An international, Bayesian platform adaptive, randomized, placebo-controlled trial assessing the effectiveness of candidate interventions in preventing COVID-19 disease in adults

CROWN CORONATION: COVID-19 **R**esearch **O**utcomes **W**orldwide **N**etwork for **CORONA**virus preven**TION**

CORE PROTOCOL

Version 8.0 dated 12 October 2021

Clinical Trial of Investigational Medicinal Product

Full title of trial	An international, Bayesian platform adaptive, randomized, placebo-controlled trial assessing the effectiveness of candidate interventions in preventing COVID-19 disease in adults
Short title	CROWN CORONATION: **C**OVID-19 **R**esearch **O**utcomes **W**orldwide **N**etwork for **CORONA**virus preven**TION**
Version and date of protocol	Version 8.0 dated 12 Oct 2021
ISRCTN / Clinicaltrials.gov no:	NCT04333732
ACTIVE IMP(s):	Will vary according to study arms (see appendices)
PLACEBO IMP(s):	Placebo dependent on study arm (see appendices)
Phase of trial	Phase 3
Sites(s)	Multi-site, Parallel protocol

Protocol Version History

Version Number	Date	Protocol Update Finalized By (insert name of person):	Reasons for Update
1.0	01 April 2020	Avidan	Initial Protocol
2.0	10 April 2020	Lovat	Peer Review and country-specific addenda
3.0	21 April 2020	Avidan	Addressing concerns of FDA, IRB/IECs and funders
4.0	12 May 2020	du Toit, Bekker, Biccard, Delany-Moretlwe, Avidan, Dehbi, Jones, Hague, Caverly, Araeipour, Demarest, McKinnon, Mbacham	Removed Hydroxychloroquine from protocol, addressed inconsistencies highlighted by SA regulatory authorities, combines all updates to protocol, create SA addendum, includes statistical updates, updating references and safety issues, tightening language and clarifying the outcomes, SPIRIT checklist compliant
5.0	09 June 2020	Members of CROWN COLLABORATIVE	Separation of Core Protocol from Supplementary Appendices into complementary documents

6.0	30 July 2020	Avidan, Dehbi, Sikazwe, Politi, Biccard, Lovat, Delany-Moretlwe, du Toit, Caverly, Nel	Updating with new interventions, factorial designs, and statistical plan
7.0	01 December 2020	Lovat, Caverly Delany-Moretlwe, Nel, Biccard, Avidan	Extending to include other key workers; additional administrative changes
8.0	12 October 2021	Avidan, Dehbi	Updating the outcomes to include the following secondary outcome: symptomatic laboratory test-confirmed COVID-19 by day 150

This study has been funded by a grant from the COVID-19 Therapeutics Accelerator.

AN INTERNATIONAL, BAYESIAN PLATFORM ADAPTIVE, RANDOMIZED, PLACEBO-CONTROLLED TRIAL ASSESSING THE EFFECTIVENESS OF CANDIDATE INTERVENTIONS IN PREVENTING COVID-19 DISEASE IN ADULTS

CROWN CORONATION: COVID-19 **R**esearch **O**utcomes **W**orldwide **N**etwork for **CORONA**virus preven**TION**

INVESTIGATOR'S AGREEMENT

I, Micheal Avidan, the investigator, have read this protocol and appendices and had the opportunity to discuss the objectives of this trial and the content of this protocol and appendices with the CROWN CORONATION Coordinating Center representative(s) from Washington University School of Medicine and/or the In-Country Sponsor.

I agree to conduct the trial according to this protocol and appendices and to comply with its requirements, subject to ethical and safety considerations.

I agree to comply with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and all applicable regulations and guidelines.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

Michael Avidan

Investigator Signature

11/04/2021

Date

Michael Avidan, MBBcH, FCA SA

Principal Investigator Name

Washington University In St. Louis, USA

Site Name, Country

Abstract

The coronavirus disease 2019 (COVID-19) pandemic is a major public health crisis. As a bridge to specific vaccine development and rollout, we urgently need to deploy practical, affordable and effective interventions that prevent infection and / or mitigate the severity of COVID-19. The **CROWN** (**C**OVID-19 **R**esearch **O**utcomes **W**orldwide **N**etwork) **COLLABORATIVE** is an international, transdisciplinary, research network, established to assess rigorously and efficiently promising interventions for COVID-19. **CROWN CORONATION** (**C**OVID-19 **R**esearch **O**utcomes **W**orldwide **N**etwork for **CORONA**virus preven**TION**) is a Bayesian, pragmatic, participant-level randomized, multi-center, and international placebo-controlled platform trial, assessing candidate interventions that either modify the host immune response or target the virus implicated in COVID-19 - severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The objective of CROWN CORONATION is the prevention of symptomatic COVID-19 by using combinations of approved and safe agents, with complementary mechanisms of action. The primary outcome of CROWN CORONATION is symptomatic COVID-19 by day 60 after commencement of study intervention (i.e. any of the following: cough, shortness of breath or difficulty breathing, fever, chills, muscle pain, sore throat, new loss of taste or smell, nausea, vomiting, or diarrhea) with laboratory confirmation (i.e. based on viral polymerase chain reaction). The study design is scientifically compelling and ethically robust. Study arms that are 'under-performing' may be discontinued, and additional prophylactic arms may be added. This efficient approach can limit participant allocation to futile or even harmful study arms. The CROWN COLLABORATIVE has partners across the translational continuum, spanning foundational basic science discovery, proof-of-principle human research, pragmatic effectiveness trials, and public health focused implementation science.

Contents

List of abbreviations

AE	Adverse Event
AR	Adverse Reaction
ARDS	Acute Respiratory Distress Syndrome
ARI	Acute Respiratory Infection
AUC	Area under the (receiver operator) curve
BMGF	Bill & Melinda Gates Foundation
CA	Competent Authority
CI	Chief Investigator
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DI	Designated Individual
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
e-CRF	electronic case record form
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVigilance	European database for Pharmacovigilance
GCP	Good Clinical Practice
GFATM	Global Fund for AIDS, TB and Malaria
GMP	Good Manufacturing Practice
G6PD	Glucose-6-Phosphate Deficiency
HTA	Human Tissue Authority
IB	Investigator Brochure
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IRB	Institutional Review Board
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention-To-Treat
LTFU	Loss to Follow-Up
MA	Marketing Authorisation
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
MHRA	Medicines and Healthcare products Regulatory Agency
MIA	Manufacturer/Importer Authorisation
MS	Member State
NHS	National Health Service
NHS R&D	National Health Service Research & Development
NIMP	Non-Investigational Medicinal Product
PI	Principal Investigator
PIS	Participant Information Sheet
PL	Product License
PP	Per Protocol

QA	Quality Assurance
QC	Quality Control
QP	Qualified Person (for release of trial drug)
QTc	Corrected QT interval
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAR	Serious Adverse Reaction
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SAE	Serious Adverse Event
SDV	Source Document Verification
SLE	Systemic Lupus Erythematosus
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group

1 Trial personnel

Clinical Coordinating Centre Principal Investigator (PI)	Professor Michael Avidan Dr. Seymour and Rose T. Brown Professor of Anesthesiology, Professor of Surgery, Psychiatry and Anesthesiology Washington University School of Medicine in St Louis, USA email: avidanm@wustl.edu
Data Coordinating Centre PI	Professor Ramani Moonesinghe Professor of Perioperative Medicine, UCL, UK email: ramani.moonesinghe@ucl.ac.uk
Data Coordinating Centre	Professor Nick Freemantle Director, Comprehensive Clinical Trials Unit, UCL, UK email: nicholas.freemantle@ucl.ac.uk Gemma Jones Head of Clinical Trial Operations, CCTU, UCL, UK email: gemma.jones@ucl.ac.uk Emilia Caverly Clinical Project Manager, CCTU, UCL, UK email: emilia.caverly@ucl.ac.uk Dominic Hague Clinical Project Manager for Data Science, CCTU, UCL, UK email: d.hague@ucl.ac.uk Dr Dermot McGuckin Clinical Research Fellow, UCL, UK email: d.mcguckin@ucl.ac.uk
Trial Statistician	Hakim-Moulay Dehbi, PhD Comprehensive Clinical Trials Unit at UCL, London, UK email: h.dehbi@ucl.ac.uk
International Governance & Coordination PI	Professor Helen Rees Wits Reproductive Health and HIV Institute (Wits RHI), University of the Witwatersrand, Johannesburg, SA
Country teams:	
Cameroon	Professor Wilfred Mbacham, Lab Head, & Country PI Professor Jean Claude Mbanya, Director, BTC-UY1 Professor Eugene Sobngwi. Med. Adviser, Central Hosp, Y'de The Biotechnology Centre, University of Yaounde 1 Prof Henry Luma, Director General Hospital, Douala Prof Anastase Dzudie, Cardiologist General Hospital, Douala
Canada	Professor David Mazer, St. Michael's Hospital, University of Toronto Dr. Jessica Spence, Population Health Research Institute, Hamilton, Ontario Professor Eric Jacobsohn, University of Manitoba
Ghana	Professor George Kyei

	Professor Kwadwo Koram, University of Ghana
India	(Indian team to provide details)
Netherlands	Prof. Dr. Mihai G. Netea Department of Internal Medicine Radboud University Medical Center
Republic of Ireland	Professor Ellen O'Sullivan, St James's hospital, Trinity College Dublin Professor Colm Bergin, St James 's Hospital, Trinity College Dublin Dr. Eoin Kelleher, Research Fellow
South Africa	Professor Sinead Delany-Moretlwe, Wits RHI, University of the Witwatersrand, Johannesburg Professor Bruce Biccard, Professor and Second Chair, Groote Schuur Hospital, University of Cape Town Dr. Leon Du Toit, University of Cape Town and Washington University in St. Louis Professor Linda-Gail Bekker, The Desmond Tutu Health Centre, University of Cape Town Dr Annalene Nel, Wits RHI, University of the Witwatersrand, Johannesburg
United Kingdom	Professor Laurence Lovat, University College London Professor. Joseph Standing, University College London Dr. Andrew Hill, Liverpool University Dr Clare Stephens, North Central London Clinical Commissioning Group
United States	Professor Mary Politi, Washington University School of Medicine in St Louis Professor Erik Dubberke, Washington University School of Medicine in St Louis Professor Graham Colditz, Washington University School of Medicine in St Louis Professor Eric Lenze Dr. Christian Guay Ms. Anne DeSchryver Ms. Linda Yun Mr. Ben Swan Ms. Sherry McKinnon
Zambia	Dr. Izukanji Sikazwe, Chief Executive Officer and Director Dr. Roma Chilengi, Chief Scientific Officer Center for Infectious Disease Research in Zambia
Zimbabwe	Dr. Nyaradzo Mgodi, University of Zimbabwe College of Health Sciences, Clinical Trials Research Centre, Harare Dr. Teacler Nematadzira, University of Zimbabwe College of Health Sciences, Clinical Trials Research Centre, Harare

Other Partner Organizations:

Medicines for Malaria Venture	Helen Demarest, Director Clinical Operations Tim Wells, Chief Scientific Officer Stephan Duparc, Chief Medical Officer Andre Marie Tchouatieu, Director Access and Product Management Nada Araeipour, Director Business Development
University of Michigan Center for Drug Repurposing	Dr. Jonathan Sexton, PhD, Faculty Director Kevin Weatherwax, Managing Director Professor George Mashour, MD, PhD, Executive Sponsor

