



**World Health  
Organization**

# **Feasibility, Potential Value and Limitations of Establishing a Closely Monitored Challenge Model of Experimental COVID-19 Infection and Illness in Healthy Young Adult Volunteers**

## **FINAL REPORT – DRAFT FOR PUBLIC COMMENTS**

World Health Organization Advisory Group Tasked to Consider the Feasibility, Potential Value and Limitations of Establishing a Closely Monitored Challenge Model of Experimental COVID-19 Infection and Illness in Healthy Young Adult Volunteers

This is a draft. The content of this document is not final, and the text may be subject to revisions before publication. The document may not be reviewed, abstracted, quoted, reproduced, transmitted, distributed, translated or adapted, in part or in whole, in any form or by any means without the permission of the World Health Organization.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.



**R&D Blueprint**

Powering research  
to prevent epidemics

---

DRAFT

---

<b>EXECUTIVE SUMMARY</b>	<b>6</b>
<b>CLINICAL ISSUES</b>	<b>7</b>
<b>SELECTION OF CHALLENGE VIRUS STRAINS AND OF A BSL-3 GMP MANUFACTURER</b>	<b>8</b>
<b>MEASUREMENT OF IMMUNE RESPONSES AND OF VIRUS SHEDDING</b>	<b>8</b>
<b>SUMMARY COMMENT</b>	<b>9</b>
<b>ADVISORY GROUP RECOMMENDATIONS</b>	<b>10</b>
<b>1. PREAMBLE</b>	<b>12</b>
<b>2. WHO'S ACTIVITIES TO ACCELERATE COVID-19 VACCINE DEVELOPMENT AND CLINICAL TESTING</b>	<b>12</b>
2.1. A multi-center, multi-vaccine randomized, placebo-controlled trial .....	12
2.2. Assessing a possible role for experimental challenge studies .....	13
<b>3. WHY NOW FOR AN ADVISORY GROUP TO CONSIDER THE FEASIBILITY, POTENTIAL VALUE AND LIMITATIONS OF ESTABLISHING A CLOSELY MONITORED CHALLENGE MODEL OF EXPERIMENTAL COVID-19 INFECTION AND ILLNESS IN HEALTHY YOUNG ADULT VOLUNTEERS?</b>	<b>20</b>
3.1. Terms of Reference.....	20
3.2. Logistics, timelines and costs.....	21
3.3. Some uses of a model, if established .....	22
3.4. Other related issues.....	22
3.5. Deliverables .....	22
<b>4. INTRODUCTION TO THE TASK</b>	<b>23</b>
4.1. Formation of Subgroups and Teams .....	25
4.2. A Cautious Two-Stage Approach .....	26
<b>5. CLINICAL ISSUES</b>	<b>29</b>
5.1. A Clinical Protocol Synopsis Prepared by the Subgroup on Clinical Trial Issues .....	29
<b>6. ELEMENTS OF A CLINICAL PROTOCOL</b>	<b>29</b>
6.1. Volunteer selection .....	29

6.2. Size of initial groups .....	31
6.3. Endpoints to be achieved with SARS-CoV-2 challenge model. ....	32
6.4. Method of administration .....	34
6.5. Safety Monitoring during inpatient stay .....	34
6.6. Discharge criteria.....	34
6.7. Follow-up .....	35
6.8. Laboratory studies.....	35
6.9. Treatment protocols .....	36
<b>7. ISOLATION UNITS FOR USE IN A SARS-COV-2 CHALLENGE</b>	<b>36</b>
7.1. Capabilities available on the unit .....	38
7.2. Medical expertise/support care available on the unit .....	38
7.3. Precautions for staff/third parties .....	39
7.4. Measures to address volunteers who wish to leave the study before completion.....	39
7.5. Handling of the SARS-CoV-2 challenge virus.....	40
7.6. Efficacy studies.....	40
<b>8. CONSENT FORM</b>	<b>41</b>
<b>9. VOLUNTEER COMPREHENSION TEST</b>	<b>41</b>
<b>10. SELECTION OF VIRUSES TO BE USED IN CHALLENGE STUDIES</b>	<b>43</b>
10.1. Points to consider in selecting a SARS-CoV-2 challenge virus strain.....	43
<b>11. MANUFACTURE OF GMP BATCHES OF SARS-COV VIRUS STRAINS FOR VOLUNTEER CHALLENGE STUDIES</b>	<b>46</b>
11.1. ....	46
11.2. Criteria for selection of a manufacturer of the challenge agents .....	48
11.3. Some Advisory Group suggestions to be discussed with the manufacturer .....	49
<b>12. REPORT OF THE SUBGROUP ON MEASUREMENT OF IMMUNE RESPONSES PRE- AND POST-CHALLENGE</b>	<b>50</b>
12.1. Background .....	50
12.2. Principles of immunologic study of volunteer challenges with SARS-CoV-2 .....	50

---

12.3. The volunteer challenge model can contribute to identification of .....	51
---	----

<b>13. SUBGROUP ON DETECTION OF SARS-COV-2 IN CLINICAL SPECIMENS POST-CHALLENGE</b>	<b>54</b>
---	-----------

13.1. Nucleic acid assay .....	54
--------------------------------	----

APPENDIX B .....	59
------------------	----

APPENDIX C .....	63
------------------	----

DRAFT

## Executive Summary

Recognizing the helpful role that experimental challenge studies in healthy adult volunteers have played in the development of certain vaccines, some have advocated a role for such studies with virulent SARS-CoV-2.

