification from the site PI or appropriate sub-investigator, as the IND sponsor, will report any SUSAR in an IND safety report to the regulatory authority and will notify all participating site PIs as soon as possible. Any unexpected fatal or life-threatening suspected adverse reaction will be reported to the regulatory authority as soon as possible, but in no case later than 7 calendar days after the sponsor’s initial receipt of the information. If the event is not fatal or life-threatening, the IND safety report will be submitted within 15 calendar days after the sponsor determines that the information qualifies for reporting. Relevant follow up information to an IND safety report will be submitted as soon as the information is available. Upon request from regulatory authority, the sponsor will submit any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

SAEs that are not SUSARs will be reported to the regulatory authority at least annually in a summary format which includes all SAEs.

Sites may have additional local reporting requirements (to the IRB and/or national regulatory authority).
9.4.7 Reporting Events to Subjects

Subjects will be informed of any severe AEs or SAEs that occur as part of their participation in this trial.

9.4.8 Reporting of Pregnancy

Pregnancy is not an AE. However, any pregnancy that occurs during study participation should be reported to the sponsor on the appropriate CRF. Pregnancy should be followed to outcome.

9.5 Unanticipated Problems

9.5.1 Definition of Unanticipated Problems (UP)

An Unanticipated Problem is any event, incident, experience, or outcome that meets the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

9.5.2 Unanticipated Problem Reporting

To satisfy the requirement for prompt reporting, unanticipated problems (UP) will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the Statistical and Data Coordinating Centre (SDCC)/study sponsor within 24 hours of the investigator becoming aware of the event per the above describe SAE reporting process.
- Any other UP will be reported to the IRB and to the SDCC/study sponsor within 3 days of the investigator becoming aware of the problem.

9.5.3 Reporting Unanticipated Problems to Subjects

Subjects will be informed of any UPs that occur as part of their participation in this trial.
10 STATISTICAL CONSIDERATIONS

This study is intended to allow for two types of adaptations: 1) blinded confirmation or modification of the day selected for the primary endpoint and 2) ability to add a new experimental arm if one becomes available. A brief summary is provided here. Details will be described in the statistical analysis plan.

Blinded endpoint confirmation or modification

The current plan is to evaluate the primary endpoint on Day 15. Because there is uncertainty about the clinical course and potential different trajectories according to baseline disease severity, the day of the primary endpoint may be modified based on a blinded evaluation of various timepoints (e.g., days 7-21). [Posch, 2012] This will occur after approximately 100 participants have been enrolled, by a blinded endpoint evaluation committee without knowledge of treatment assignment. Analyses will be evaluated by baseline severity (mild/moderate vs severe). For example, in mild disease, recovery may occur rapidly such that all with mild disease have resumed normal activities by Day 15. Hence, the final timepoint selected may vary accordingly.

Addition of new experimental therapies

If additional data become available to add an experimental therapy, analyses of experimental arms will be performed comparing concurrently enrolled control subjects. If one treatment crosses an efficacy stopping boundary, this treatment may become the new control arm for comparisons. This approach was used in the recent PALM Ebola therapy RCT [Mulangu, 2019].

10.1 Statistical Hypotheses

The primary outcome uses an ordinal severity scale with 7 categories, analysed using the proportional odds model. This model assumes that the treatment to placebo odds ratio of being classified in a given severity category "i" or better is the same for each category. The null hypothesis being tested is whether the odds of improvement on the ordinal scale is the same for the placebo and experimental treatment arms (i.e., whether the common odds ratio differs is 1).