2 Summary

Objectives:	***Primary Objective:*** To determine the effectiveness of the trial intervention(s) in preventing symptomatic (i.e. any of the following: cough, shortness of breath or difficulty breathing, fever, chills, muscle pain, sore throat, new loss of taste or smell, nausea, vomiting, or diarrhea), laboratory test-confirmed COVID-19 in adults with repeated exposures to SARS-CoV-2 by day 60 after receiving trial interventions. ***Secondary objectives:*** 1. To determine the effectiveness of the trial interventions(s) in preventing symptomatic (i.e. any of the following: cough, shortness of breath or difficulty breathing, fever, chills, muscle pain, sore throat, new loss of taste or smell, nausea, vomiting, or diarrhea), laboratory test-confirmed COVID-19 in adults with repeated exposures to SARS-CoV-2 by day 150 after receiving trial interventions. 2. To determine the effectiveness of the trial interventions in mitigating the severity of COVID-19 in adults who become infected with SARS-CoV-2 by day 60 after receiving trial intervention. Severity will be graded on a simplified version of the ordinal WHO COVID-19 severity scale. 3. To determine the effectiveness of the trial interventions in mitigating the severity of COVID-19 in adults who become infected with SARS-CoV-2 by day 150 after receiving trial interventions. Severity will be graded on a simplified version of the ordinal WHO COVID-19 severity scale. 4. To determine the effectiveness of the trial interventions in preventing/reducing the incidence of SARS-CoV-2 infection (by serology) over up to 150 days (5 months) of follow-up (see trial duration per participant below).
Type of trial:	An international, randomized, placebo-controlled, Bayesian platform clinical trial. Frequent interim analyses will be performed in a Bayesian manner to modify the trial early for overwhelming evidence of efficacy, futility or harm, using pre-specified thresholds.
Trial design and methods:	Participants will be randomized to receive trial interventions.
Trial duration per participant:	Participants will be followed up for 150 days from randomization. Participants who complete 60 days of follow up (primary outcome ascertainment) will be followed up for a further 3 months (i.e. a total of 150 days (5 months) of participant follow-up).
Estimated total trial duration:	1 year

Planned trial sites:	Participants will be recruited from sites in Canada, Ghana, India, Ireland, South Africa, UK, USA, Zambia, and Zimbabwe, as well as other possible countries
Total number of participants planned:	There is no fixed pre-specified target for enrolment. The Bayesian design includes frequent interim analyses; stopping rules for efficacy, harm or futility are specified. It is likely that no more than 30,000 participants will be included overall.
Main inclusion/exclusion criteria:	**Inclusion criteria** 1. Volunteers without clinical evidence of COVID-19 infection aged 18 years and older. 2. Participants who are at high risk of SARS-CoV-2 infection, defined as adults whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19. (see country specific addendum if needed to define further) 3. Must have a mobile phone and access to the Internet for data collection purposes. 4. Participants who are willing and able to provide informed consent via an electronic consent process. **Exclusion criteria** 5. Weight outside range 50 kg – 120 kg (110 lbs – 265 lbs). 6. Self-reported or laboratory confirmed previous or current diagnosis of SARS-CoV-2. 7. Self-reported current acute respiratory infection. 8. Concurrent and/or recent use of the investigational product, a product considered to be equivalent to the investigational product, or any other product that is likely to interfere with the investigational products in this trial or the interpretation of trial data . 9. Self-reported known allergies to any of the IMPs and excipients of the IMPs and placebo. 10. Self-reported presence or history of the conditions listed in the appendices. 11. Self-reported current use of medication with known to interact with any of the medications listed in the appendices. 12. Inability or unwillingness to be followed up for the trial period.
Statistical methods and analysis:	The analysis of the primary endpoint will be by Bayesian logistic regression, adjusting for age as fixed effect, and sites as random effects. The secondary severity endpoint will be analyzed by Bayesian proportional odds model, with the same adjustment strategy. Interim analyses will be performed regularly for efficacy, futility and harm.

3 Background and Rationale

BACKGROUND

A. The Crisis of COVID-19

Over the past few months, a health crisis wrought by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has swept the world, taking a massive toll on people and nations; it has inflicted substantial societal and economic devastation, and threatens to overwhelm healthcare systems. This new deadly contagion has an estimated overall infection fatality rate of up to 2%.[1] It is a zoonotic infection that crossed to humans in late 2019, it rapidly causes mild to severe respiratory symptoms, and it is readily transmitted from human to human by droplet spread (R0 = 2.5, compared to the 2009 H1N1 influenza pandemic that had an R0 of 1.5; the R0 of seasonal influenza is even lower). The resulting infectious disease has been termed COVID-19. Most infections are mild and similar in severity to the common cold. However, about 20-25% of those with documented infection have more severe symptoms, and approximately 5% of those infected have life-threatening complications (*Figure 1*),[2] including a severe acute respiratory syndrome, pneumonia, respiratory failure, sepsis, delirium, cardiogenic shock, acute kidney injury, liver injury, and multi-organ failure. SARS-CoV-2 belongs to the Beta-coronavirus family, which also includes severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV).[3] Some epidemiologists estimate that between 30% and 70% of the world's adult population could contract SARS-CoV-2 over the coming year, although this might be modifiable with appropriate behavioral modification and other measures.[4] There is thus an urgent need to develop and deploy multiple behavioral and pharmacologic interventions in order to mitigate the harm of the current SARS-CoV-2 pandemic, as well as to inform management of future pandemics. In addition, the disease is likely to spread more easily between individuals living in vulnerable areas with condensed living conditions, including many low and middle-income countries, where large proportions of the population living together in close quarters. The extent of physical distancing that has proved effective in certain countries will not easily be implementable in many lower and middle-income countries, where living conditions are often informal, extremely dense and crowded. Furthermore, while suppression of the epidemic curve by physical distancing is known to be effective, it requires a high level of compliance that is unlikely to be maintainable for an extended duration even in economically advantaged countries, and it is economically and socially ruinous. Hence there is urgency to identify effective prophylactic, mitigation, and therapeutic options, as a bridge to the development of an effective vaccine. In response to this need, the COVID-19 Therapeutics Accelerator has been created as a collaborative initiative with contributions from an array of public and philanthropic donors, intended to support research and development in order to make effective COVID-19 treatments accessible to the world as quickly and as widely as possible. The **C**OVID-19 **R**esearch **O**utcomes **W**orldwide **N**etwork (CROWN) Collaborative is a research platform, established with the intention of being one of the organizations to realize the vision of the COVID-19 Therapeutics Accelerator.

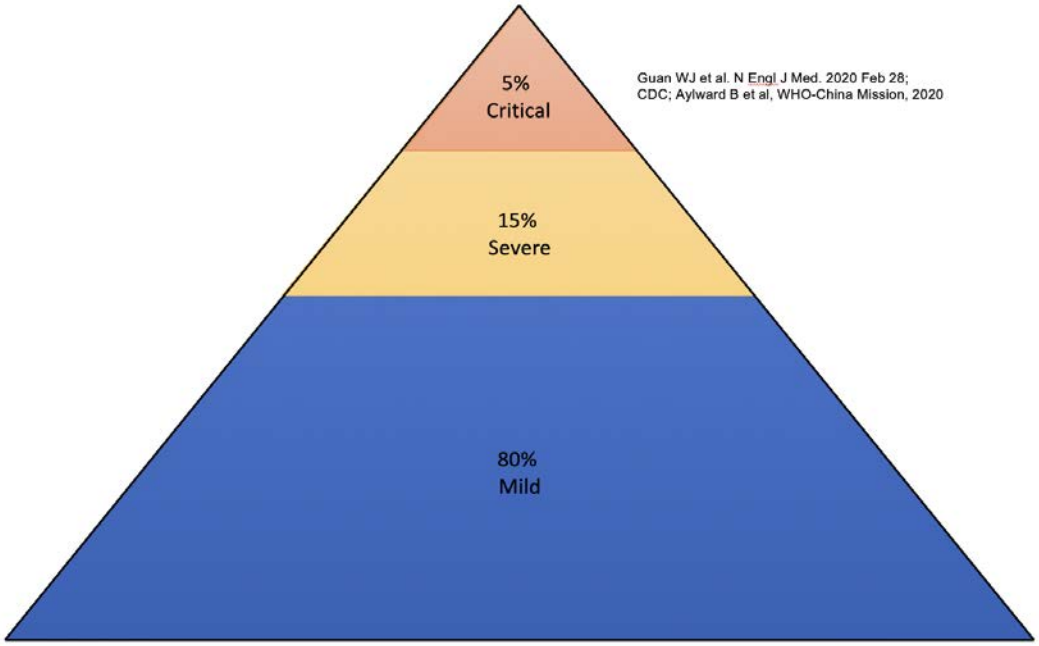

Figure 1: The incidence of mild, severe and extremely severe COVID-19. ***From Guan et al (2020).***[2]

B. The Extent of the Danger

SARS-coronavirus-2 is extremely dangerous for several specific reasons,[5] including:

(i) with no prior exposure, people have no immunity and are exquisitely susceptible to infection;

(ii) the virus is easily contracted by inhalation of viruses expelled into the air from coughs and sneezes (large and small droplets), and by touching infected people or contaminated surfaces (fomites), and then putting a hand to one's mouth, nose, or eyes;

(iii) infection spreads at an exponential rate through non-immune communities (R0 = 2.5);

(iv) the virus can be spread from people who are asymptomatic or who are in the prodromal phase of illness;

(v) infection is associated with a risk of pneumonia, acute respiratory failure, and death in a percentage of people, particularly older adults and those with comorbidities.

C. Susceptible Populations

Some groups within society are especially vulnerable to severe manifestations of COVID-19. Interestingly, unlike some other viral infectious diseases such as measles and influenza, this infection has largely spared children, or if they are becoming infected, symptoms are typically mild. On the other hand, morbidity and mortality are high in certain demographics, including older men, obese adults, those with immunosuppression, and those with various co-morbidities including cardiorespiratory diseases and diabetes. In these high-risk groups, mortality from COVID-19 infection is likely to be between 10% and 20%, with even higher rates of serious complications. As of 15 November 2020, the World Health Organisation (WHO) reports 53.7 million confirmed cases of COVID-19 associated with 1.3 million deaths.[6] The rate of new cases and deaths continues to increase and community transmission is entrenched in many countries.[7]

D. No Proven Prevention, Mitigation, or Treatment

Worldwide, non-pharmacological interventions like stay-at-home regulations, travel bans, and universal masking policies are used to reduce the reproductive number (R0), but such measures relying on socials distancing are not applicable to healthcare workers who have to be in close contact with people as part of their job. Whilst barrier interventions, namely personal protective equipment such as respirators, face protection, gowns and gloves are indicated as the minimum standard of prevention for healthcare workers who come into contact with SARS-CoV-2,[8,9] these equipment measures are not

infallible and not always available. For other populations, barrier interventions such as face masks and personal screens are even less available. No pharmacological therapy been proven as effective for prevention or mitigation although remdesivir has been shown in some studies to reduce duration of ventilation and dexamethasone reduces mortality in severely ill patients. An ounce of mitigation is worth a pound of cure; this is especially true for highly virulent, pathogenic, and prevalent infectious diseases like SARS-CoV-2. Several specific vaccines for the SARS-CoV-2 have shown significant protective benefit, however several relevant caveats remain including:

(i) it will take time to roll out a COVID-specific vaccine with an established safety profile to all at-risk populations;

(ii) new strains of the virus might emerge for which the vaccine will not work.

(iii) the vaccine might confer only brief immunity, since antibodies to SARS-CoV-2 often wane over a period of a few months.

We should therefore not simply rely on the development of a new vaccine and must also explore other pre-emptive and mitigation options. In order to have substantial positive impact, a pre-emptive therapy would have to either decrease the incidence of symptomatic COVID-19 or mitigate its average severity (duration of illness and complication rates).