However, several factors collectively warrant that special caution must be taken in working with SARS-CoV-2, including:

- the severity of COVID-19 disease, as evidenced by its high case fatality risk in certain sub-populations (elderly, diabetics, hosts with pre-existing pulmonary and cardiac disease);
- severe disease requiring ventilator support and deaths (albeit uncommon) also occurs in young adults, although risk factors for these outcomes in this age group remain uncharacterized; increasing recognition of severe thromboembolic events in young adults;
- the high transmissibility of SARS-CoV-2 from person-to-person directly by respiratory droplets and at further distances by airborne droplet nuclei;
- the virus' ability to remain viable on some fomites for hours; with each passing month, new acute presentations and forms of illness that SARS-CoV-2 infection can elicit have been described;
- finally, as of early June 2020, a reliable "rescue treatment" has not yet been identified that can predictably arrest the progression of COVID-19 illness from a mild/moderate illness to serious, potentially life-threatening, illness.

Understandably, among experienced challenge model investigators the topic of undertaking challenge studies with fully virulent SARS-CoV-2 has generated discussion about whether the conditions can be assured to perform challenge studies safely and what the priority goals should be for such studies.

Taking into account the reasons for caution cited above, if conditions were deemed suitable to undertake development of a closely monitored SARS-CoV-2 challenge model in healthy young adult volunteers, important information could accrue such as:

- to determine whether an initial challenge infection confers significant protection against a subsequent challenge with the homologous virus (and perhaps in subsequent studies to address whether infection-derived protection extends to other virus clades);
- to identify immunologic correlates of protection against clinical illness and shedding of virus that might accompany recovery from a prior experimental challenge with SARS-CoV-2;
- to allow studies of different COVID-19 vaccine candidates to estimate the extent to which they protect and whether protection, if observed, is against COVID-19 clinical disease or against SARS-CoV-2 infection, or both; and
- to contribute to the development of correlates of protection against clinical illness and against shedding of virus in vaccinated volunteers; to compare the protection afforded by different types of vaccines (e.g., mRNA, DNA, protein, viral vectored, live attenuated, inactivated whole virus, etc.).

In April 2020 the World Health Organization convened a multi-disciplinary, international group of experts to discuss from different perspectives the concept of volunteer challenge studies with SARS-CoV-2. This Advisory Group (AG) included experts with experience in: design and performance of many types of volunteer challenge studies; SARS-CoV-2 virology; measurement of human immune responses to SARS-CoV-2 and to other microbial pathogens; clinical management of COVID-19 clinical disease in different geographic settings; regulatory considerations associated with testing and emergency pre-licensure use of vaccines and with larger-scale post-licensure deployment; and GMP manufacture of virulent viruses under BSL-3 containment. The AG was sub-divided into four Subgroups to address: Clinical Trials Issues, Challenge Virus Strain Issues, Measurement of Immune Responses Pre- and Post-Challenge, and Detection of SARS-CoV-2 in Clinical Specimens Post-challenge. The AG agreed to monitor the progress of evaluation of potential treatments to interrupt the progression of SARS-CoV-2 clinical disease from mild/moderate to severe, even as it diligently undertook to identify the myriad of technical issues that must be addressed to set up such a model.

**This represents a preparatory strategy so that if conditions are deemed appropriate, there will be a technically valid roadmap of what needs to be done to initiate a closely monitored challenge model of SARS-CoV-2 infection.**

---

## Clinical Issues

**Stage 1, undertaken when there has been no previous volunteer experience with the challenge virus strains.** To address the high transmissibility of SARS-CoV-2 and how challenges might proceed in periods when there is little or no natural ongoing transmission of SARS-CoV-2 in a community, and to protect clinical research staff, the AG recommended that the early (**Stage 1**) dose-escalation studies should be performed in High-Level Isolation Units that allow rigorous physical and biological containment, while assuring facile access/transport to intensive care for volunteers, should the need arise.

To protect household contacts of challenged volunteers and community contacts, the AG recommends that these studies, in co-ordination with local public health and civil authorities, be performed under legal Quarantine (a health authority issued state of Compulsory Isolation). With revisions of enforced isolation and Quarantine laws that have been enacted in many countries (and state and municipal jurisdictions therein) in recent years, many persons with extensively drug-resistant tuberculosis have been kept in Compulsory Isolation until they were no longer infectious. Moreover, there is a well-known precedent for establishing Quarantine for early cholera challenge studies performed with community volunteers in Baltimore, MD, USA, in the mid-1970s.

Multiple AG members affirmed that health ordinances exist in their countries that could facilitate establishment of Quarantine. If so, a volunteer who decides that she/he wishes to leave the study after it begins (which is her/his right) could do so (no more procedures, etc.) but she/he would not be allowed to leave the Isolation Unit until the study ends. Volunteers would have to be stringently screened to enroll only those who are deemed to be diligent and committed and who understand clearly this unusual concept.