10.2 Sample Size Determination

The proportions of patients in the different categories of the ordinal scale at day 15 in the placebo and treatment arm assuming an odds ratio (OR) of 2 are given below. The odds ratio represents the odds of improvement in the ordinal scale for treatment relative to placebo control [Whitehead, 1993] shows that the sample size to detect a given odds ratio for 1:1 randomization using a 2-tailed test at level $\alpha$ is given by

$$\frac{12(z_{\alpha/2} + z_\beta)^2}{\theta^2(1 - \sum_{i=1}^6 p_i^3)}$$
where $\theta$ is the log odds ratio, $p_i$ is the overall probability (combined over both arms) of being in the $i$th category of the ordinal outcome, and $z_{\alpha/2}$ and $z_{\beta}$ are the $1 - \alpha/2$ and $\beta$th quantiles of the standard normal distribution.

Table 4 displays four scenarios considered for outcomes under placebo for sample size determination. There is significant uncertainty with these assumptions given the limited data available.

Table 5 shows a range of sample sizes for odds ratios ranging from 1.5 to 2.5 for 85% power. For 90% power, increase the sample size by 17%. Table 6 displays the probabilities of being in different categories of the ordinal scale under an odds ratio of 2. A total sample size of 354 gives approximately 85% power to detect an odds ratio of 2 using a 2-tailed test at level $\alpha = 0.05$. To allow for approximately 10% of participants to be lost to follow-up, the targeted sample size will be 394.

**Table 4. Possible scenarios for outcomes at day 15.**

<table>
<thead>
<tr>
<th>Severity Outcome</th>
<th>Anticipated</th>
<th>Alternative Scenarios</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Scenario 1</td>
<td>Scenario 2</td>
</tr>
<tr>
<td></td>
<td>outcome (%)</td>
<td>outcome (%)</td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Hospitalized, on mechanical ventilation or ECMO</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hospitalized, on non-invasive ventilation or high flow oxygen devices</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Hospitalized, requiring supplemental oxygen</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Hospitalized, not requiring supplemental oxygen</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Not hospitalized, limitation on activities</td>
<td>38</td>
<td>40</td>
</tr>
<tr>
<td>Not hospitalized, no limitations on activities</td>
<td>42</td>
<td>50</td>
</tr>
</tbody>
</table>
Table 5. Sample size calculations for scenarios in Table 4 for a two-arm study assuming 85% power and various true odds ratios.

<table>
<thead>
<tr>
<th>True odds ratio</th>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
<th>Scenario 4</th>
<th>Scenario 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>774</td>
<td>837</td>
<td>798</td>
<td>746</td>
<td>709</td>
</tr>
<tr>
<td>1.75</td>
<td>412</td>
<td>447</td>
<td>425</td>
<td>396</td>
<td>374</td>
</tr>
<tr>
<td>2.0</td>
<td>272</td>
<td>296</td>
<td>281</td>
<td>261</td>
<td>245</td>
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<tr>
<td>2.25</td>
<td>201</td>
<td>220</td>
<td>208</td>
<td>193</td>
<td>180</td>
</tr>
<tr>
<td>2.5</td>
<td>159</td>
<td>175</td>
<td>165</td>
<td>152</td>
<td>143</td>
</tr>
</tbody>
</table>

Table 6. Treatment ordinal outcome proportions under odds ratio of 2 for five scenarios in Table 4 at day 15.

<table>
<thead>
<tr>
<th>Severity Outcome</th>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
<th>Scenario 4</th>
<th>Scenario 5</th>
<th>Anticipated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control %</td>
<td>Treatment %</td>
<td>Control %</td>
<td>Treatment %</td>
<td>Control %</td>
<td>Treatment %</td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0.5</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Hospitalized, on mechanical ventilation or ECMO</td>
<td>1</td>
<td>0.5</td>
<td>1</td>
<td>0.5</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Hospitalized, on non-invasive ventilation or high flow oxygen devices</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0.5</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Hospitalized, requiring supplemental oxygen</td>
<td>7</td>
<td>3.8</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>2.6</td>
</tr>
<tr>
<td>Hospitalized, not requiring supplemental oxygen</td>
<td>8</td>
<td>4.7</td>
<td>5</td>
<td>2.7</td>
<td>7</td>
<td>3.9</td>
</tr>
<tr>
<td>Not hospitalized, limitation on activities</td>
<td>38</td>
<td>29.7</td>
<td>40</td>
<td>28.1</td>
<td>40</td>
<td>29.8</td>
</tr>
<tr>
<td>Not hospitalized, no limitations on activities</td>
<td>42</td>
<td>59.2</td>
<td>50</td>
<td>66.7</td>
<td>45</td>
<td>62.1</td>
</tr>
</tbody>
</table>