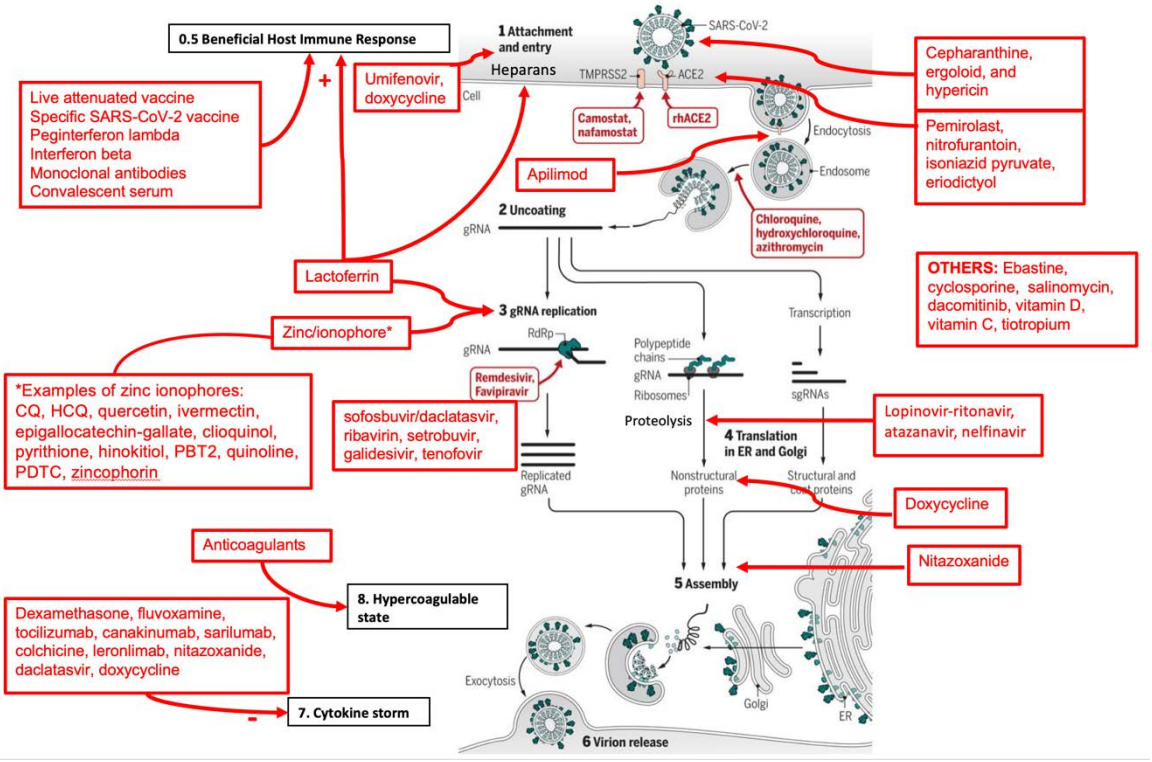

Figure 2: Sites of action of candidate therapeutic agents for preventing and treating COVID-19. COVID-19, coronavirus disease 2019; CQ, chloroquine; ER, endoplasmic reticulum; gRNA, genomic RNA; HCQ, hydroxychloroquine; PDTC, ammonium pyrrolidinedithiocarbamate, RdRp, RNA- dependent RNA polymerase; rhACE2, recombinant human angiotensin-converting enzyme 2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; sgRNA, subgenomic RNA; TMPRSS2, transmembrane protease serine 2. Modified from Guy RK et al. Science 22 May 2020[10]

Information on the agents that will be used initially in the CROWN CORONATION trial is provided in the supplementary appendices. As this is a platform trial, it is important to emphasize that therapeutic arms might be discontinued based on external evidence (from other studies) and internal evidence (generated from this trial). Additional candidate therapies might be added based on emerging evidence. Decisions to include candidate interventions in the platform trial will be made on the basis of a combination of evidence for anti-SARS CoV-2 activity, safety and tolerability profile, mode of

delivery and adherence considerations, cost, access and potential to scale up delivery if demonstrated to be effective.

The intention is to begin the trial with a 2-arm parallel design, in which participants will be randomized to receive the MR or the MMR vaccine (depending on in-country availability), or a placebo injection. Subsequent to an initial period of enrolment (estimated at 5,000 participants), a second agent (Drug A) will be added, and the trial will follow a 4-arm 2-by-2 factorial design:

Arm 1: Education and surveillance plus placebo
Arm 2: Education and surveillance plus MR (or MMR) vaccine
Arm 3: Education and surveillance plus Drug A
Arm 4: Education and surveillance plus Drug A + MR (or M/MR) vaccine

After another period of enrolment (estimated at 10,000 further participants), a third agent (Drug B) will be added, and the trial will follow an 8-arm 2-by-2-by-2 factorial design:

Arm 1: Education and surveillance plus placebo
Arm 2: Education and surveillance plus MR (or MMR) vaccine
Arm 3: Education and surveillance plus Drug A
Arm 4: Education and surveillance plus Drug A + MR (or MMR) vaccine
Arm 5: Education and surveillance plus Drug B
Arm 6: Education and surveillance plus Drug B + MR (or MMR) vaccine
Arm 7: Education and surveillance plus Drug A + Drug B
Arm 8: Education and surveillance plus Drug A + Drug B + MR (or MMR) vaccine

E. Protection

All those who participate in the trial will benefit not only from possible effective prophylaxis and mitigation, but also from heightened awareness, education, and screening. If interventions used in this trial are effective at preventing or mitigating the severity of COVID-19, participants might be less likely to contract SARS-CoV-2 infection, and if they do become infected, they might have a less severe form of COVID-19. With the adaptive approach, the education and surveillance plus placebo arm might be dropped early if there is a strong signal suggesting benefit attributable to interventions, without safety concerns. If participants do develop symptomatic COVID-19, they could be given information about treatment studies with the option to participate, if available and if they are eligible.

F. Strong International Representation

This trial is being conducted by a strong trans-disciplinary group of experienced investigators around the world. Importantly, this will allow us to enrol participants in diverse settings. Taken together, we believe that implementing this trial in a number of geographic regions will provide rich information for the generalizability of the intervention, the current pandemic and also for future pandemics.

G. Strengths and Limitations

This study has several important strengths. Most notably, it is designed to address a clinically highly relevant question with great importance to society. The question is whether interventions can be used preemptively to prevent the occurrence of COVID-19 or to mitigate its severity at risk populations. As a large, pragmatic trial, conducted across multiple continents, this trial will generate precise estimates and generalizable results. Importantly it might provide relevant information for future pandemics as well as the current coronavirus pandemic. There are also important limitations. Event rates (incidence of COVID-19) may vary over time and are somewhat uncertain. These might be higher than anticipated, which would allow the study to reach a conclusion more rapidly, or lower than estimated, which would make this trial too small to detect a difference attributable to the interventions. We plan to increase enrolment at sites where COVID-19 incidence is the highest and decrease enrolment at sites with low event rates. It will be difficult to maintain blinding in this trial. This is especially challenging with a platform design, where arms can be added or dropped. Also

distinct tastes, mode of administration, and side effects of certain interventions can render blinding difficult. The difficulty in including an education and surveillance plus placebo group presents scientific challenges. It is possible that many participants would wish to be assigned to active intervention arms and would be reluctant to take an inert placebo. We aim to address this by conveying to participants the real uncertainty regarding the benefit of prophylactic peri-exposure interventions. Indeed, there is the possibility of harm with any intervention, and a potential of side effects and possibly toxicity with high doses, depending on which intervention is used. We also plan to provide benefit to all participants in the trial through education and improved surveillance of symptoms.

H. Future Directions

As a bridge to vaccine development and roll-out, the COVID-19 Therapeutics Accelerator has identified that we urgently need to test and then deploy practical, affordable and effective prophylactic and therapeutic interventions, as well as those that mitigate the severity of COVID-19. In line with this priority, the CROWN (COVID-19 Research Outcomes Worldwide Network) COLLABORATIVE is a research platform, established to assess rigorously and efficiently promising interventions for COVID-19. The CROWN CORONATION trial is designed as a platform trial, such that interventions or combinations of interventions can be added as an arm or arms, if recommended by the Trial Management Group. Interventions that will be tested in this platform trial will be selected based on certain criteria including affordability, safety, accessibility, and scalability, particularly within low- and middle-income countries (LMIC). However, there is no guarantee that participants will be able to access any of the interventions tested post trial.

I. Conclusions

Over the next year, the number of people who have been infected by SARS-CoV-2 is predicted to be substantial, with many people experiencing severe COVID-19 disease, and millions dying. Even with the advent of effective vaccines for this deadly pathogen, a strategy of mitigation would be most beneficial particularly if access if constrained. What is urgently needed is a preemptive intervention that can safely be administered to in order to decrease the occurrence of symptomatic COVID-19, and to mitigate its severity and impact on the health system.

3.1 Assessment and management of risk

The risks associated with this study do not outweigh the potential benefits. There is a rare risk of breach of confidentiality. There is a theoretical risk that participants will be less scrupulous with respect to personal protection if they believe that they are receiving an intervention, which effectively prevents or mitigates the severity of COVID-19. However, this is unlikely given the potential severe consequences of COVID-19, and the unproven value of the interventions that will be used in this platform trial. The risks of specific interventions are addressed in the supplementary appendix. Participants may feel some mild discomfort or pain associated with the self-collected nasal swabs and the finger prick for the dried blood spot. Participants will not incur any study-related expenses, nor will they be financially compensated for their participation.

The trial design and procedures aim to mitigate risk to investigators. The trial has a light-touch design that not only reduces the burden on the participant by removing the need for follow-up visits but also this remote design also reduces potential exposure to investigators. At the points where investigators are in contact with participants (e.g. the point of dispensing Investigational Medicinal Product (IMP) or placebo, or at any point where investigators are required to take part in samples collection, appropriate PPE will be used by the investigators).

4 Objectives

Primary objective:

To determine the effectiveness of the active arm(s) in preventing symptomatic (i.e. any of the following: cough, shortness of breath or difficulty breathing, fever, chills, muscle pain, sore throat, new loss of taste or smell, nausea, vomiting, or diarrhea), laboratory test-confirmed COVID-19 in participants with repeated exposures to SARS-CoV-2 by day 60 after receiving trial interventions.

Secondary objectives:

1. To determine the effectiveness of the trial interventions(s) in preventing symptomatic (i.e. any of the following: cough, shortness of breath or difficulty breathing, fever, chills, muscle pain, sore throat, new loss of taste or smell, nausea, vomiting, or diarrhea), laboratory test-confirmed COVID-19 in adults with repeated exposures to SARS-CoV-2 by day 150 after receiving trial interventions.

2. To determine the effectiveness of the treatment arm(s) in mitigating the severity of COVID-19 in participants who become infected with SARS-CoV-2 by day 60 after commencement of trial intervention. Severity will be graded on a simplified Ordinal WHO COVID-19 severity scale.

3. To determine the effectiveness of the trial interventions in mitigating the severity of COVID-19 in adults who become infected with SARS-CoV-2 by day 150 after receiving trial interventions. Severity will be graded on a simplified version of the ordinal WHO COVID-19 severity scale.
4.

5. To determine the effectiveness of the trial interventions in preventing/reducing the incidence of SARS-CoV-2 infection (by serology) over up to 150 days (5 months) of follow-up (see trial duration per participant below).

5 Trial design

5.1 Overall design

Study Design

CROWN CORONATION is a large, Bayesian adaptive, pragmatic, participant-level randomized, multi-site, international placebo-controlled trial. Randomization will be stratified by age (<50 and ≥50),site and previous vaccination with a SARS-C0V-2 specific vaccine. Participants will be individuals at risk of contracting SARS-CoV-2. Participants will be randomized to education and surveillance plus Placebo or to a study arm with active interventions for a period of up to 60 days. The details can be found in the relevant appendices.

All participants will require a mobile phone to participate. This is standard in all the countries in this study. The participant, with help from the local trial team if required, will enrol online using the web-based eCRF system and record basic demographic and eligibility information.
The database will be hosted on UK-based servers which are expected to be managed by Sealed Envelope Ltd. Local investigators will have access to the part of the CRF to enable recording of adverse events, outcome data and/or severity of COVID-19 symptoms. Participants will be sent emails with a link to complete an initial participant health questionnaire and the regular data logs.

Participants will complete weekly SMS surveys. Participants who develop symptomatic COVID-19 during the last month of observation will at a minimum be followed-up until symptom resolution and at a maximum until 150 days (5 months) after randomization (whichever comes first).