The AG recommends that the virus inoculum be instilled into the nostrils of the volunteer (0.5 ml per nostril) using a pipette, rather than to utilize a nasal spray device intended to generate large particles (~25-50 microns), because the sprays may inadvertently produce some minor proportion of particles that are small enough to reach the lower respiratory tract. The AG concluded that initially this step of dose preparation and intranasal administration of challenge virus to volunteers should be performed in a High-Level Isolation Unit with rigorous safeguards against droplet and droplet nuclei airborne transmission. This is to minimize the risk of virus spread to research staff and to the community.

The AG proposes that dose levels of  $1 \times 10^2$  TCID<sub>50</sub>,  $1 \times 10^3$  TCID<sub>50</sub> and  $1 \times 10^4$  TCID<sub>50</sub> be the three initial dose levels to be investigated in different groups of volunteers in dose-escalation fashion to try and achieve a 70% clinical attack risk for mild upper respiratory illness accompanied by shedding of SARS-CoV-2. There is no way to predict whether multiple passages in tissue culture will have attenuated the challenge viruses or whether, by contrast, clinical illness in some volunteers may prove to be severe (an outcome to be avoided).

A Data Safety Monitoring Board will review safety and shedding data from all the volunteers participating in each dose level and will advise the investigators of their decision to approve, or not, escalation to the next higher dose. Volunteers will remain on the High-Level Isolation Unit until they have exceeded the usual upper range of incubation (14 days) and have ceased shedding virus (confirmed by RT-PCR) for three consecutive days; uncommonly RT-PCR positivity may continue well beyond 14 days after onset of clinical (or subclinical infection) and could persist for up to 28 days.

**Stage 2 studies. Once the model of closely monitored SARS-CoV-2 experimental infection is established under Stage 1 conditions.** If the stepwise dose-escalation studies investigating different SARS-CoV-2 clades yield a safe model, **Stage 2** studies involving

---

larger numbers of volunteers could proceed. Examples of such studies could be challenge/re-challenge to assess the level of protection against clinical illness and against virus shedding deriving from an initial SARS-CoV-2 infection. Other examples of Stage 2 studies could be preliminary assessments of the level of protection against clinical illness and shedding of virus that follows immunization of young adults with COVID-19 vaccines of different varieties.

## **Selection of challenge virus strains and of a BSL-3 GMP manufacturer**

The AG concluded that two separate isolates should be selected from clade B1 (currently circulating in Europe and North America) and two isolates from clade A (original outbreak strain that circulated in China) to be sent to the manufacturer chosen to prepare GMP batches of each virus. A lengthy list of potential isolates has been assembled from which to select challenge viruses.

Use of an engineered virulent SARS-CoV-2 derived by reverse genetics was also discussed; while not an option on the immediate horizon, this should be considered as an attractive back-up.

Upon arrival at the manufacturer, each candidate isolate will undergo plaque purification x 3 in a validated cell line in the BSL-3 facility. It is expected that 5-10 passages of each virus will be necessary to obtain adequate yields.

The challenge strains should undergo New Generation Sequencing (NGS) at the start and end of manufacturing to detect mutations. The AG and prospective manufacturers mutually concluded that screw top vials containing frozen liquid harboring virus is the preferred formulation (as opposed to lyophilized material in vials that would have to be reconstituted to prepare each dose prior to use). Thus, there would be fill and finish of vials with frozen liquid corresponding to each dose level of each virus.

An experienced courier service confirmed the precise details needed to transport the vials of SARS-CoV-2 to potential challenge study sites.

The manufacturer must prepare a stability plan for each dose level to monitor stability of virus counts over time and must assure that there will be sufficient vials set aside for the stability studies, as well as supplying vials for the challenge studies.

## **Measurement of immune responses and of virus shedding**

The AG discussed the importance of measuring a wide array of innate, adaptive humoral (serum and mucosal) as well as cell-mediated immune responses to SARS-CoV-2. Measurements in larger Stage 2 studies, such as challenge/re-challenge studies and preliminary assessments of one or more vaccines, may allow identification of immunologic correlates of protection. Methods to monitor virus shedding were also proposed.

---

## Summary comment

In view of the urgent need to develop vaccines against the SARS-CoV-2 virus, the WHO convened an Advisory Group (AG) to consider the feasibility, potential value and limitations of establishing a closely monitored challenge model of experimental SARS-CoV-2 infection and illness in healthy young adult volunteers.

This report details issues that make such a model special and daunting to establish, such as its potential to cause severe and fatal illness and its high transmissibility.

The report provides solutions to address many of the issues. Detailed instructions for selection of potential challenge viruses, guidelines for manufacture, formulation, and presentation of challenge doses, ways to achieve containment of the virus and to prevent transmission to household and community contacts have been proffered.

