World Health Organization

WHO R&D Blueprint

novel Coronavirus

COVID-19 Therapeutic Trial Synopsis

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R&DBlueprint

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COVID-19 Therapeutic Trial Synopsis

A randomized multi-center adaptive 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).

The trial will be carried out under a Master Protocol to continue across outbreak sites until the scientific questions of interest are addressed.

The trial will be conducted in two stages: the first will be a Pilot Stage and the second will be a Pivotal Stage.

1. Objectives

Primary objective of the Pilot Stage
--To engage multiple sites to achieve timely insights about important design and feasibility issues of recruitment rate and protocol adherence, integral to finalizing the design of the Pivotal Stage; and, to derive more precise estimates of patient characteristics, markers of evolution of illness and clinical outcomes in order to refine eligibility criteria, variables for randomization stratification, outcome measures and determine sample sizes for to investigate plausible effect sizes in the Pivotal Stage.

Primary objective of the Pivotal Stage
--To evaluate the effect on the primary endpoint (to be specified), for each of several experimental regimens involving investigational therapeutic agents, through pairwise comparisons of each experimental regimen with a standard-of-care control arm, and under a sequential design.

Secondary objectives of the Pivotal Stage:
--To evaluate the safety and tolerability of each experimental regimen relative to the standard-of-care control arm.

--To evaluate effects of each of the experimental regimens on secondary endpoints, including mortality.

2. Pilot and Pivotal Stages

Pilot Stage

The trial will have a Pilot Stage engaging multiple study sites. In this stage, participants will be randomized between a standard-of-care control arm and several experimental regimens, each involving an investigational therapeutic agent(s) provided in addition to standard-of-care. While the exact sample size of the Pilot Stage will be determined after establishing the Pilot Stage population, interventions, comparators and outcomes, it is likely the Pilot Stage will have approximately 50-100 participants. These data will provide valuable insights regarding the design, conduct and analysis of the Pivotal Stage, including trial feasibility – recruitment rate and protocol adherence – and further refinement in the eligibility criteria, more precise estimates of enrolled patient characteristics, markers of evolution of illness and clinical outcomes, leading to a disease-, patient population- and intervention-responsive definition of the primary and secondary endpoints, and procedures to enhance quality of trial conduct.

When the sample of patients in the Pilot Stage has been enrolled, the enrollment into the Pivotal Stage will proceed immediately. Enlightened by analyses of the data from the Pilot Stage, the Steering Committee will make timely recommendations for finalizing the design of the Pivotal Stage. A decision will be made regarding whether the data from the Pilot Stage would be included in the primary analyses of the Pivotal Stage data. Importantly, to preserve the integrity of the Pivotal Stage, such inclusion of the Pilot Stage data would be appropriate only if those using the Pilot Stage data to enlighten decisions about finalizing 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.

Pivotal Stage

The Pivotal Stage of the trial will be designed with intention to provide reliable evidence about the efficacy and safety of multiple experimental regimens, each involving one or more investigational therapeutic agents provided in addition to standard-of-care. The efficacy and safety of these experimental regimens will be assessed through pairwise comparisons with the standard-of-care control arm.

3. Endpoints

Primary endpoint

The primary endpoint should be responsive to the eligible patient population, intervention and course of illness of COVID-19. While all-cause mortality (ACM) is an important outcome, depending upon event rates observed in the Pilot Stage, the primary endpoint should be a composite measure of clinical improvement and/or survival, assessed at a pre-specified time (such as 28 days) post randomization. A special WHO committee arrived at the ordinal scale (given in the table below and the *Appendix*) that measures illness severity over time. The primary outcome could be a measure of patients' clinical status at a particular time point after enrolment, depending upon frequency of outcome assessment (e.g., 14, 28, or 60 days). Agreement and consistency in recording of individual outcome events at particular time points will facilitate interpretation and combination of results across studies and trials. The definition of the endpoint should be fine-tuned for the Pivotal Phase, based on the Pilot Phase of the trial.

Ordinal Scale for Clinical Improvement

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized Mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8

Secondary endpoints

Secondary endpoints likely will include a separate endpoint of ACM, unless it is determined that the trial could be adequately powered to reliably assess the effects on ACM as a primary endpoint.