The study flow overview is outlined in *Figure 3.* In the case of oral medications, the trial will provide adherence support interventions that have been shown in randomized controlled trials to improve adherence to Human Immunodeficiency Virus (HIV) treatment and adapted for HIV Pre-Exposure Prophylaxis (HIV PrEP) (e.g. two-way SMS with check in for those that report symptoms or adverse events).

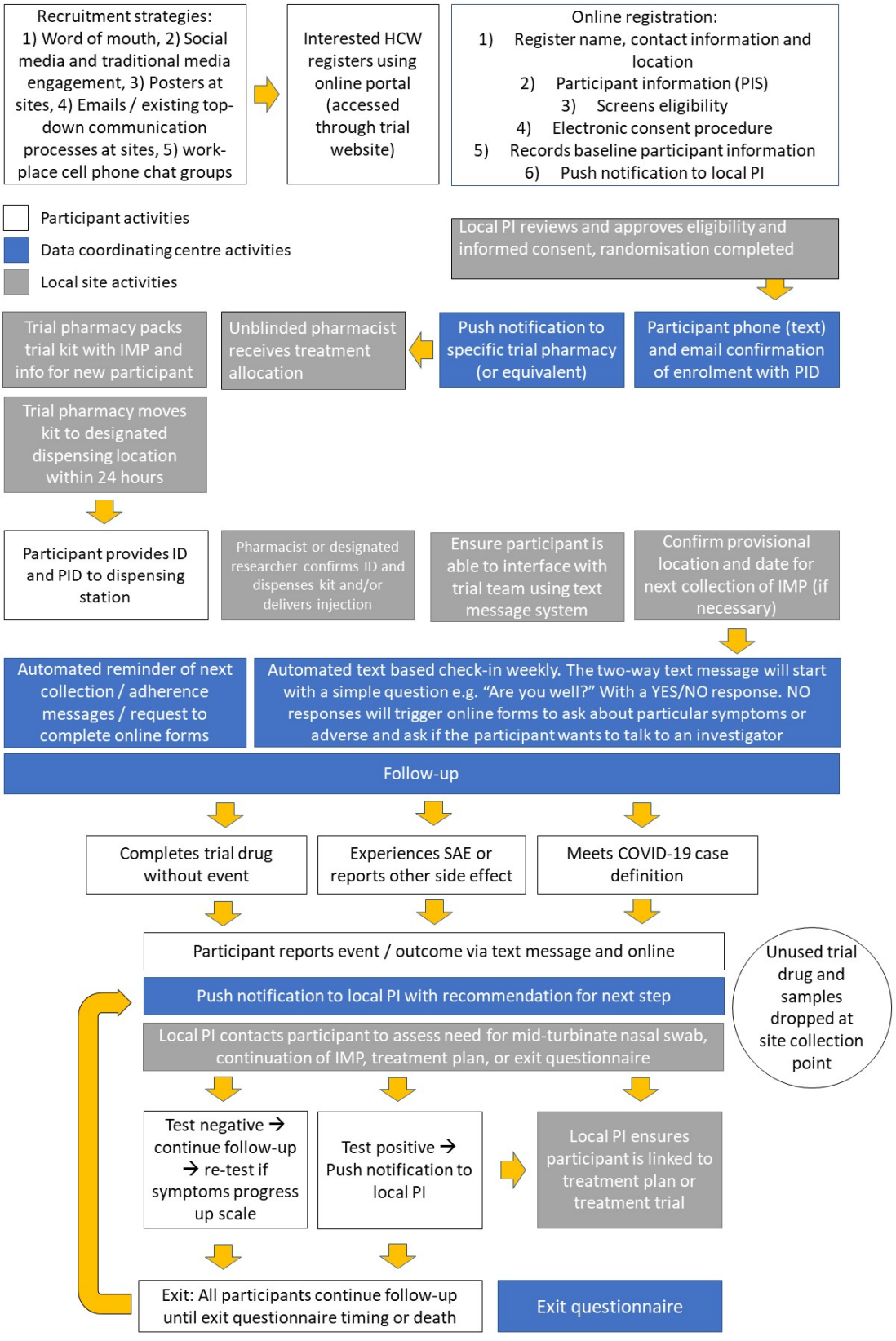

Figure 3a: Detailed chart outlining the likely flow for each participant in the trial. This may be modified by individual centers.

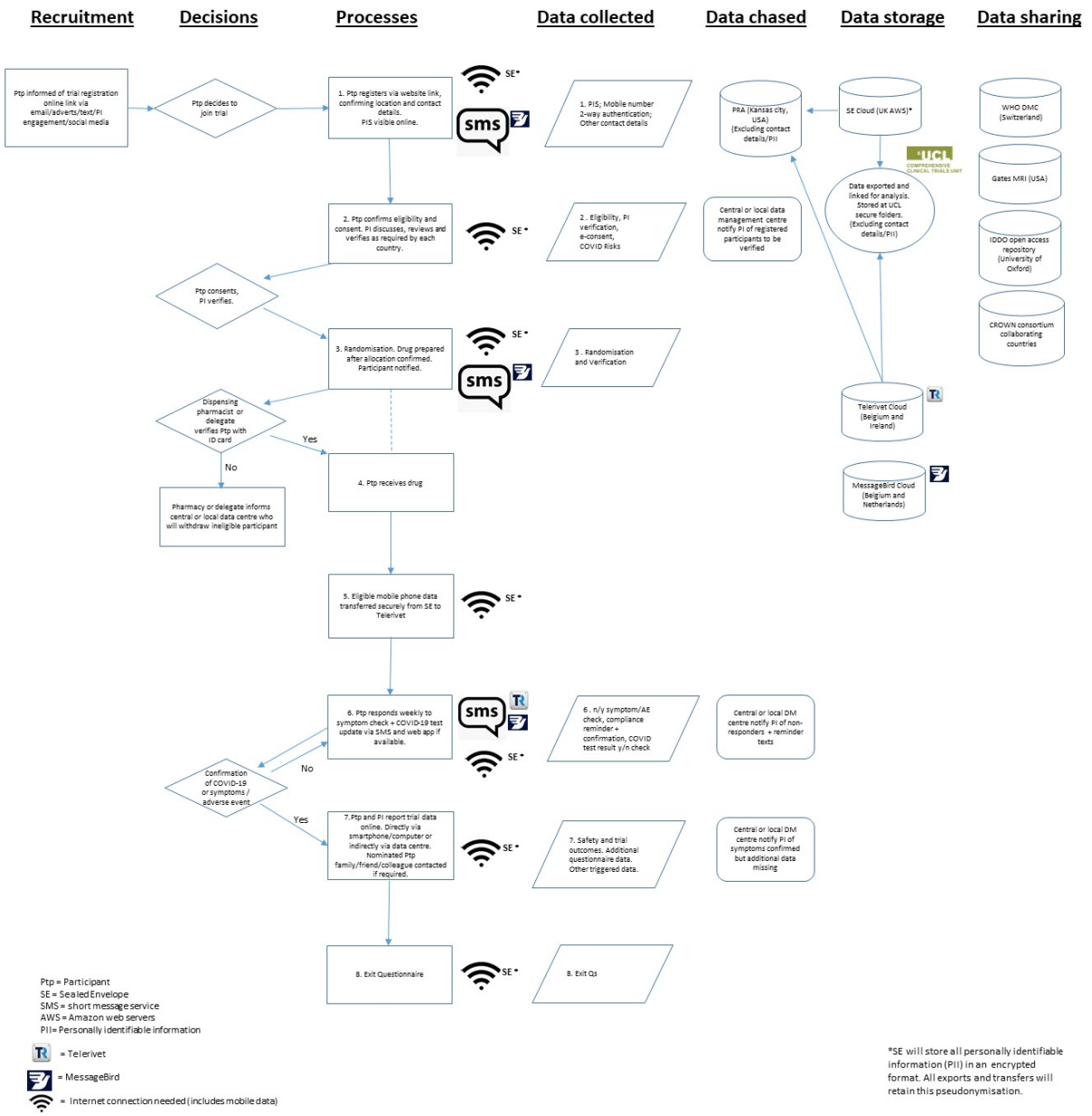

Figure 3b: Flow Diagram showing mixed use of internet and tele-messaging through the course of the trial.

Sites

CROWN CORONATION is an international, multi-site trial with sites in Canada, Ghana, India, Ireland, South Africa, UK, USA, Zambia and Zimbabwe. Sites will be selected in settings such as community-based clinics, general practice facilities and hospitals where IRB/REC approval is in place that the study can be conducted there. Access to laboratory testing and a research pharmacy are required. The research site will be associated with a healthcare facility or organization whose staff are considered to be at high risk of contracting COVID-19 and where there are personnel who have received adequate GCP and protocol training and are able to conduct the study procedures. Preferably, each site should be able to recruit at least 20 participants during the trial period although in rural locations, this number may be smaller. Consideration will also be given to whether there has been a report of COVID-19 outbreak in the local area, as this will increase the risk of individuals contracting the disease.

Participants
Participants will include adults (18 years or older) who are at risk for contracting SARS-CoV-2 based on their work in hospitals or in the community. See the country-specific addenda for country-specific definitions of individuals at risk for SARS CoV-2 exposure.

The reason that participants are at risk will be recorded in the CRF. Participants will be enrolled in low, middle, and high-income countries, including, Canada, Ghana, India, Ireland, South Africa, UK, USA, Zambia and Zimbabwe. Other countries may be added with time. All participants will be fully informed about the trial and will provide informed consent (electronically).

Baseline Data
At the time of enrolment, demographic information will be collected from participants, and relevant data on their medical histories, comorbidities, concurrent medication, and risk factors for severe COVID-19 will be documented. They will also provide information on the nature of their work and the contexts in which they are likely to encounter people infected with SARS-CoV-2. They will also provide information on their access to and use of personal protective equipment during high-risk encounters. In addition, they will be asked to nominate at least one other person to contact in case they become unwell so that we can establish what happened to them. This will all be done in line with local data protection legislation.

Interventions
As this is a pragmatic trial, other than administration of the intervention, all decisions regarding other measures taken to prevent SARS-CoV-2 infection or to mitigate its severity (e.g. use of personal protective equipment, limiting high risk exposures) will be at the discretion of the participant. Educational material regarding both social and clinical practice that could prevent or delay infection will be provided alongside trial information. The trial will track participants at a minimum of weekly for symptoms of infection and compliance with drug self-administration, and should participants contract SARS-CoV-2, we would offer them the option of participating in a treatment trial if it is available.

6 Investigational Medicinal Products (IMPs) and Non-Investigational Medicinal Products

6.1 Name and description of IMP(s)

Specific details regarding the IMP(s) used in each country is elaborated in the appendices. New dosage-based arm(s) or drugs might be added or removed following review and approval by relevant regulatory authorities. Each label for an IMP (active drug or placebo) will include the description of the study product and the information of the source (manufacturer/supplier, batch/lot number and expiry or best use by date).

Placebo will be aligned to the active IMP in terms of dosing schedule. The interventions will be continued for (up to) 60 days from enrolment; or until the participant is diagnosed with COVID-19; or development of a complication or safety concern or side effect necessitating stopping the intervention; or the intervention arm is stopped; or participants are no longer at risk of contact with SARS-CoV-2 infected patients (e.g. no longer new COVID-19 cases at the participating site). Treatment groups may be discontinued at interim analyses, and new treatment groups might be initiated. If a treatment group is discontinued due to perceived harm, participants in that group will be informed as soon as possible to stop taking the IMP.

6.2 Source of IMP(s), Manufacture, Distribution and Storage

The IMPs (see appendices) will be manufactured and QP released for use in the study by the holder of an MIA (IMP) license (or international equivalent). Sourcing of the IMP(s) is also discussed in the relevant site-specific IMP management plans.

6.3 Storage and handling of IMP(s) at site

All IMP aspects of the trial at participating sites are the responsibility of the site PI, who may delegate this duty to the local pharmacist or other appropriately trained personnel. The delegation of duties must be recorded on the Staff Signature and Delegation of Tasks log. Storage and handling (e.g., reconstitution, labeling) of the IMP will be completed in accordance with the relevant summary of product characteristics (SPC) and local IMP management plan. Treatment allocation will be sent to the pharmacist preparing the intervention at the point of randomization. The site pharmacist(s) will be unblinded to the treatment arm, they will dispense IMP(s) or placebo(s) in accordance with the treatment allocation and dosing regimen. Final presentation of the IMP or placebo will ensure participants are not aware of the treatment allocation. Detailed instructions are contained in the local IMP management plan.