Prudent strategies for stepwise model development and for detailed measurement of immune responses and virus shedding are offered. Such a model could potentially demonstrate protection against virus shedding and/or clinical illness induced either by prior infection with the challenge virus or by immunization with a candidate vaccine. A limitation of the model is that evidence of efficacy obtained in healthy young adults cannot *per se* be extrapolated to predict vaccine efficacy in certain high-risk target populations such as the elderly or adults with underlying diabetes, cardiac and pulmonary conditions; so, this issue was not addressed in depth by the AG.

Attitudes for undertaking Stage 1 studies to establish the model are influenced by whether or not a proven effective treatment exists that can prevent moderate disease from progressing to serious illness and death, with one half of the AG cautioning to await such a treatment as a prerequisite for starting and others urging an initiation of challenge studies even absent such a treatment.

Ongoing controlled clinical trials of potential therapeutic interventions will be closely watched for signs of a breakthrough to obtain an effective treatment, while steps to manufacture GMP challenge inocula proceed.

---

## Advisory Group Recommendations

1. The clinical trials to establish a model of COVID-19 infection and illness should be divided into an incremental STAGE 1 / STAGE 2 strategy in which STAGE 1 are early studies that establish the model through first-in-human, stepwise, dose-escalation studies with three different dose levels and close monitoring of the volunteers to reveal the clinical response and the virus shedding pattern. The subsequent STAGE 2 studies with much larger numbers of volunteers would address questions such as the level of protection conferred by infection-derived immunity and the preliminary efficacy of different types of vaccines.
2. The age range of the volunteers should be restricted to healthy individuals 18-25 years of age, as that age group has a lower-case fatality risk among hospitalized cases than older adults.
3. To address the high transmissibility of SARS-CoV-2 and the need to administer the virus to volunteers intranasally in a high level of containment that minimizes consequences of droplet and aerosol generation, and to protect clinical research and ancillary staff, the STAGE 1 studies to establish the model should be performed in High-Level Isolation Units (i.e., high-level clinical containment facilities) as described in APPENDIX B.
4. To allow challenge studies to proceed during periods when there is little or no ongoing COVID-19 disease in the community, and to protect household contacts and community contacts of challenged volunteers, the High-Level Isolation Unit for Stage 1 studies should be placed under legal Quarantine (Compulsory Isolation) during the period of the study so that if a participating volunteer decides that she/he wishes to “leave the study” (thus, no more specimens have to be given, etc.), which is their right, they will nevertheless not be allowed to leave the Quarantined Isolation Unit until the study ends. This will require close coordination with and cooperation of the local public health and civil authorities in the municipality and/or state where the High-Level Isolation Unit is located. Many local health authorities will be familiar with Compulsory Isolation from applying it to health care facilities where persons with extensively drug-resistant tuberculosis patients are kept until they are no longer infectious. There is a long precedent for establishing Quarantine for challenge studies from the early cholera challenge studies in community volunteers carried out in the Baltimore, Maryland, USA during the period 1977 until 1995.
5. The Advisory Group recommends that there should be two isolates selected from Clade B1 (main clade circulating in Europe and North America) and two isolates selected from Clade A (early virus that is still associated with a small proportion of disease in parts of China and East Asia) to be sent to a selected GMP manufacturer to have batches of each virus prepared in appropriate formulation for use in a SARS-CoV-2 model.
6. If funding is available, the specific four selected viruses should be sent to a GMP manufacturer with BSL-3 capability where the viruses would be plaque-purified x3 in qualified cells, sequenced by New Generation Sequencing (NGS) before and after, and the GMP batches of the four viruses manufactured, finished and filled to produce vials of the recommended frozen liquid formulation at the three requested dose levels. GMP batches and stability testing over time should only proceed for viruses that demonstrate adequate growth characteristics.

- 
7. The dose levels proposed for the Stage 1 stepwise, first-in-human, dose-escalation studies of each virus are “1x10<sup>2</sup> TCID<sub>50</sub>, 1x10<sup>3</sup> TCID<sub>50</sub>, 1x10<sup>4</sup> TCID<sub>50</sub>, respectively, as the low”, “medium” and “high” dose levels. As necessary, a log higher dose level may have to be prepared for one or more viruses.
  8. The various therapeutic regimens for COVID-19 disease that are being tested in large randomized, controlled clinical trials worldwide should be closely followed to see if within the coming weeks or months an intervention emerges that might serve as a credible “rescue treatment” for use in a SARS-CoV-2 volunteer challenge model.
  9. Whereas the votes of the Advisory Group members on the above-mentioned eight technical recommendations were either unanimous or nearly unanimous, the Group was split almost in half in voting on the final three questions shown below.
  10. When asked whether challenge studies should begin if properly formulated challenge viruses in the three desired dose levels become available in the next few months but there is not yet a recognized “rescue treatment” to arrest the progression of COVID-19 illness from a mild or moderate severity to a severe illness, 10 voted “to begin” without a treatment and 9 voted “not to begin” without a treatment.
  11. When asked to opine whether efficacy results in young adults in a challenge model will predict efficacy in elderly and high-risk adults, the Advisory Group was again split with 8 of 19 respondents stating their belief that the model would and 11 stating their opinion that the model would not predict efficacy in elderly and high-risk adults.
  12. When requested to give their opinion on whether results of volunteer challenges in young adults would accelerate the timeline for progressing a vaccine to achieve emergency use authorization and ultimately licensure for use in segments of the population suffering high mortality burden (elderly, diabetics, etc.), compared to the performance of large-scale randomized, controlled field trials of efficacy in the high risk target population, the Advisory Group was again split with 9 votes for challenge studies, 9 votes for field trials and one abstention?