Other secondary endpoints likely include effects on other measures for how participants feel, function and survive, such as clinical measures of disease severity, health-related quality of life, as well as biomarkers of illness, such as clearance of virus from body sites.

Candidate measures include (at pre-specified time points or in time to event analyses): virological clearance of nasopharyngeal or respiratory samples, blood, urine or stool; admission to critical care unit; need for supplemental oxygen, mechanical ventilation/oxygenation or ECLS; need for intravenous vasoactive medications; need for renal replacement therapy; death in critical care unit, death in hospital and at vital status (death) at 28 days; hospital-free days, ICU-free; and biological and immunological markers of illness.

Further information about secondary endpoints is given in the Appendix.

4. Study arms

The trial will include the SOC (+ placebo if blinded) arm, as well as selected antiviral(s) + SOC arms, with more therapeutic or immunological/biological interventions considered for addition as they become available and are deemed to have sufficient evidence of activity and safety to be evaluated in a clinical trial. It may be impossible to include a placebo for certain therapeutic agents.

5. Study Population and Sites

The trial is intended to include as many sites as possible affected by the epidemic.

The trial protocol can be implemented in sites where patients with COVID-19 seek care.

Study subjects will include adults and children, as appropriate for the interventions, admitted to hospital with positive PCR test for COVID-19 and acute respiratory infection (i.e., not admitted only for control/isolation reasons).

Decisions on inclusion of pregnant and lactating women, immunodeficient people, children, infants and neonates should be informed by a risk and benefit analysis of each considered investigational product.

Final decisions about eligibility would depend on additional understanding of the epidemiology and clinical characteristics of the disease, including a better understanding of the source of infection, extent of exposure and other risk factors for infection and disease severity; however, proposed eligibility criteria, with an intention to be as inclusive as possible, are specified below.

Eligibility Criteria for Hospitalized Patients:

Inclusion Criteria:

(1) Admission to hospital **AND**
(2) Fulfills WHO case definition, including a positive PCR for COVID-19 from any specimen (e.g. respiratory, blood, urine, stool, other bodily fluid)

Exclusions Criteria:

(1) Active indication and use for one of the investigational products (e.g. HIV positive if antiretroviral agents were used)
(2) Allergy or other contraindication or one of the investigational products
(3) In the opinion of the clinical team, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments.

Eligibility Criteria for Non-hospitalized Patients:

Depending upon interventions proposed, there may also be a desire to have non-hospitalized patients included in the Pilot and/or Pivotal Stage and inclusion criteria might be modified to: fulfilling the WHO case definition, including a

positive PCR for COVID-19 from any specimen (e.g. respiratory, blood, urine, stool, other bodily fluid); with similar and appropriate exclusion criteria.

Informed consent by patient or next of kin or legally authorized representatives should be sought, respecting good research practice, age of consent and assent specific to each country.

6. Study and Participant duration

The trial will continue under a master protocol until the evidence reliably answers the questions the trial was designed to address. Individual regimens will continue to be investigated until there is reliable evidence that they have a favorable benefit-to-risk profile or until futility is established; according to a priori established clinical and statistical criteria.

Study participants will continue in the trial for the pre-specified duration of their participation or until they formally withdraw their consent. It is important that the term withdrawal of consent should not be used simply because the participant no longer wishes to receive randomized treatment or actively continue to return for follow-up assessments or simply to justify why efforts are not being made to continue to follow some participants who have discontinued their randomized intervention. Rather, the term should be used only when the participant no longer wishes to participate in the trial and no longer authorizes the investigators to make efforts to continue to obtain their outcome data. Ideally, if participants withdraw their consent, it should be done verbally or by writing and documented by the study team. It is important that investigators be educated and evaluated about the proper use of the term withdrawal of consent, and data monitoring committees should regularly assess whether the term was being used properly.

7. Randomization

Randomization will be in a 1:1: …. :1 ratio to therapeutic A, therapeutic B, etc. and/or combinations or standard of care (SOC).

All trial participants will receive SOC.

A minimization procedure may be used to achieve balance across key baseline factors (e.g., age, time since symptom onset, disease severity, comorbid conditions that contribute to severity). Stratification at enrolment for severity of illness (e.g. a severity of illness score, need for ventilation or ICU admission) at entry will likely be used.