6.4 Accountability of IMP(s)

IMP shipping arrangement instructions for sites will be described in each local IMP management plan. In each country, standardized procedures for monitoring of temperature and transport conditions of the IMP will apply and will be documented on the IMP shipping form in accordance with local requirements.

Upon receipt of the IMP, the site pharmacy will confirm receipt of the IMPs by emailing back the accompanying shipping form to the coordinating center and copies retained at the trial site's file. In cases where the IMP was damaged or not stored correctly this will warrant an urgent notification to the supplier and a replacement will be arranged. The supplier will be responsible for dispatching replacement IMPs to sites. Site pharmacy will be responsible for logging receipt of the IMPs on the site accountability log within the site pharmacy file. Site pharmacy will be responsible for storing the IMP in line with storage requirements as per the local IMP management plan. Site pharmacy will monitor temperature of IMP storage and report to the sponsor any temperature excursions that have occurred. Details of reporting temperature excursion are in the IMP management plan or country specific SOP for IMP Management. Full IMP accountability will be conducted during the trial. All IMP dispensed by pharmacy will be logged on the site accountability log within the site pharmacy file. In case of delay in drugs reaching the participants, it is important that the drug should have stability data supplied by the supplier to show that it is stable for at least 4 months and ideally longer than this.

IMP administration will be specific to the intervention and is detailed in the relevant appendix. Additionally, where relevant, participants will be reminded to adhere during the weekly SMS messaging. In vaccine arms, the IMP or placebo will be administered as a single dose by study personnel, making proper use of PPE.

All used/unused IMPs will be reconciled with site pharmacy, to be then updated in the IMP accountability log in the pharmacy site file. IMP destruction or disposal will be conducted, once authorized by the sponsor and in accordance with local practice, and this will be documented in the IMP destruction log in the site pharmacy file.

7 Selection of Participants

7.1 Eligibility of trial participants

7.1.1 *Trial participant inclusion criteria*

1. Volunteers without clinical evidence of COVID-19 infection aged 18 years and older
2. Participants who are at high risk of SARS-CoV-2 infection, defined as adults whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19. (see country specific addendum if needed to define further)
3. The participant must have a mobile phone and access to the Internet for data collection purposes.
4. Participants who are willing and able to provide informed consent via an electronic consent process.

7.1.2 *Trial participant exclusion criteria*

Exclusion criteria (these could be modified depending on the choice of interventions in the platform trial)

1. Weight outside range 50 kg – 120 kg (110 lbs – 265 lbs).
2. Prior enrolment into this or other COVID-19 interventional prevention or treatment trials (observational trials not excluded).
3. Self-reported or laboratory confirmed previous or current diagnosis of SARS-CoV-2 or COVID-19.
4. Self-reported current acute respiratory infection.
5. Concurrent and/or recent use of the investigational product/s, a product considered to be equivalent to the investigational product/s, or any other product that is likely to interfere with the investigational products in this trial or the interpretation of the trial data.
6. Self-reported known allergies to any of the IMPs and excipients of the IMPs and placebo.
7. Self-reported presence or history of the conditions listed in the appendix relevant to that IMP
8. Self-reported current use of medication with known to interact with any of the medications listed in the appendices.
9. Inability or unwillingness to be followed up for the trial period.

Additional to the set of exclusions in the core protocol, each arm of the trial (e.g. “MR vs Placebo” arm or “MMR vs Placebo” arm) will have their own set of additional exclusion criteria (refer to the appendix). Participants will only be randomized to those arms for which they are eligible.

7.2 Recruitment

Each region will adopt an approach that is appropriate for enrolment according to local conditions, and one that is in compliance with its IRB/REC and national regulatory body guidelines. Recruitment may include advertisements (via posters, emails and social media messages at each site) that will alert relevant potential at risk participants to the study. Participants will self-identify and self-enrol by reading the participant information sheet (PIS) and then offering electronic informed consent through an online website using computer or smartphone. Participants will be asked to confirm their eligibility, i.e. that they meet all the inclusion criteria and that they do not meet any of the exclusion criteria. Formal verification based on participant responses will be needed by the site PI of the suitability of the proposed participant.

Participant recruitment at a site will only commence when the trial has:

- Been initiated by the Sponsor (or the delegated representative), and
- Issued with the ‘Open to Recruitment’ letter.

7.3 Informed consent procedure

Informed consent procedures will be implemented in accordance with local IRB/IEC and national regulatory authority requirements. The participant must sign the approved version of the informed consent form online before any study specific procedures are performed. See country-specific addenda for further details on site-specific procedures and documents.

The online participant information will be presented and will detail the exact nature of the study, what it will involve for the participant, the implications and constraints of the protocol, the known side effects and risks involved in taking part. Additional consent may be sought for long-term sample storage in selected jurisdictions. This will be detailed in the country-specific addenda. All the site-specific participant information sheets (PIS) describe the safety issues associated with interventions as described in the relevant package inserts. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care and with no obligation to give the reason for withdrawal.

For this trial, all consent will be obtained electronically after the participant has read the information. Given the urgency of the clinical question, the pressure under which staff members are working and the simplicity of the trial design, if a participant wishes to enrol online after reading the PIS, this will be permitted, unless specifically excluded in an individual country specific appendix, with the site PI able to remotely approve the application without physically examining the participant. The participant will be given as much time as wished to consider the information, and to question the PI and study team before they decide whether they will participate in the study. The consent process may be modified as required to meet local regulatory requirements.

The participant will confirm they have read the PIS via the consent form. It will be clearly stated that participants are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason. They will be asked for consent to access their medical records for study purposes should they become ill. No clinical trial procedures will be conducted prior to the participant giving consent by signing the electronic consent form. Consent will not denote enrolment into trial. The PIS and consent form will be reviewed and updated if necessary, throughout the trial (e.g. where new safety information becomes available) and participants will be re-consented as appropriate.

8 Trial procedures

Given the infectious nature of COVID-19, the traditional approach to trials will be adapted to data collection through telephone interviews or self-data collection. For this reason, we aim to ensure that all participant-reported data are collected through a combination of an online system and SMS messaging. See appendix 1 for the trial schedule of evaluations.

8.1 Screening / Pre-Enrolment Assessments

The following pre-enrolment assessments and procedures will be performed:

- The participant will be invited to view the trial website.
- Potential participants will be shown the participant information online and asked to complete a simple e-questionnaire to ensure that they understand the nature of the trial.
- If potential participants wish to speak to a member of the study team before giving consent, a mechanism will be offered for them to do so.
- Participants will be invited to offer consent online.

- They will be asked screening and eligibility questions. Eligibility will be confirmed by the online system based on the responses given.
- Participants will also confirm that they expect to continue to have a mobile phone and will have access to the Internet for the duration of the trial directly or indirectly (i.e. via local center in remote settings).
- Participants will be asked for details of at least one alternative contact in case they become sick and are unable to respond to the study team. This will allow the study team to find out what has happened
- If required by country legislation, the alternative contact person will be invited to confirm that they are prepared to be registered for this purpose within the trial in line with prevailing data security legislation.
- Site lead will confirm that the participant meets eligibility criteria through the online platform.
- A new case record will be created on the secure online platform. Basic demographic information and details of past medical history, concomitant medications, allergies, smoking, alcohol and other drug intake will be noted.
- Baseline samples will be collected for batched SARS CoV2 serology testing.
- Screening failures (i.e. participants who do not meet eligibility criteria at time of screening) will be allowed to be rescreened once.

See country-specific addenda for details on alternate contacts.

8.2 Enrolment / Randomization Procedures

Participant registration will be undertaken online using computer or smartphone.

Following participant consent, and confirmation of eligibility (see section 8.1 for pre-treatment assessments) the registration and randomization procedure described below will be carried out.

Coordinated on-line registration and allocation of participant trial numbers will be required to enrol participants. Blocked randomization list will be used to allocate study participants to one of the groups, stratified by age, study location. The lists will be created by the study statistician based at the UCL CCTU and will be implemented through the online randomization portal, supplied by Sealed Envelope Ltd.

Participants will be assigned to treatment groups through consecutive allocation of subject numbers, and the use of a Trial Subject Enrolment Log which will be stored on the Sealed Envelope system. Participants will only be randomized to arms that they are eligible for (refer to section 7.1 and relevant appendix).

Participants are considered to be enrolled into the trial following: consent, pre-treatment assessments (see section 8.1) including confirmation of eligibility, completion of the registration/randomization process, allocation of the participant trial number and treatment by the central coordinating team/remote system.

8.3 Procedure for Allocating Intervention/s

The site PI or designee will be notified when a new participant has joined the study. The site PI will satisfy themselves that the participant meets the study eligibility requirements. Once e-consent and PI verification are complete the participant can be randomized in the system and the unblinded pharmacist will be sent the treatment allocation. The local IMP supplier (usually the facility's pharmacy or a research pharmacy) will be alerted that a new participant has joined the study. IMP will be prescribed and prepared for the participant using a locally agreed standard operating procedure. Once the IMP is ready, it will be dispensed to the participant after verifying ID.

8.4 Dose Modifications

If an adverse event is recorded (see Section 9), the site PI or designee will be immediately alerted. If the site PI or designee deems that the adverse event is not related to the IMP and is therefore not an adverse reaction, and if the site PI or designee deems it safe for the participant to continue in the trial, the participant may continue to take the IMP, where relevant. If the site PI or designee deems it better for clinical reasons to stop taking the IMP, the participant should do so. No dose reductions or other modifications will be included in the trial.

8.5 Subsequent Assessments and Procedures

All participants will complete online questionnaires of symptoms, general well-being (and compliance with drug taking where relevant) at enrolment and then at days 30 and 60 and further timepoints up to 150 days after enrolment to the study. The system is currently expected to be supplied by Sealed Envelope Ltd, a UK company that stores data in the UK. At each time point, where relevant, participants will also be asked to confirm their current concomitant medication use. This study is taking place in individuals at a time of great concern about COVID-19 so we do not expect adherence will be a major challenge but as this is a pragmatic trial, the outcomes are likely to reflect real world drug adherence. If participants are aware that they are receiving placebo, adherence might be decreased. All efforts will be made to conceal the treatment allocation.

All participants will also receive an SMS message once a week to ask about their health. If relevant it will also remind them to take their study medications. The platform used is currently expected to be Telerivet Inc and will integrate with the Sealed Envelope system. Telerivet stores its data in EU data centers. If the participant does not respond for one week, the site PI or designee will be prompted to contact the participant. If the participant cannot be contacted, the site PI or designee will contact the alternate contacts provided (see section 8.1).

If a participant experiences symptoms consistent with COVID-19 they will be asked to register this on the online system. They will then be asked to complete an extra online questionnaire regarding symptoms, general well-being, and compliance with study product at the time of diagnosis. They will also be asked to confirm their current medication use. They will be prompted to undergo testing for active infection to confirm the COVID-19 diagnosis if this has not been done as part of their routine clinical care. We anticipate that the sequence of events will be that a participant experiences symptoms, reports those and is prompted to arrange or self-collect samples for testing for active infection. Those with a negative test and ongoing symptoms may need a second test. This may be collected from their routine health care provider. We plan to evaluate sample integrity under the storage/transport conditions we will be using to collect mid-nasal swab specimens or equivalent sample collection.[13,14] Where feasible, we will attempt to quantify viral RNA in participants with SARS-CoV-2 infection. A confirmed diagnosis would then prompt additional follow up. Participants who receive a confirmed diagnosis elsewhere will be asked to register this online. Similar questions about symptoms and study product compliance will be assessed. Where a participant may undergo testing for active infection outside of the trial procedures, consent will be sought at baseline to enable research staff to access the data. In addition, permission will be sought at baseline to access other data sources such as hospital records and death records.