---

## 1. Preamble

The COVID-19 Public Health Emergency of International Concern (PHEIC) that is presently traversing the planet as a global pandemic, has already taken an enormous toll of cases and fatalities in high-income countries in North America, South America, Europe and East Asia, despite their sophisticated healthcare infrastructures, intensive care units and pulmonary intensive care capability. And COVID-19 is now invading sub-Saharan Africa, where many regions have few, if any, intensive care beds and pulmonary care support is scarcely available, if at all. Medical and public health authorities worldwide agree on the critical importance of developing vaccines and other interventions to prevent COVID-19 disease for all the world's populations. There is a similar consensus to identify drugs and immunotherapies to curtail the progression to severe pulmonary disease and to lower case fatality. Many therapies are being developed and some are undergoing intense evaluation in clinical trials.

Over 200 SARS-CoV-2 vaccine candidates are in some stage of preclinical development and at least 10 have already entered clinical trials, with a few progressing to Phase 2 trials at the time of this report.<sup>1</sup> Many of these vaccines intended to prevent COVID-19 disease are based on strategies to induce immune responses, including engendering neutralizing antibodies, directed against the spike protein of SARS-CoV-2 (including stabilized pre-fusion forms of the spike) or the spike's receptor binding domain. There is a broad global consensus that innovative ways must be devised to accelerate the development of promising vaccine candidates including by shortening the time required to estimate their efficacy.

Convincing evidence of a vaccine's efficacy, along with data that document the vaccine's safety and immunogenicity, finalization of the vaccine's formulation and a practical immunization schedule, as well as a suitable large-scale manufacturing establishment capable of producing large numbers of doses, would underpin broad deployment of that vaccine. A precedent for achieving this is the pre-license use of *Ebola Zaire* live vector [rVSVΔG-ZEBOV-GP] Ebola vaccine that was used as an investigational vaccine under a monitored emergency use program to help control an Ebola outbreak in southeast Guinea in 2016,<sup>2</sup> and then as a Monitored Emergency Use of Unregistered and Investigational Interventions (MEURI) in the Democratic Republic of the Congo in 2018.<sup>3</sup> This Ebola live vector vaccine was licensed in 2019 as Ervebo™, Merck Vaccines, by the FDA and the EMA.<sup>4,5</sup> The US FDA and the European Union EMA have agreed to try and coordinate their efforts to accelerate regulatory approvals for Emergency Use of specific COVID-19 vaccines if the supporting data so warrant.

## 2. WHO's activities to accelerate COVID-19 vaccine development and clinical testing

### 2.1. A multi-center, multi-vaccine randomized, placebo-controlled trial

The World Health Organization is playing a key role in assisting the development of tools to accelerate assessments of the efficacy of candidate vaccines to prevent COVID-19 disease. One tool is a large multi-site international placebo-controlled field trial to assess vaccine efficacy in high-risk adults, including healthcare workers, that is designed to achieve rapid and scientifically rigorous evaluation of multiple vaccines. (<https://www.who.int/publications-detail/an-international-randomised-trial-of-candidate-vaccines-against-covid-19>). In this trial, enrollment will ensue under the supervision of investigators at many clinical trial sites in low- and middle-income countries, as well as high-income countries, in both the Northern and Southern hemispheres. In this way, momentum in generating efficacy data will be

---

maintained, even if SARS-CoV-2 is found to exhibit influenza-like seasonality, with peak months of transmission being reversed between the Northern and Southern hemispheres.

## 2.2. Assessing a possible role for experimental challenge studies

Recognizing the helpful role that experimental challenge studies in healthy adult volunteers have played (and are still playing) in the development of other vaccines,<sup>6-21</sup> some have advocated a role for such studies with virulent SARS-CoV-2.<sup>22-25</sup> However, several factors collectively warrant that special caution must be taken in working with SARS-CoV-2. These factors include:

- The severity of COVID-19 disease as evidenced by its high case fatality risk in certain sub-populations (elderly, diabetics, hosts with pre-existing pulmonary and cardiac disease);
- Severe disease requiring ventilator support and deaths (albeit uncommon) also occur in young adults, although the risk factors for these outcomes in this age group are yet to be characterized);
- The increasing recognition of severe thromboembolic events in young adults;
- The high transmissibility of SARS-CoV-2 from person-to-person directly by respiratory droplets and at further distances by airborne droplet nuclei;
- The virus' ability to remain viable on some fomites for several hours.<sup>26</sup>

Moreover, this is a new disease that health care workers have dealt with clinically for only six months. During that time the breadth and scope of the pathology in humans that this virus can wreak has been recognized incrementally. Children, believed at the beginning of the pandemic to be virtually spared from COVID-19 disease, are now being seen among hospitalized cases that manifest a new pediatric inflammatory multisystem syndrome (MIS-C). Thus, with each passing month more is being learned about the acute presentations and forms of morbidity that SARS-CoV-2 infection can elicit. Understandably, among experienced challenge model investigators the topic of undertaking challenge studies with fully virulent SARS-CoV-2 has generated discussion about whether the conditions can be assured to perform challenge studies safely and what the priority goals should be for such studies.