Note that columns may not sum to exactly 100 due to rounding errors.
10.3 Populations for Analyses

The primary analysis will be based on an intention-to-treat population, including participants randomized. Similarly, safety analyses will be based on a modified intent-to-treat population consisting of all participants who received at least one infusion.

10.4 Statistical Analyses

10.4.1 General Approach

This is a double-blind placebo controlled randomized trial testing a superiority hypothesis with a two-sided type I error rate of 0.05. Secondary hypotheses have been ordered according to relative importance. These will be described according to the appropriate summary statistics (e.g., proportions for categorical data, means with 95% confidence intervals for continuous data, median for time-to-event data).

A statistical analysis plan (SAP) will be developed and filed with the study sponsor prior to unblinding of study and database lock.

10.4.2 Analysis of the Primary Efficacy Endpoint

The ordinal scale will be used to estimate a proportional odds model. The primary hypothesis test will be based on a test of whether the common odds ratio for treatment is equal to one. As noted earlier, the hypothesis test is, for large sample sizes, nearly the same as the Wilcoxon rank sum test.

Therefore, the procedure produces a valid p-value regardless of whether the proportional odds model is correct. Nonetheless, estimation and confidence intervals do require the model to be correct. Accordingly, we will evaluate model fit using a goodness-of-fit likelihood ratio test. A stratified hypothesis test to account for baseline severity of disease will be used.

The distribution of severity results will be summarized by treatment arm as percentages. The validity of the proportionality assumption will be evaluated and tested. Efforts to minimize loss-to-follow-up will be considerable. However, small amounts of missing data may occur. In such cases, participants without final outcome data will be excluded from the analysis. Sensitivity analyses will evaluate the impact of making different assumptions about missing observations. These sensitivity analyses will be fully defined in the SAP.
10.4.3 Analysis of the Secondary Endpoint(s)

1) Differences in time-to-event endpoints (e.g., time to a one category improvement in ordinal scale) by treatment will be summarized with Kaplan-Meier curves and 95% confidence bounds.

2) Change in ordinal scale at specific time points will be summarized by proportions (e.g., proportion who have a 1-, 2-, 3-, or 4-point improvement or 1-, 2-, 3-, 4-point worsening).

3) Duration of event (e.g., duration of mechanical ventilation) will be summarized according to median days with quartiles.

4) Incidence data (e.g., incidence of new oxygen use) will be summarized as a percent with 95% confidence intervals.

5) Categorical data (e.g., 28-day mortality or ordinal scale by day) will be summarized according to proportions with confidence intervals on the difference or odds ratios for a binary or multiple category scale, respectively.

Missing data procedures will be described in the SAP.

10.4.4 Safety Analyses

Safety endpoints include death through Day 28, 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.

10.4.5 Baseline Descriptive Statistics

Baseline characteristics will be summarized by treatment arm. For continuous measures the mean and standard deviation will be summarized. Categorical variables will be described by the proportion in each category (with the corresponding sample size numbers).

10.4.6 Planned Interim and Early Analyses

Early analyses

An initial blinded endpoint-evaluation phase will be enrolled prior to specification of the primary endpoint. Analysis and decision making will be restricted to a blinded endpoint evaluation committee (a BEEC). BEEC membership will be defined elsewhere and will
A Multi-centre, Adaptive, Randomized, Double-Blind Placebo-Controlled Clinical Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19

consist only of individuals who are blinded to treatment assignment. Principles of blinded endpoint-evaluation will be defined in a separate document.