8. Blinding

In order to minimize bias related to patient selection, retention, co-interventions, treatment and outcome assessment, blinding to all involved in a trial (patients and family, clinician team, trial personnel, etc.) is preferred, especially if the primary endpoint may be sensitive or responsive to decisions of clinical judgment which could be subconsciously or consciously influenced by knowledge of treatment allocation. However, blinding may not always be possible, and we recognize the operational difficulties associated with drug administration regimens, preparation of placebos and timelines necessary to initiate experimental research during an epidemic. Blinding will be considered, depending upon the interventions used, and when appropriate, for as long as possible, for patients, family members, clinical team members, trial team personnel, outcome assessors and analysts; acknowledging that this may not be possible for some roles at the point-of-care of patients.

9. Statistical Considerations

Primary analyses methods for Primary and Secondary Endpoints

This section will specify the primary and secondary endpoints as well as the pre-specified methods for the analyses of these endpoints. This section will include insights about stratification of analyses.

Primary Analysis Population

This section will specify that all primary efficacy analyses will be conducted in the Intention-to-treat (ITT) population; thus, all randomized patients should be included in the primary analysis.

Statistical Power and Sample Size Calculations

This section will specify the null and alternative hypotheses to be assessed, and the sample size needed to achieve pre-specified false positive and false negative error rates.

Statistical Monitoring Boundaries

This section will provide the pre-specified monitoring boundaries that will guide recommendations of the Data Monitoring Committee regarding continuation or termination recommendations during the Pivotal Stage. Any adaptive features of the trial design also will be pre-specified.

Secondary Pre-specified Subgroup analyses

This section will specify the baseline covariates used to define descriptive subgroup analyses to enlighten the generalizability of study results.

Methods to enhance quality of retention

This section will provide pre-specified methods to enhance the capture of outcome data, clearly distinguishing multiple reasons for termination of randomized treatments (i.e. non-adherence) from the only reasons for termination of follow-up (i.e., non-retention), that would be death or formal written withdrawal of consent

10. Data Monitoring Committee, Steering Committee and Interim Analyses

The Steering Committee (SC) and the Data Monitoring Committee (DMC) will be responsible for safeguarding the interests of clinical trial participants and for enhancing the integrity of the trial. To address this mission, the DMC will have ongoing access to efficacy and safety data, and information regarding the

quality of study conduct. The DMC will review emerging evidence provided by the independent statistical center on a periodic basis (e.g. every two to three months, or as appropriate for outbreak circumstances and enrolment) and at appropriate times, where the interpretation of safety will be performed in the context of this emerging efficacy data. The DMC will also have planned formal interim analysis meetings. In addition, the DMC will hold ad hoc teleconference meetings to discuss safety or trial conduct information as needed, with input provided by the SC during open sessions of DMC meetings.

A Steering Committee (SC) will be in place to collaborate with the study Sponsor(s) in issues regarding trial design, conduct and analysis. The SC will ensure the conduct of the trial in each site is harmonized with respect to the important variables such as data collected, laboratory tests, implementation of treatments and standard of care. There will ideally be a centralized database for all the trial sites to contribute data.

The trial will be designed with pre-specified formal statistical monitoring boundaries to guide the DMC in their recommendations regarding continuation or termination of regimens or of the entire trial, either due to persuasive evidence of efficacy or futility, or unacceptable safety issues.

In assessing the acceptability of the safety profile of each regimen, the DMC will consider the totality of information regarding benefits and risks. To contribute to enhancing the integrity of the trial, the DMC may also formulate recommendations relating to the rates of recruitment and eligibility of participants, improving adherence to protocol-specified regimens, retention of participants, and the timeliness of data capture and adjudication of trial endpoints.

Based on its insights from emerging evidence, the DMC will provide recommendations to the SC, including a recommendation regarding trial continuation, discontinuation or modification. The DMC will be advisory to the SC, who will be responsible for promptly reviewing the DMC recommendations, discussing them with the DMC if necessary, the study sponsor, and making decisions about their implementation.

A separate DMC Charter further describes the role of the DMC and the SC. The Statistical Analysis Plan will provide the complete specification of the statistical methods for the interim analyses.