Taking into account the reasons for caution cited above, if conditions were deemed suitable to undertake development of a closely monitored SARS-CoV-2 challenge model in healthy young adult volunteers, important information could accrue such as:

- To determine whether an initial challenge infection confers significant protection against a subsequent challenge with the homologous virus and perhaps in subsequent studies whether infection-derived protection, if it occurs, is virus-clade specific;
- To identify immunologic correlates of protection against clinical illness and against shedding of virus that might accompany recovery from a prior experimental challenge with SARS-CoV-2.
- To allow studies of different COVID-19 vaccine candidates to determine if they protect;
- To contribute to the development of correlates of protection against clinical illness and against shedding of virus in vaccinated volunteers;
- To compare the protection afforded by different types of vaccines (e.g., mRNA, DNA, protein, viral vectored, live attenuated, inactivated whole virus, etc.).

---

### **2.2.1. Could a volunteer challenge model accelerate the time required to generate data to support public health decisions for vaccine deployment relative to the time required without volunteer challenge studies?**

One particular focus of discourse has been whether volunteer challenge studies can markedly accelerate proof of efficacy of a candidate COVID-19 vaccine to the point where data could support the deployment of that vaccine to achieve public health goals.

#### **2.2.1.1. The classical testing paradigm for endemic or common epidemic infectious diseases.**

For non-PHEIC [Public Health Emergency of International Concern] infectious diseases that are typically less lethal, often endemic infections, and for which no licensed vaccines currently exist, the classical paradigm is to evaluate vaccine candidates through a series of clinical trials referred to as Phase 1, Phase 2 and Phase 3.<sup>27,28</sup> First-in-human Phase 1 trials primarily focus on safety and often commence in adults even if the ultimate target may be infants and toddlers. Phase 1 trials also provide preliminary assessments of the immunogenicity of ascending dose levels of vaccine and may compare subjects who receive one dose with those who receive two or more vaccine doses, depending on the immunization schedule. Phase 1 studies involve dozens or scores of subjects but may include more. Phase 1 studies sometimes include controls who are randomly allocated to receive placebo or no vaccine candidate. They are never statistically powered to detect uncommon adverse reactions, some of which may be severe. Data indicating clinical acceptability and immunogenicity in Phase 1 lead to Phase 2 trials that often compare several different immunization schedules or different formulations of the vaccine and may be carried out in several different age groups, often in an age-descending fashion. Ideally, randomized, placebo-controlled, double-blind Phase 2 trials utilize a formulation that will be amenable to large-scale manufacture and a presentation suitable for practical public health use in the target populations. Phase 2 studies can enroll hundreds or several thousand participants and are powered to detect a certain difference in the frequency of adverse events among vaccine versus placebo recipients; the more common the adverse event, the greater is the statistical power to incriminate it. Immunogenicity and safety results of Phase 2 trials determine whether a vaccine progresses to large-scale Phase 3 trials that are designed to establish whether participants who received the vaccine have a substantially lower incidence of (usually laboratory-confirmed) cases of the target infectious disease compared to randomly allocated controls who received placebo or an irrelevant vaccine. Phase 3 also assesses the safety of the vaccine in large numbers of vaccinated persons versus controls, usually through passive surveillance. Assessments of clinical acceptability, reactogenicity and immunogenicity also derive from nested studies in subsets of participants who undergo active follow-up for one or more weeks after each dose. Depending on the incidence of the target infectious disease, Phase 3 studies may involve tens of thousands, scores of thousands, or even hundreds of thousands of participants. The historically strong focus on documenting the safety of a vaccine, as well as its efficacy, in large Phase 3 trials remains as important as ever with the emergence of vaccine hesitancy in a segment of the population that now permeates societies in LMIC as well as high-income countries.<sup>29</sup>

Phase 3 trials are performed with a formulation of vaccine that will be identical to that manufactured with high consistency at large-scale for future widespread implementation. Either nested within the Phase 3 trial or performed as a separate safety/ immunogenicity trial, the manufacturer must document in clinical trials the consistency of manufacture of at least three separate lots of the vaccine. Generation of convincing evidence of safety, immunogenicity, and efficacy along with documentation of lot-to-lot consistency of manufacture provides the manufacturer of a vaccine the data needed to submit a Biologics

---

License Application to a National (or supranational) Regulatory Agency. Typically, this “classic” paradigm takes approximately a decade to complete and is extremely costly.