Additional early analyses include monitoring enrolment, baseline characteristics, and follow-up rates throughout the course of the study by the study team. Analyses will be conducted blinded to treatment assignment.

Interim analyses

A data and safety monitoring board (DSMB) will monitor ongoing results to ensure patient well-being and safety as well as study integrity. The DSMB will be asked to recommend early termination or modification only when there is clear and substantial evidence of a treatment difference. More details about the interim analyses are described in section 0 and 0 below as well as a separate guidance document for the DSMB.

Interim Safety Analyses

Interim safety analyses will occur at approximately 25%, 50%, and 75% of total enrolment. Safety analyses will evaluate serious AEs by treatment arm and test for differences using a Pocock spending function approach with a one-sided type I error rate of 0.025. This approach is less conservative than what will be used to test for early efficacy results because proving definitive harm of the experimental agents is not the focus of this study. Pocock stopping boundaries at the looks described correspond to z-scores of (2.37, 2.37, 2.36, & 2.35). This contrasts with the z-score stopping boundaries for the Lan-DeMets spending function that mimics O’Brien-Fleming boundaries: (4.33, 2.96, 2.36 & 2.01). The unblinded statistical team will prepare these reports for review by the DSMB.

Interim Efficacy Review

The Lan-DeMets spending function analog of the O’Brien-Fleming boundaries will be used to monitor the primary endpoint as a guide for the DSMB for an overall two-sided type-I error rate of 0.05. Interim efficacy analyses will be conducted after the BEEC has selected the primary efficacy endpoint at approximately 50%, 75% and 100% of total information.

Conditional power will be presented as an additional guide to the DSMB. Conditional power allows computation of the probability of obtaining a statistically significant result by the end of the trial given the data accumulated thus far, incorporating and assuming a hypothesized treatment effect (e.g., the treatment effect assumed for sample size determination) thereafter. If conditional power is less than 20% under the original trial assumptions, consideration should be given to stopping the trial.

The unblinded statistical team will prepare these closed reports for DSMB review and recommendations. Analyses will be presented with blinded codes for treatment arms to
A Multi-centre, Adaptive, Randomized, Double-Blind Placebo-Controlled Clinical Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19

10.4.7 Sub-Group Analyses

Subgroup analyses for the primary outcomes will evaluate the treatment effect across the following subgroups: geographic region, duration of symptoms prior to enrolment, age and sex. A forest plot will display confidence intervals across subgroups. Interaction tests will be conducted to determine whether the effect of treatment varies by subgroup.

10.4.8 Exploratory Analyses

An exploratory analysis will compare treatment efficacy estimates according to the various scales outlined in section 9.1.3. Specifically, the probability of falling into category “i” or better will be compared between arms for each i.
11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1 Regulatory, Ethical, and Study Oversight Considerations

This study will be conducted in conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research and the ICH E6(R2).

IRBs will review and approve this protocol, associated informed consent documents, recruitment material, and handouts or surveys intended for the subjects, prior to the recruitment, screening, and enrolment of subjects. Site IRBs may have additional national and local regulations.

Any amendments to the protocol or consent materials will be approved by the IRB before they are implemented. IRB review and approval will occur at least annually throughout the duration of the study. The investigator will notify the IRB of deviations from the protocol and SAEs, as applicable to the IRB policy.

DMID must receive the documentation that verifies IRB-approval for this protocol, informed consent documents, and associated documents prior to the recruitment, screening, and enrolment of subjects, and any IRB-approvals for continuing review or amendments as required by the DMID.

11.1.1 Informed Consent Process

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continuing throughout the individual’s trial participation. Investigators or designated research staff will obtain a subject’s informed consent in accordance with the requirements of 45 CFR 46, 21 CFR 50 and 21 CFR 56 for FDA-regulated studies, state and local regulations and policy, and ICH E6 GCP before any study procedures or data collection are performed.

