World Health Organization

WHO R&D Blueprint

novel Coronavirus

COVID-19 Therapeutic Trial Synopsis

February 18, 2020, Geneva, Switzerland

R&DBlueprint

Powering research
to prevent epidemics

Table of Contents

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