### **2.2.1.2. A new paradigm for vaccine testing needed for new PHEIC emerging infections**

The emergence of PHEIC infectious diseases such as H1N1 influenza (2009), Ebola in West Africa (2014) and Kivu Province of the Democratic Republic of the Congo (2018), Zika (2015-2016), and the current COVID-19 pandemic creates situations where the usual paradigm for the design/construction, pre-clinical testing and clinical testing of potential vaccines to prevent these infectious diseases must be greatly accelerated. Obviously, whether accelerated randomized controlled field trials can be accelerated depends on multiple factors including, the availability of vaccine candidates, populations where the disease is still occurring in adequate numbers, identification of high risk subpopulations, an adequate supply of the doses needed and in a final or near final formulation, and preliminary evidence of safety and immunogenicity of vaccine administered in a relevant immunization schedule. For COVID-19, the global research enterprise mobilized impressively such that for an infection that only emerged in late 2019, several vaccines were already in Phase 1 clinical trials by March 2020 and by May 2020, ten vaccine candidates were in Phase 1 or 2 clinical trials. Attention is now focusing on how quickly efficacy data on some of these COVID-19 candidate vaccines can be obtained.

The paradigm for a highly accelerated pace of testing a candidate PHEIC vaccine in clinical trials that showed efficacy in an accelerated manner and led to both pre-licensure emergency use after efficacy was shown and ultimately to licensure was set during the West African Ebola epidemic with the VSV-vectored Ebola vaccine expressing Ebolavirus Zaire glycoprotein (rVSVΔG-ZEBOV-GP) (Ervebo, Merck & Co., Inc.).<sup>4</sup> For Ebola, an international consortium of investigators led by WHO coordinated the accelerated development of what is now a licensed vaccine from a clinical experience of a single vaccinated subject (August 2014) to documentation by June 2015 of that vaccine’s efficacy in a cluster-randomized trial in a target population where contacts (and contacts of contacts) of cases received vaccine either immediately or after a delay of 21 days.<sup>30</sup> The timetable for this historic effort is summarized below.

- For Ebola, the time required to go from virtually no human clinical experience with any vaccine candidate (mid-August 2014) to convincing evidence of efficacy (June 2015) was a period of 10 months. Prior to August 2014 the rVSVΔG-ZEBOV-GP vaccine had been evaluated in but only been given to a single human being.<sup>31</sup>
- The time from analysis of the Phase 1 and 2 trial results that established the dose level and evidence of immunogenicity of rVSVΔG-ZEBOV-GP vaccine (circa January 2015),<sup>32,33</sup> until initiation of the field trial of efficacy of the vaccine in Guinea (March 2015) was two months.<sup>30</sup> This included setting up the trial site in Guinea, training clinical, field and laboratory staff in Good Clinical Practices,<sup>34</sup> arranging monitoring for the trial,<sup>34</sup> and installing an on-site data management system.<sup>35</sup>
- The time period until the randomized controlled field trial provided clear evidence of efficacy was four months (March through June 2015).<sup>30</sup>
- It is important to appreciate that this field trial of efficacy of rVSVΔG-ZEBOV-GP was performed in Guinea, a low-income country without a research infrastructure or clinical investigators and field staff experienced in the tenets of Good Clinical Practice (GCP).<sup>34</sup> In contrast, COVID-19 vaccines can be assessed in many high-income country sites with experienced clinical and laboratory research staffs, as well as in LMIC.
- In addition to the “Ebola ça Suffit” trial’s legacy of experienced clinical investigators in West Africa,<sup>34</sup> there now exist multiple sites throughout sub-Saharan Africa with

---

experienced clinical trial teams that could participate in a multi-center field efficacy trial to assess the efficacy of COVID-19 vaccines relevant to conditions in that geographic region of the world.

The need for flexible and responsive vaccine trial designs to be used to assess efficacy in public health emergencies, the key information that must be generated and the types of field trial designs best suited to yield the most useful information have been reviewed.<sup>36</sup> Some of the points made in this review based on WHO experience include:

- The field trial population should be representative of the target population defined in the vaccine Target Product Profile.<sup>36</sup> For a COVID-19 vaccine intending to protect critical high-risk sub-populations, this would include healthcare workers, emergency medical technicians, police and firefighters. If a public health goal for use of the vaccine is to reduce the number of COVID-19 deaths overall, the targets would have to include senior adults, adults of all ages with known risk factors (diabetes, cardiovascular disease, chronic pulmonary disease, etc.) and senior citizens in long-term care facilities. Workers in food production industries constitute another prominent target for vaccine use. Finally, if the vaccine is intended to interrupt transmission of SARS-CoV-2 within the general population, it will be appropriate to target young adults and children, in particular, school age children.
- Randomized trials are the study design of choice for evaluating vaccines against PHEIC infections, and exceptions to use of randomized designs should “occur only under very exceptional circumstances following a robust risk-benefit analysis”.<sup>36</sup>
- “More than one vaccine candidate may be suitable for efficacy testing, in which case multi-arm trials sharing a single placebo or comparator vaccine arm are expected to require fewer resources than multiple, independent two-arm trials.”<sup>36</sup>