Subjects will receive a concise and focused presentation of key information about the clinical trial, verbally and with a written consent form. The key information about the study will be organized and presented in lay terminology and language that facilitates understanding why one might or might not want to participate.

ICFs will be IRB-approved, and subjects will be asked to read and review the consent form. Subjects (or legally authorize representatives) must sign the ICF prior to starting any study procedures being done specifically for this trial. Once signed, a copy of the ICF will be given to the subject for their records.
New information will be communicated by the site PI to subjects who consent to participate in this trial in accordance with IRB requirements. The informed consent document will be updated, and subjects will be re-consented per IRB requirements, if necessary.

**Requirements for Permission by Parents/Guardians and Assent by Children (in case of a minor)**

**Other Informed Consent Procedures**

Subjects will be asked for consent to collect additional blood, the use of residual specimens, and samples for secondary research. Extra blood will be drawn for secondary research during each visit when a study blood samples are obtained.

The stored samples will be labelled with barcodes to maintain confidentiality. Research with identifiable samples and data may occur as needed, however, subject confidentiality will be maintained as described for this protocol and with IRB approval.

Samples designated for secondary research use may be used for understanding the SARS-CoV-2 infection, the immune response to this infection, and the effect of therapeutics on these factors.

Samples will not be sold for commercial profit. Although the results of any future research may be patentable or have commercial profit, subjects will have no legal or financial interest in any commercial development resulting from any future research.

There are no direct benefits to the subject for extra specimens collected or from the secondary research. No results from secondary research will be entered into the subject’s medical record. Incidental findings will not be shared with the subject, including medically actionable incidental findings, unless required by law.

Subjects may withdraw permission to use samples for secondary use at any time. They will need to contact the study site and the samples will be removed from the study repository after this study is completed and documentation will be completed that outlines the reason for withdrawal of permission for secondary use of samples.

**11.2 Study Termination and Closure**

In Section 0, Study Intervention Discontinuation and Subject Discontinuation/Withdrawal, describes the temporary halting of the study.

This study may be prematurely terminated if there is sufficient reasonable cause, including but not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Results of interim analysis
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or not evaluable
- Regulatory authorities

If the study is prematurely terminated, the site PI will promptly inform study subjects and the IRB as applicable. The site PI will assure appropriate follow-up for the subjects, as necessary.

The sponsor will notify regulatory authorities as applicable.

11.1.3 Confidentiality and Privacy

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover clinical information relating to subjects, test results of biological samples and genetic tests, and all other information generated during participation in the study. No identifiable information concerning subjects in the study will be released to any unauthorized third party. Subject confidentiality will be maintained when study results are published or discussed in conferences.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

All source records including electronic data will be stored in secured systems in accordance with institutional policies and federal regulations.

All study data and research specimens that leave the site (including any electronic transmission of data) will be identified only by a coded number that is linked to a subject through a code key maintained at the clinical site. Names or readily identifying information will not be released unless DMID approves and it aligns with the consent form, or according to laws for required reporting.

11.1.4 Secondary Use of Stored Specimens and Data

Secondary Human Subject Research is the re-use of identifiable data or identifiable biospecimens that were collected from some other “primary” or “initial” activity, such as the data and samples collected in this protocol. Any use of the sample or data for secondary research purposes, however, will be presented in a separate protocol and require separate IRB approval.

Each sample will be labelled only with a barcode and a unique tracking number to protect subject confidentiality. Secondary research with coded samples and data may
occurs, however, subject confidentiality will be maintained as described for this protocol. An IRB review of the secondary research using coded specimens is required.

The subject’s decision can be changed at any time by notifying the study doctors or nurses in writing. If the subject subsequently changes his/her decision, the samples will be destroyed if the samples have not been used for research or released for a specific research project.