Dried blood spots will be collected from all participants to test for antibodies to SARS-CoV-2 at the time of entry, 60 days, and at 150 days when follow-up is completed.

For any woman who is pregnant on starting the study or becomes pregnant during the 60-day study primary outcome period, an assessment of pregnancy outcome will be conducted at 6 weeks post-partum.

See Appendix 1 for schedule of assessments.

8.6 Laboratory Assessments and Procedures

The primary outcome of the trial is symptomatic (i.e. any of the following: cough, shortness of breath or difficulty breathing, fever, chills, muscle pain, sore throat, new loss of taste or smell, nausea, vomiting, or diarrhea) COVID-19 infection confirmed by a RT-PCR test. This will be assessed in symptomatic participants by (self-collected) mid-turbinate nasal swab or equivalent if not otherwise collected for local clinical purposes. These have been shown to have equivalent sensitivity to health care worker collected nasopharyngeal (NP) swabs but faster, better tolerated, and with less potential for sneezing, coughing and gagging, than an NP swab.[15] Depending on local circumstances, at enrolment participants may be provided with a pack which includes step-by-step instructions for sample self-collection. A swab plus viral transport medium (or saline) will be packaged together for ease of use. Participants will be advised to place the swab in the transport medium and to place the tube in a transport bag provided. If a participant prefers not to take their own swab they can seek assistance with sample collection at their nearest COVID-19 testing center or to their regular healthcare provider. We will describe the methodology and performance characteristics of the quantitative RT-PCR assay(s) used in this study in a laboratory analytical manual. Where feasible, we will attempt to quantify viral RNA when viral shedding is assessed in the nasal swab samples collected from participants with SARS-CoV-2 infection. RT-PCR testing will take place in the country of participation.

The purpose of serology is to provide additional information for **secondary analyses**. A sample collected at baseline will provide information on the proportion of participants exposed to infection prior to randomization. Given that optimization of serological assays is still underway, we will collect these samples for testing later. Details of testing will be specified in the laboratory manuals. Participants will be provided with the necessary equipment and instructions for obtaining dried blood spots (e.g. alcohol swab, lancet, filter paper). Each site will have a procedure for obtaining the dried blood spot specimens from participants. Sample processing and storage will be completed per site-specific standard operating procedures. The DBS might also to conduct serology for measles and rubella antibody titers to evaluate against immunization history and also because there are cases of reported primary vaccination failure.

Additional sampling and testing procedures will be detailed in country-specific addenda.

8.7 Clinical Procedures and Data Collection

Participants will respond to weekly SMS surveys in combination with secure CRF login to a self-report online system, to be completed monthly, with questions around symptoms, exposure and self-reported treatment adherence and SAEs.

If the participant becomes ill and is admitted to hospital, the study team may review the hospital records in line with hospital policies, and if the participant has consented to medical record access.

8.8 Assessment of IMP compliance

Adherence (where applicable) will be assessed at each monthly questionnaire along with weekly SMS prompts.

8.9 Discontinuation / withdrawal of participants

In consenting to participate in the trial, participants are consenting to trial treatment, assessments, follow-up and data collection. The importance of safety follow-up will be emphasized to the participant in the PIS. Each participant has the right to withdraw from the study at any time. If a participant

expresses their wish to withdraw from trial treatment, sites will seek permission to allow use of routine follow-up data from routine health records to be used for trial purposes. The participant may choose to decline this request.

The decision of the participant to withdraw from treatment will be recorded in the CRF/online database. The participant may withhold their reason for withdrawal however, if the participant gives a reason for their withdrawal, this will be recorded in the CRF/online database. If a participant explicitly states they do not wish to contribute further data to the trial their decision will be respected and recorded in the CRF/online database. Trial data already collected will not be deleted.

Additionally, a participant may be withdrawn from trial treatment whenever the site lead investigator considers it necessary. Reasons for discontinuing IMP may include:

- if the safety risk in an arm warrants discontinuation of all participants in that arm in the opinion of the Data Monitoring Committee (DMC);
- if the participant develops confirmed symptomatic COVID-19 they will stop the trial intervention where applicable;
- unacceptable toxicity; either self-reported on based on assessment by the site PI using grading tables;
- intercurrent illness which prevents further IMP administration;
- participants withdrawing consent to further trial treatment;
- any alterations in the participant's condition which justifies the discontinuation of IMP in the site investigator's opinion;
- persistent non-compliance to protocol requirements.

The decision to discontinue IMP, where applicable, must be recorded in the electronic CRF. For participants who remain in the trial for the purposes of follow-up for safety and / or data analysis, they will be managed according to the treatment arms to which they have been originally randomised.

Loss to follow-up

If a participant moves from the area where they started the study, every effort will be made for the participant to be followed up at another participating trial site and for this new site to take over the responsibility for the participant. If a participant is lost to follow-up at a site, efforts will be made to contact the participant's alternate contact or relevant laboratory, healthcare or hospital network (if the participant has given consent), to obtain information on the participant's status.

8.10 Replacements

Withdrawn participants will not be replaced.

8.11 Stopping Rules

The trial may be stopped before completion for the following reasons:

- On the recommendation of the DMC (see section 13).
- On the recommendation of the sponsors and CI.

If a safety trigger is reached safety data will be reviewed and a decision on continuation will be made by the DMC with input from the sponsor.

8.12 Definition of End of Trial

The expected duration of the trial is one year from recruitment of the first participant. The end of trial is five months after the last participant is enrolled when the database is locked, and all queries are

resolved. If further resources become available and the Trial Management Group (TMG) recommends continuation, the trial may be extended for up to two years from enrolment of the last participant.

9 Recording and reporting of adverse events and reactions

9.1 Definitions

Definitions of harm of the EU Directive 2001/20/EC Article 2 based on the principles of ICH GCP apply to this trial in all sites.

Table 1: Safety Event Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
Adverse Reaction (AR)	Any untoward and unintended response in a participant to an investigational medicinal product which **is related** to any dose administered to that participant. This includes medication errors, uses outside of protocol (including misuse and abuse of product).
Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction	Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that: ● results in death, ● is life-threatening*, ● requires hospitalization or prolongation of existing hospitalization**, ● results in persistent or significant disability or incapacity, or ● consists of a congenital anomaly or birth defect
* A life- threatening event, this refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. ** Hospitalization is defined as an in-patient admission, regardless of length of stay. Hospitalization for pre-existing conditions, including elective procedures do not constitute an SAE.	
Suspected Unexpected Serious Adverse Reaction (SUSAR)	An unexpected adverse reaction which is also categorized as serious.
Important Medical Event	These events may jeopardize the participant or may require an intervention to prevent one of the above characteristics/consequences. Such events should also be considered 'serious'.

In addition to the definition above, Adverse Events (AEs) include but are not limited to the following:

- an exacerbation (i.e. increase in the frequency or intensity) of a pre-existing illness, episodic event or symptom (initially observed at the screening), that is detected after IMP administration/trial intervention
- Occurrence of a new illness, episodic event or symptom, that is detected after IMP administration/trial intervention

AEs do NOT include:

- Medical or surgical procedures: the condition that leads to the procedure is the AE
- Pre-existing disease or a condition present before treatment that does not worsen
- Hospitalization where no untoward or unintended response has occurred e.g. elective cosmetic surgery
- Overdose of medication without signs or symptoms

9.2 Procedures for recording and reporting of adverse events (AEs) and serious adverse events (SAEs)

Non-serious AEs as well as SAEs will be self-reported by the participant via online platform or SMS system. Participants are requested to provide details of any symptoms they have experienced and details of any hospitalizations. The investigator will be notified by the online system of all events self-reported by the participant in order to perform their assessment of the event and complete the 'Investigator Adverse Event Report. If the participant becomes very unwell, they will not be able to respond to the weekly SMS messages. As long as they have given consent for an alternative contact to be contacted (in line with local data protection requirements), the alternate contacts will be contacted. If the alternative contact confirms that the participant is unwell, or if they cannot be contacted, the site PI will be informed. The PI or delegate will investigate, assess the event and complete an AE form, called 'Investigator Adverse Event Report' on the online system, immediately and no later than within 24 hours if the event meets SAE criteria.

A notification will be also sent to the sponsor for all AEs meeting serious criteria, including those self-reported by the participant or assessed as SAEs by the PI or delegate. Treatment should be discontinued in line with Section 8.5. Automated reminders will be sent to participant or investigator if safety event related forms are not completed in the expected timelines.

9.3 Assessments of Adverse Events

Adverse events will be assessed for causality, seriousness and expectedness as described below.

9.3.1 *Seriousness assessment*

When an AE occurs, the investigator will confirm if the event is serious as per the definition given in section 9.1. If the self-reported adverse event details provided by the participant are not sufficient for the investigator to make an assessment, they will contact the participant for further information. If the event is classified as 'serious' then additional information may be requested to be completed by the participant to aid in the assessment of causality.

9.3.2 *Severity assessment*

The investigator will assess all SAEs for severity. Where possible the system used by CTCAE (Common Terminology Criteria for Adverse Events) v5.0 27-Nov-2017 should be used for event name and severity as outlined here:

Table 2: Severity Grade Definitions

GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE THREATENING	GRADE 5 DEATH
Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death related to AE

9.3.3 *Causality assessment*

The site investigator or delegated medically trained person, will assess the causality of all adverse events or reactions in relation to the IMP using the definitions in the table 3 below.

Once an AE is self-reported by a participant a notification will be sent to the site investigator or a delegated medically trained person. The causality assessment will be based on the information provided by the participant when the AE is reported. If this information is not sufficient to assess causality the assessor will contact the participant for further details to complete the process. If the assessor gets further relevant AE information from the participant that has not been added on the self-reported form, the assessor will provide new details on the online 'Investigator Adverse Event Report'.

Table 3: Causality Definitions

Category	Definition
Related	A causal relationship between an IMP/investigational treatment and an adverse event is at least a **reasonable possibility**, i.e., the relationship cannot be ruled out.
Not related	There is **no reasonable possibility** of a causal relationship between an IMP/investigational treatment and an adverse event.

9.3.4 *Expectedness assessment*

If there is at least a possible involvement of the trial interventions, the medically qualified staff delegated by sponsor must assess the expectedness of the event. An unexpected adverse reaction is one that is not reported in the current and approved version of the SPCs, or one that is more frequently reported or more severe than previously reported. See section 4.8 of the current and approved SPCs for a list of expected toxicities associated with IMPs used in this trial. If a SAR is assessed as being unexpected it becomes a SUSAR (suspected, unexpected, serious adverse reaction) and relevant Regulatory Authorities and Ethics Committees reporting guidelines apply.

9.4 Notifications

The site Investigator or designee will receive an automated notification of the AE when it is initially self-reported by the participant. The investigator (or delegated medically trained person) must complete the causality and seriousness assessment. CCTU will receive notifications of all SAEs. Automated reminders will be sent to participant or investigator if safety event forms are not completed in the expected timelines. The site investigator will be notified of AEs via the electronic system, occurring from the time of randomization until 150 days after randomization. The Clinical Reviewer (medically qualified staff delegated by sponsor) will review all SAE reports received. In the event of disagreement between the causality assessment given by the investigator (or delegated medically trained person) and the Clinical Reviewer, both opinions and any justifications will be provided in subsequent reports. The Clinical Reviewer will review the assessment of expectedness based on possible wider knowledge of the reference material for the treatment. Country leads are responsible for the reporting of SUSARs to principal investigators and for ensuring reporting to relevant IRB/REC and national regulatory authorities as appropriate. Fatal and life threatening SUSARs must be reported to the regulatory authorities within 7 days of becoming aware of the event; other SUSARs must be reported within 15 days. Sponsor will keep country leads informed of any safety issues that arise during the course of the trial.

9.4.1 *Emergency Unblinding*

Every effort will be made to conceal the treatment allocation from participants and the trial teams. The trial code should only be broken for valid medical or safety reasons e.g. in the case of a severe adverse event where it is necessary for the investigator or treating health care professional to know which treatment the participant is receiving before the participant can be treated. Subject always to clinical need, where possible, members of the research team should remain blinded.