11.1.5 Data Sharing for Secondary Research

Data from this study may be used for secondary research. All of the individual subject data collected during the trial will be made available after de-identification. The SAP and Analytic Code will also be made available. This data will be available immediately following publication, with no end date.

The investigator may request removal of data on individual study subjects from NIH data repositories in the event that a research subject withdraws or changes his or her consent. However, some data that have been distributed for approved research use cannot be retrieved.

11.3 Key Roles and Study Governance

The study is sponsored by DMID. Decisions related to the study will be made by a protocol team that includes representatives from all countries, and separate networks within a country.

11.2.1 Safety Oversight

Protocol team oversight

The protocol team will review blinded pools of AE data every 2 weeks to ensure there is no significant number of unexpected AEs (Aes that do not fit with the known course of COVID-19). If there are a significant number of unexpected Aes, the DSMB will be asked to review unblinded safety data in an ad hoc meeting.

Data Safety Monitoring Committee

Safety oversight will be conducted by a Global DSMB that is an independent group of experts that monitors subject safety and advises DMID. The Global DSMB members will be separate and independent of study personnel participating in this trial and should not have scientific, financial or other conflict of interest related to this trial.

The Global DSMB will consist of members with appropriate expertise to contribute to the interpretation of the data from this trial. The Global DSMB should be as broadly
informed as possible regarding emerging evidence from related studies as well as from
the conduct of this Master Protocol. The Global DSMB will operate under the guidelines
of a charter that will be written at the organizational meeting of the DSMB. The DSMB
will review SAEs on a regular basis and ad hoc during this trial. The Medical Monitor will
be responsible for reviewing SAEs in real time. The DSMB will review SAEs on a regular
basis and ad hoc during this trial.

The DSMB will conduct the following reviews:
• After every 50 subjects are dosed. If this trigger occurs more than every 4 weeks,
the meeting can be delayed until approximately 4 weeks after the last meeting.
• Ad hoc meeting if the protocol team raises any concerns
• A final review meeting after final clinical database lock, to review the
  cumulative unblinded safety data for this trial.

The study will not stop enrolment awaiting these DSMB reviews, though the DSMB may
recommend temporary or permanent cessation of enrolment based on their safety
reviews.

Additional data may be requested by the DSMB, and interim statistical reports may be
generated as deemed necessary and appropriate by DMID. The DSMB may receive
data in aggregate and presented by treatment arm. The DSMB may also be provided
with expected and observed rates of the expected Aes in an unblinded fashion and
may request the treatment assignment be unblinded for an individual subject if
required for safety assessment. The DSMB will review grouped and unblinded data in
the closed session only. As an outcome of each review/meeting, the DSMB will make a
recommendation as to the advisability of proceeding with study interventions (as
applicable), and to continue, modify, or terminate this trial.

11.2.2 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial
subjects are protected, that the reported trial data are accurate, complete, and
verifiable. Clinical Monitoring also ensures conduct of the trial is in compliance with the
currently approved protocol/ amendment(s), ICH, GCP, and with applicable regulatory
requirement(s) and sponsor requirements. Clinical monitoring will also verify that any
critical study procedures are completed following specific instructions in the protocol-
specific MOP.

Monitoring for this study will be performed by DMID. Details of clinical site monitoring are
documented in a clinical monitoring plan (CMP). The CMP describes in detail who will
conduct the monitoring, at what frequency monitoring will be done, at what level of
detail monitoring will be performed, and the distribution of monitoring reports.
Monitoring visits will include, but are not limited to, review of regulatory files,
accountability records, CRFs, ICFs, medical and laboratory reports, site study
intervention storage records, training records, and protocol and GCP compliance. Site monitors will have access to each participating site, study personnel, and all study documentation according to the DMID-approved site monitoring plan. Study monitors will meet with site PIs to discuss any problems and outstanding issues and will document site visit findings and discussions.