If the person requiring the unblinded information is not the coordinating PI or national PI then that healthcare professional will contact the Investigating team to request the code break. Unblinding will take place if in the opinion of a treating physician a participant's health is compromised. The authorized individual will break the code and immediately inform the treating healthcare professional of the participant's treatment allocation. The treating physician has the ultimate decision and right to unblind the participant.

The code breaks for the trial are held on the online system and are the responsibility of the local site PI. The local site PI who will be authorized and delegated to perform code break by the national PI. If the person requiring the unblinded information is a member of the Investigating team then a request to the authorized individual to unblind will be made and the treatment allocation information obtained.

On receipt of the treatment allocation details the site PI or treating health care professional will treat the participant's medical emergency as appropriate. The site PI will document the breaking of the code and the reasons for doing so on the CRF and unblinding log and will file this in the site file. It will also be documented at the end of the trial in any final trial report and/or statistical report.

The Investigating team will notify the CCTU in writing as soon as possible following the code break detailing the necessity of the code break.

9.4.2 *Unblinding for the submission of SUSAR reports*

The following procedure will be used to unblind for the submission of a SUSAR report to the regulatory agencies. The Sponsor will be authorized to access the code break system for the purposes of unbinding for the submission of a SUSAR. On receipt of the treatment allocation, the Sponsor will

provide the unblinded SUSAR information to the relevant regulatory agencies. SUSAR reports will be disseminated to Investigators at site(s) and will remain blinded. The unblinded information will not be forwarded to the trial team and will be kept in a separated file with limited access.

9.5 Development Safety Update Reports

The sponsor will provide the main IRB/REC and relevant national drug regulatory agencies with Development Safety Update Reports (DSUR). The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

9.6 Overdose

IMP adherence and SAEs will be self-reported. In the event of an SAE associated with an overdose, the site, national and coordinating PIs and sponsor will be informed. Incidents will be recorded on the deviation log.

9.7 Reporting Urgent Safety Measures and other safety events

If any urgent protocol deviations for safety measures are taken the site PI shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the national PI and sponsor who will inform the relevant IRB/REC and national medicines regulatory authority of the measures taken and the circumstances giving rise to those measures. Data Coordinating Centre (DCC) or global CRO (PRA) will provide a report on all SAEs for submission to all national IRB/RECs and relevant national drug regulatory authorities in accordance with local requirements.

9.8 Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to affect to a significant degree –
(a) the safety or physical or mental integrity of the participants of the trial; or
(b) the scientific value of the trial.
The sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of:
(a) the conditions and principles of GCP in connection with that trial; or (b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.
The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase.

10 Data management and quality assurance

10.1 Confidentiality

All data will be handled in accordance with the UK Data Protection Act 2018 and GDPR, and any relevant local country-specific guidance. Participants and trial investigators will record data on using SMS messaging and password-protected electronic CRF, both of which are hosted on a secure, access-restricted server. Participants registering on the secure electronic CRF will be assigned a pseudonymized identifier, which will be used for identification within the dataset. The dataset accessible for analysis will not bear any personally identifiable data. The site PIs will have access to participants’ names and contact details to enable verification of eligibility, consent and in the event of an SAR or other medically important event. Participant contact details (mobile phone number) will be shared with the SMS service to enable data collection. This will be clearly explained to the participant in the Participant Information Sheet. Participant consent for this will be sought.

10.2 Data collection tools and source document identification

Data will be collected using SMS messaging in combination with a trial specific electronic CRF (eCRF), directly entered by participants and trial investigators. Standard Operating Procedures (SOP) for completing the e-CRF will be implemented prior to the start of the trial. Text messages, push notifications and e-mail reminders will be used to maximize completeness of data. A system will be included to enable users to recover lost login IDs and passwords. Data will be entered into the eCRF by participants and trial investigators. The site investigator will be responsible for confirming the data in the CRF prior to data lock. Investigators may enter on behalf of the participants without internet access, where assistance is required or for those that become too unwell to respond. The eCRF system will audit when this has taken place and it should be documented by site. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

The source data will be the eCRF with the exception of when participants are hospitalized and information may be recorded in the medical notes.

10.3 Data handling and analysis

The data for the CROWN CORONATION trial will be owned jointly by all the participating international sites. The Data Coordinating Centre (DCC) will be at University College London (UCL). The DCC will take responsibility for governance in relation to the data. Data will be de-identified and mirrored in a data warehouse curated by the Gates Medical Research Institute. A global CRO (PRA) will assist with data chases and querying. Pseudonymised data will be provided to them by the DCC and stored in the USA.

A trial specific data management SOP will be in place for the trial. This will contain details of the software to be used for the database, the process of database design, data entry, data quality checks, data queries, data security and database lock.

UCL will be responsible for data analysis for the whole study. Direct access will be granted to authorized representatives of University College London and any host institution for monitoring and/or audit of the study to ensure compliance with regulations. Each participating site will have the right to request access to its own data. Access to unblinded data (by participating sites) will not be granted until the trial is unblinded. The trial's three coordinating principal investigators (Avidan, Moonesinghe and Rees) will arbitrate disputes regarding requests for data access.

Where data are transferred electronically this will be in accordance with the UK Data Protection Act 2018 and GDPR as well as UCL Information Security Policy and Trust Information Governance Policy, and relevant local, country-specific requirements. There will be a documented record of data transfer and measures in place for the recovery of original information after transfer. Appropriate measures will be taken to ensure non-disclosure of information that is potentially harmful to participants. All data will be stored in the UK or the EU. Only non-identifiable data will be transferred outside the EU in line with GDPR regulations.

11 Statistical Considerations

11.1 Outcomes

11.1.1 *Primary outcome*

Symptomatic COVID-19: Clinical diagnosis of COVID-19 with laboratory confirmation (i.e. based on viral PCR), and symptoms of COVID-19 (cough, shortness of breath or difficulty breathing, fever, chills,

muscle pain, sore throat, new loss of taste or smell, nausea, vomiting, or diarrhea) by day 60 after receiving trial intervention. An independent endpoint adjudication committee will be established to adjudicate endpoints across the trial. The terms of reference of this committee will be detailed in a separate document.

11.1.2 *Secondary outcomes*

The following secondary outcome is of special interest: Severity of COVID-19 over the study period

i) Uninfected – no clinical or virologic evidence of infection (Score = 0)
ii) Ambulatory – no limitation of activities (score=1) or with limitation (Score=2)
iii) Hospitalized – mild no oxygen (Score=3) or with oxygen (Score=4), hospitalized severe – Score=5-7*, dead (Score=8)

*Score 5 is non-invasive ventilation or high flow oxygen; Score 6 is intubation with mechanical ventilation; Score 7 is intubation with additional organ support (e.g. vasopressors, renal replacement therapy (RRT), extra corporeal membrane oxygenation [ECMO]).

These outcome definitions are based on WHO R&D Blueprint consensus definitions for COVID-19. The study period refers to the 60 days following commencement of trial intervention and an additional 3 months of observation period of participants i.e. 150 days in total. Moreover, severity will be reported based on a 60-day timeframe.

The secondary clinical outcomes consist of:

- Primary endpoint, but instead of the 60-day timeframe, over the course of the first 30 days after receiving trial interventions;
- Primary endpoint, but instead of the 60-day timeframe, over the course of the first 150 days after receiving trial interventions;
- Symptomatic COVID-19 (with subsequent virological confirmation) during the 150-day study period;
- Incident COVID-19 during the 60-day study period, which includes asymptomatic infections identified by serology samples taken at the time-point of study exit.

Table 4: Classification of Outcomes

Outcome	Baseline serology	60-day serology	150-day serology	RT PCR while symptomatic	COVID-19 symptoms
1. Nucleic acid confirmed COVID-19	+/-	+/-	+/-	+	+
2. Severe COVID-19	+/-	+/-	+/-	+	+ (scaled according to WHO ordinal severity scale)
3. Asymptomatic COVID-19	-	At least one of 2- or 5-month serology must be +	At least one of 2- or 5-month serology must be +	Not done	-
4. Presumed prior infection	+	+/-	+/-	- / not done	+/-
5. Other acute respiratory illness during trial	+/-	+/-	+/-	-	+

6. Symptomatic nucleic acid negative COVID-19; not primary outcome	-	At least one of 2- or 5-month serology must be +	At least one of 2- or 5-month serology must be +	-	+

Safety Outcomes
Safety outcomes will be determined according to the CTCAE (Common Terminology Criteria for Adverse Events) v5.0 27-Nov-2017 for grading severity of adult adverse events.

Implementation and Process Outcomes
In addition to monthly confirmation of treatment adherence, where appropriate, we will ask participants to self-report on their compliance with the assigned regimen at the time they exit the trial, or at the time they develop the primary outcome. At the same time point we will ask participants to self-report on whether they used open label treatments that are used in the active arms of the trial (outside of the trial protocol) during the trial.

11.2 Sample size and recruitment

11.2.1 *Sample size calculation*

We considered different event rates, depending on the following assumptions. Firstly, we assumed that 30-50% of the participants may become infected with SARS-CoV-2 over the course of the study period. Of these, the percentage of participants who will experience the primary endpoint or laboratory test-confirmed symptomatic COVID-19 (i.e. any of the following: cough, shortness of breath or difficulty breathing, fever, chills, muscle pain, sore throat, new loss of taste or smell, nausea, vomiting, or diarrhea) is uncertain. We use a range of 15-50%. The estimated event rate is therefore 0.15 * 0.30 = 0.045 (or 4.5%, rounded to 5%) to 0.50*0.50 = 0.25.

We declare the superiority of a treatment arm if the probability that the Odds Ratio (OR) of the treatment is less or equal to 1 is greater than 95%, i.e. P(OR < 1) > 95%. The remaining Bayesian statistical triggers of the adaptive trial are specified in section 11.5.

A 2-arm trial was simulated to assess the required sample size for the study. The OR was assumed to be 0.7. Three event rates for control arm were used: 5%, 10% and 15%. We are interested in the lower end of the 5-25% range for the control rate since a higher sample size is required when the event rate in the control arm decreases for a given effect size.

Figure 5 below reports the probability that the simulated trial concludes superiority of the treatment arm depending on the sample size per arm.

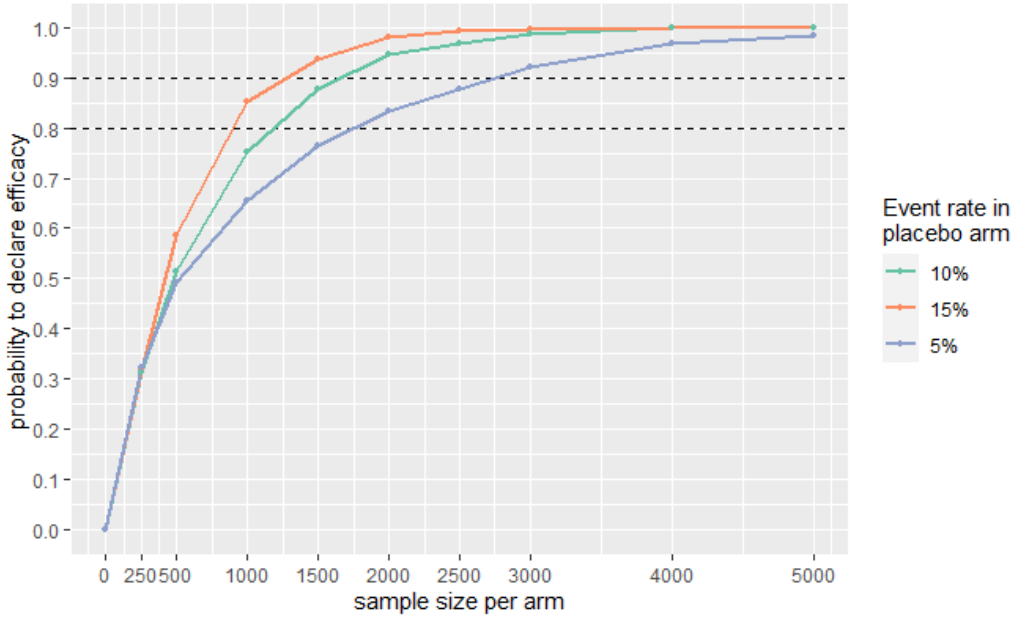

Figure 5: Sample size estimation for the first phase of the trial (2-arm)

The simulations show that the probability of declaring efficacy depends on the event rate in the placebo arm. With 2000-2500 participants per arm, even if the event rate is 5% in the control arm, the study has >80% chance to declare efficacy.