11.2.3 Data Handling and Record Keeping

Data Collection and Management Responsibilities

Data collection is the responsibility of the study personnel at the participating clinical study site under the supervision of the site PI. The site PI must maintain complete and accurate source documentation.

Clinical research data from source documentation (including, but not limited to, AE/SAEs, concomitant medications, medical history, physical assessments, clinical laboratory data) will be entered by the clinical study site into CRFs via a 21 CFR Part 11-compliant internet data entry system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. AEs and concomitant medications will be coded according to the most current versions of MedDRA and WhoDrug, respectively.

The SDCC for this study will be responsible for data management, quality review, analysis, and reporting of the study data.

The IND sponsor is responsible for review of data collection tools and processes, and review of data and reports.

AEs will be coded according to the MedDRA dictionary version 23.0 or higher.

A separate study specific Study Data Standardization Plan (SDSP) appendix will be developed which describes the technical recommendations for the submission of human study data and related information in a standardized electronic format throughout product development.

At the end of the study, a copy of all datasets including annotated CRFs and data dictionary will be provided to DMID.

Study Record Retention

Study related records, including the regulatory file, study product accountability records, consent forms, subject source documents and electronic records should be maintained for a period of 2 years following the date a marketing application is
approved for the investigational product for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified. These documents should be retained for a longer period, however, if required by local policies or regulations. No records will be destroyed without the written consent of DMID. Consent forms with specimen retention linked to identifiable specimens will be maintained for as long as the specimens remain in identifiable format, and a minimum of three years after use of the identifiable specimens in non-exempt human subject research.

Source Records

Source data are all information in original records (and certified copies of original records) of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH GCP, regulatory, and institutional requirements. Data recorded in the CRF derived from source documents should be consistent with the data recorded on the source documents.

Interview of subjects is sufficient for obtaining medical history. Solicitation of medical records from the subject’s primary care provider is not required.

11.2.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, any process that is noted in the protocol and refers to details in the protocol-specific MOP, or GCP requirements or any critical study procedures with specific instructions in ancillary documents referenced in the protocol such as a protocol-specific MOP.

The noncompliance may be either on the part of the subject, the investigator, or the study site staff. Following a deviation(s), corrective actions should be developed by the site and implemented promptly. All individual protocol deviations will be addressed in subject study records.

It is the responsibility of the site PI and personnel to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation, or within five working days of the scheduled protocol-required activity. All deviations must be promptly reported per the protocol deviation reporting procedures. Protocol deviations must be sent to the local IRB/IEC per their guidelines. The site PI and personnel are responsible for knowing and adhering to their IRB requirements. A completed copy of the Protocol Deviation Form must be maintained in the Regulatory File, as well as in the subject's chart if the deviation is subject specific.
11.2.5 Publication and Data Sharing Policy

To avoid premature release of data, this Master Protocols specifies that efficacy data from a trial that has not yet been completed due to insufficient enrolment should not be released. After an outbreak has ended at a given site, the study would be paused.

An independent monitoring committee would review results from an interim analysis of study data to make recommendations regarding whether the study should continue or stop for efficacy, futility, or safety, guided by the pre-specified monitoring plan.

Importantly, under this master protocol, the investigators would remain blinded to any results of analyses; the study data would only be released if the trial were either stopped on the basis of a recommendation from the monitoring committee or had reached its targeted number of endpoints or amount of participant follow-up.

11.2.6 Human Data Sharing Plan

See above.

11.2.7 Publication

Following completion of the study, the lead PI is expected to publish the results of this research in a scientific journal, with consideration to the clarifications under section 10.1.10 above.

11.2.8 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. DMID has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.
12. Additional Considerations

Research Related Injuries

For any potential research related injury, the site PI or designee will assess the subject. Study personnel will try to reduce, control, and treat any complications from this study. Immediate medical treatment may be provided by the participating study site.

As needed, referrals to appropriate health care facilities will be provided to the subject. The site PI should then determine if an injury occurred as a direct result of the tests or treatments that are done for this trial.

If it is determined by the participating site PI that an injury occurred to a subject as a direct result of the tests or treatments that are done for this trial, then referrals to appropriate health care facilities will be provided to the subject.

Study personnel will try to reduce, control and treat any complications from this trial. Immediate medical treatment may be provided by the participating site, such as giving emergency medications to stop immediate allergic reactions.

Include insurance statement on liability and compensation in case of SAEs.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
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<tr>
<td>ALT</td>
<td>Alanine Transaminase</td>
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<td>AST</td>
<td>Aspartate Transaminase</td>
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<td>BP</td>
<td>Blood Pressure</td>
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<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<td>CLIA</td>
<td>Clinical Laboratory Improvement Amendments</td>
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<td>CMP</td>
<td>Clinical Monitoring Plan</td>
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<td>CMS</td>
<td>Clinical Material Services</td>
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<td>Cr</td>
<td>Creatinine</td>
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<td>CRF</td>
<td>Case Report Form</td>
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<td>CROMS</td>
<td>Clinical Research Operations and Management Support</td>
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<td>CSR</td>
<td>Clinical Study Report</td>
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<tr>
<td>CQMP</td>
<td>Clinical Quality Management Plan</td>
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<td>EC</td>
<td>Ethics Committee</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>FWA</td>
<td>Federal Wide Assurance</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>GLP</td>
<td>Good Laboratory Practices</td>
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<td>Hgb</td>
<td>Haemoglobin</td>
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<tr>
<td>HR</td>
<td>Heart Rate</td>
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<tr>
<td>IB</td>
<td>Investigator's Brochure</td>
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<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
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<td>ICF</td>
<td>Informed Consent Form</td>
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<td>ICH</td>
<td>International Council for Harmonisation</td>
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<td>IND</td>
<td>Investigational New Drug Application</td>
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<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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<td>IV</td>
<td>Intravenous</td>
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<tr>
<td>MCG</td>
<td>Microgram</td>
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<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
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<tr>
<td>MERS</td>
<td>Middle East Respiratory Syndrome</td>
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<tr>
<td>MOP</td>
<td>Manual of Procedures</td>
</tr>
<tr>
<td>N</td>
<td>Number (typically refers to subjects)</td>
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<tr>
<td>NDA</td>
<td>New Drug Application</td>
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<tr>
<td>PHI</td>
<td>Protected Health Information</td>
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<tr>
<td>PI</td>
<td>Principal Investigator</td>
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<td>PLT</td>
<td>Platelet</td>
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<tr>
<td>PP</td>
<td>Per Protocol</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>PT</td>
<td>Prothrombin Time</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<td>SAP</td>
<td>Statistical Analysis Plan</td>
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<tr>
<td>SARS</td>
<td>Severe Acute Respiratory Syndrome</td>
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<tr>
<td>SDCC</td>
<td>Statistical and Data Coordinating Centre</td>
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<td>SDSP</td>
<td>Study Data Standardization Plan</td>
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<tr>
<td>SMC</td>
<td>Safety Monitoring Committee</td>
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<td>SNP</td>
<td>Single Nucleotide Polymorphisms</td>
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<td>SOA</td>
<td>Schedule of Activities</td>
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<td>SOC</td>
<td>System Organ Class</td>
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<td>SOP</td>
<td>Standard Operating Procedure</td>
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<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
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<tr>
<td>T. Bili</td>
<td>Total Bilirubin</td>
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<tr>
<td>UP</td>
<td>Unanticipated Problem</td>
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<tr>
<td>US</td>
<td>United States</td>
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<tr>
<td>WBC</td>
<td>White Blood Cell</td>
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## Protocol Amendment History

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Description of Change</th>
<th>Brief Rationale</th>
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