We propose to retain the option of reaching a maximum of 2,500 participants per arm. We will aim to enrol a maximum of 5,000 participants in total in the first phase of the trial to allow for possible loss-to-follow-up (LTFU), withdrawal, protocol deviation, non-adherence and other methodological challenges. Further phases may be added to the trial until a maximum of 30,000 participants is reached.

The assumptions underlying the sample size calculations will be reviewed at each interim analysis based on the observed data.

11.2.2 *Planned recruitment rate*

The participants for the first phase of the study are estimated to be recruited within 12 months, depending on the rate of site activation.

11.3 Randomization methods

Participant-level randomization will be used in the study.

The randomization sequence will be computer generated with permuted blocks. There will be initially equal numbers of participants (1:1) in each of the groups. Randomization will be stratified by age (<50 and ≥50) and site.

If the education and surveillance plus placebo arm is discontinued at an interim analysis, participants from this arm will be randomized to the remaining arms.

Modifications to the number of active treatment arms

Other arms can be added to CROWN CORONATION if evidence emerges that there are other suitable candidate prophylaxis options.

Participants will only be randomized to arms for which they are eligible. (e.g. pregnant women will not be randomized to the “vaccine vs placebo” arm).

11.4 Statistical analysis plan

This section provides a general overview of the statistical analysis plan (SAP). A more detailed SAP will be written by the trial statistician and approved by the TMG and Data Monitoring Committee (DMC) prior to any substantial analysis of the data.

11.4.1 *Summary of baseline data and flow of participants*

A CONSORT diagram will be produced to report of the flow of participants in the study.

Summary of baseline characteristics, by study arms, will be by frequency and percentage for categorical variables, and for continuous variables by mean and standard deviation (or median and inter-quartile range for non-normally distributed data).

11.4.2 *Primary outcome analysis*

The threshold for declaring that an education and surveillance plus therapeutic agent(s) arm is superior to education and surveillance plus placebo will be based on the OR for the specific arm compared to education and surveillance plus placebo. The objective is to obtain sufficient certainty (95% at least) that OR < 1. In mathematical terms, this quantity is referred to as P(OR < 1) > 95%.

Primary analysis models:
The primary endpoint of incidence of symptomatic laboratory-confirmed COVID-19 infection will be analysed using a Bayesian logistic regression, including as covariates the treatment arm, age (<50 vs. ≥50), and a random effect for site.

The prior distribution corresponding to the education and surveillance plus placebo arm will be such that it is centered on 15% for the event rate, midway between the 5%-25% range that we consider. The prior distribution corresponding to the OR of the treatment arm will be such that the OR is centered on 1. Further details on the prior distributions are provided in the SAP.

Additional multivariable analyses will be conducted, taking into account the following variables: sex, smoking, body mass index, HIV infection, pre-existing respiratory disease, diabetes (recent HbA1c), hypertension, and coronary artery disease.

Secondary outcomes:

The endpoint of severity of symptoms on the WHO scale will be analysed using a Bayesian proportional odds model, using the same adjustment approach as the primary endpoint.

Other secondary outcomes that are binary in nature will be analysed using Bayesian logistic regression, using the same adjustment methods as previously described.

In addition, time-to-event models will be used to assess the effect of the interventions on the time to incidence of symptomatic laboratory-confirmed COVID-19 infection over the 150-day period since receiving trial interventions.

11.4.3 *Sensitivity and other planned analyses*

Subgroup analyses will be pre-specified and performed using an interaction term in the model between the treatment arm and the characteristics of interest. The factors of interest are: age, HIV status, geographic region, ethnicity and sex.

11.5 Interim analyses

This Bayesian trial will perform frequent interim analyses for efficacy, futility and harm. This means that the DMC will regularly consider the balance of benefit and risk. Strong evidence of benefit, futility, or harm will result in the advice to modify or stop the trial.

The objective of interim analyses is two-fold: 1/ identify whether an active arm is futile, if the probability that its OR≥0.9 is high, greater than 95%, 2/ identify whether there is sufficient evidence that an active arm is superior to the control arm. The following table contains the statistical triggers for efficacy, futility and harm at interim analyses and for the final analysis.

Probability	**Threshold at interim analysis**	**Threshold at final analysis**	**Evidence for:**
P_1 = P (OR < 0.8 | data)	99%	95%	Marked clinical benefit
P_2 = P (OR ≥ 0.9 | data)	99%	95%	Non clinically relevant (i.e. futile) treatment (or harm when OR ≥ 1)

Posterior predictive probabilities will also be calculated at each interim analysis to inform the potential adaptation decisions.

Platform trial

In the study there exists a possibility of adding treatment arm(s) at interim analysis or during the course of the study. If a treatment arm is added, all comparisons will be made with concurrent control participants.

For the main effects of individual treatments (i.e. when given on their own), the thresholds for superiority and futility described above will apply to the same manner to the additional treatment(s).

For treatments that are given in combination in the context of a potential factorial design, the quantity of interest will be P(interaction term < 1 | data) ≥ 0.95% (or 99% at interim analysis) to declare evidence of synergy. The prior distribution for the interaction term will be specified in exactly the same way as the prior of the OR of the individual treatments. Only its interpretation changes.

The SAP contains additional details regarding the monitoring of the trial, including the cumulative probability of declaring efficacy depending on the underlying simulated hazard ratio.

11.6 Other statistical considerations

All randomized participant data will be included in the Intention-To-Treat (ITT) analysis according to the arm they were randomized to, irrespective of the actual study drug that they took. This ITT analysis will be the main strategy for the primary outcome and will be followed by a per protocol analysis.

Moreover, a modified ITT analysis will be performed at the end of the study, based on serology results. Participants with evidence of COVID-19 infection at the start of the study will be removed from the analysis set.

12 Record keeping and archiving

At the end of the trial, all essential documentation will be archived securely by the CI and trial sites for a minimum of 10 years or as required by local regulation from the declaration of end of trial. Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of Good Clinical Practice and all applicable regulatory requirements. The sponsor will notify sites when trial documentation can be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

13 Oversight Committees

The following committees will be in place for the trial: Trial Management Group (TMG) and independent Data Monitoring Committee (DMC). The terms of reference for these committees will need to be provided in separate documents.

13.1 Trial Management Group (TMG)

The TMG will include the three coordinating Principal Investigators, national principal investigators and key trial staff. The TMG will be responsible for overseeing the trial. The group will meet regularly (monthly) and will send updates to site PIs. The TMG will review recruitment figures, SAEs and substantial amendments to the protocol prior to submission to the IRB/REC and/or relevant national drug authority. All site PIs will be kept informed of substantial amendments through the sponsor or designee and/or national PIs.

The TMG acts on behalf of the funder(s) and Sponsors.

13.2 Data Monitoring Committee (DMC)

The role of the DMC is to provide independent advice on data and safety aspects of the trial. A specific DMC charter will be developed to outline the terms of reference, membership, and frequency of meetings. The DMC is advisory to the TMG and can recommend premature closure of the trial.

14 Direct Access to Source Data/Documents

The investigator(s)/ institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes. Source data for most self-reported data points will be the original entry on to the SMS or electronic CRF system.

15 Ethics and regulatory requirements

All international participating sites will obtain approval from the relevant local IRB/REC and national regulatory authorities. The national Principal Investigators and sponsor will ensure that the trial protocol, PIS, consent form and submitted supporting documents have been approved by the

appropriate regulatory body and the appropriate research ethics committees responsible for the proposed recruitment sites. The protocol, all other supporting documents including and agreed amendments, will be documented, and submitted for ethical and regulatory approval as required. Amendments will not be implemented prior to receipt of the required approval(s), except where necessary to eliminate apparent immediate hazards to trial participants. The in-country sponsor is responsible for obtaining insurance coverage. Details on each specific country are not included in this core protocol.

16 Monitoring requirement for the trial

The sponsor will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly. The degree of monitoring will be proportionate to the objective, purpose, phase, design, size, complexity, blinding, endpoints, and risks associated with the trial. A trial specific oversight and monitoring plan will be established. The trial will be monitored in accordance with the agreed plan. The research team will monitor the study for adverse events. All serious adverse events will be reported to the relevant IRB/REC, according to the local stipulations. The monitoring plan for this study is appropriate for the planned pragmatic trial.

The CROWN CORONATION trial will have an appropriate data and safety monitoring plan. There will be a charter to guide the functions of the DMC, and the DMC will produce reports in accordance with relevant guidelines. The DMC will provide independent oversight of the CROWN CORONATION trial and will review the general conduct of the trial as well as study data for participant safety. The DMC will comprise independent, multidisciplinary experts who will make recommendations regarding the continuation, modification, or termination of the trial. The members will have the requisite expertise to examine accumulating data, to protect the integrity of the clinical experiments in which the participants have consented to partake, and to assure the regulatory bodies and the public (and possibly funding agencies) that conflicts of interest do not compromise either participant safety or trial integrity. There will be a provision for early stoppage for safety concerns, as well as for efficacy and for futility.

Attempts will be made to track adherence to the treatment regimens (based on daily or minimum twice weekly participant logs from their mobile phone). Questions will also be asked about use of other mitigation, including personal protective equipment. Participants will also be asked to document the frequency of high-risk contacts (e.g., number of patients with COVID-19 they had contact with every day).

Local investigators at all participating sites will report serious adverse events, or unanticipated problems involving risks to participants or others, to their IRB/REC and to the Trial management group. If such problems are considered related to the trial, then they will also be reported to IRB/RECs at other participating sites and to the chairperson of the DMC.

The members of the DMC will have no direct involvement in the conduct of the CROWN CORONATION trial. Neither will they have financial, proprietary, or professional conflicts of interest, which may affect the impartial, independent decision-making responsibilities of the DMC. Letters of invitation to prospective DMC members will include language similar to the following: “Acceptance of this invitation to serve on the DMC confirms that I do not have any financial or other interest with any of the collaborating or competing pharmaceutical firms or other organizations involved in the COVID-19 trials that constitute a potential conflict of interest.” All DMC members will sign a Conflict of Interest Certification to confirm that no conflict exists. The DMC will be advisory rather than executive on the basis that it is the sponsor and the CROWN CORONATION trial investigators who are ultimately responsible for the conduct of the trial.

The risks associated with this study are low. There is a rare risk of breach of confidentiality. Side effects of the IMPs will be listed in the IMP appendices.

As part of the informed consent process for this study, participants will be informed of the risks. In the unlikely event that serious side effects occur, they will be documented and also reported to the IRB/REC in accordance with local regulatory requirements and to the study's DMC. Participants will not incur any study-related expenses, and nor will they be financially compensated for their participation.

17 Finance

Funding has been secured from the COVID-19 Therapeutics Accelerator. Further funding is being sought from other international and national funding bodies for individual countries.

18 Publication policy

The findings from the trial will be published in peer-reviewed journals. Discussions are in place to ensure that meta-analyses will be possible with other studies in the field. The coordinating principal investigators together with all the country lead investigators in participating countries will discuss, review and agree on publications. They will also jointly make decisions on authorship. Disputes will be resolved by the three principal investigators (Avidan, Moonesinghe and Rees).

Data generated from this study will adhere to the 2020 statement from the Wellcome Trust: Coronavirus (COVID-19): sharing research data. They will also adhere to the Bill & Melinda Gates Foundation Open Access Policy - Bill & Melinda Gates Foundation.

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