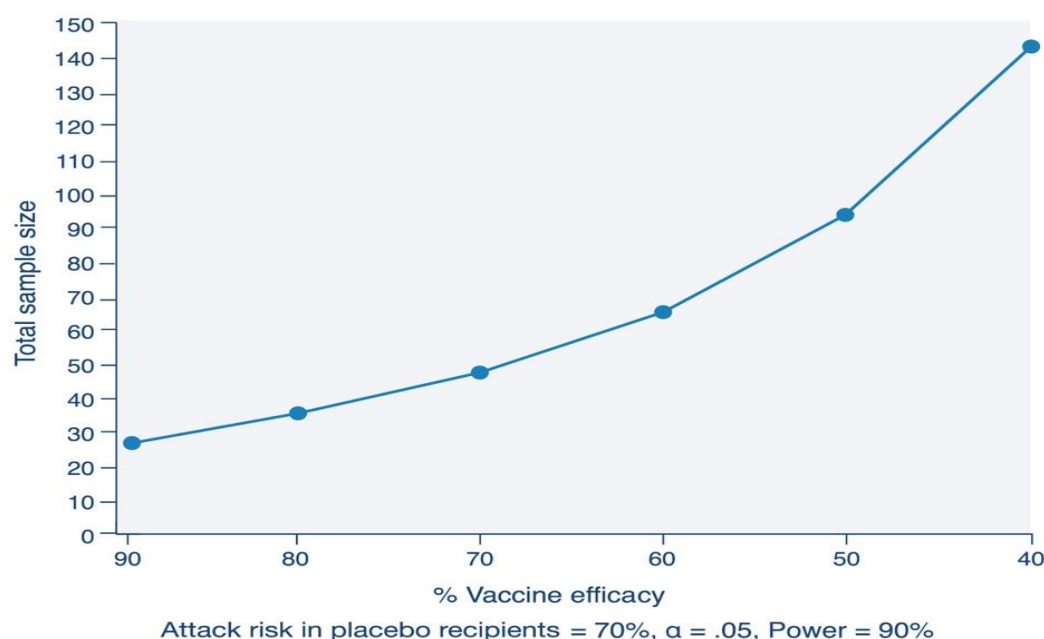
### **2.2.1.3. What would be a realistic timetable for testing the efficacy of candidate COVID-19 vaccines in a volunteer challenge model?**

Heretofore, it has not been possible to estimate the time that it would take to test the efficacy of a candidate COVID-19 vaccine in a volunteer model because early advocates of a volunteer model were not experienced in the details of establishing a challenge model, particularly one with the complexities posed by COVID-19. Accordingly, the WHO Advisory Group, which includes multiple individuals who have considerable experience in establishing and performing volunteer challenge models of various viral, bacterial and parasitic infections, undertook to delineate the steps that will be necessary to establish a closely monitored SARS-CoV-2 challenge model for healthy adult volunteers, while taking into account the unusual constraints of working with this highly infectious agent that is potentially capable of causing severe illness.

Since the time interval from when Phase 1 and 2 safety/immunogenicity trials identified the dose level of rVSVΔG-ZEBOV-GP to be used in a field trial of efficacy until initiation of the field trial was only 2 months, and the time to prepare the field site, perform the field trial of the rVSVΔG-ZEBOV-GP vaccine in Guinea, and analyze the results was only four months, arguably, the volunteer challenge model should be compared against these benchmarks. Thus, the time required to establish the volunteer model, including to identify the optimal challenge strain in dose-escalation studies and to formalize the model to the point where a vaccine candidate could be tested, would be compared to the two months required to set up the field trial site in Guinea. Similarly, the time to enroll a sufficient number of vaccinated volunteers and placebo controls in a challenge study and to reach evidence of efficacy would be compared against the four months that it took from the initiation of the Guinea field trial until analyzed data demonstrated efficacy.

If a vaccine candidate were to be tested using the volunteer model with assumptions of a 70% attack risk of laboratory-confirmed COVID-19 among the placebo controls, a vaccine efficacy of at least 65%, 95% confidence (i.e., 2-tailed alpha error of 0.05), continuity correction to the normal approximation of the discrete distribution, 90% power to detect a statistically significant difference, and a 1:1 ratio of randomly allocated vaccine to placebo recipients, 28 analyzable volunteers would be required in each trial arm. A smaller number of volunteers would be required if one assumes the vaccine to be even more efficacious while, *vice versa*, if one wants to be powered to detect an efficacy of less than 70%, the sample sizes need to be increased as graphically depicted in Figure 1 below.

**Figure 1. Estimated total sample size for a two-sample proportions test**



Note - To generate the samples size shown in Figure 1 the following Stata command was used **power twoprop .7 (0.42 0.35 0.28 0.21 0.14 0.07), p (.9) graph continuity** and then used Stata's graph editor to replace attack risk on the vaccine arm (0.07, 0.14, 0.21, 0.28, 0.35, 0.42) with the corresponding efficacies ( on the X-axis).

Given the importance of not discarding a vaccine candidate which could be of value, the Advisory Group does not recommend estimating sample sizes with less than 90% power. Thus, the Advisory Group would be loath to recommend a trial with 80% power, which would translate to an appropriately efficacious vaccine candidate being discarded in an average of 1 in 5 challenge SARS-CoV-2 vaccine trials.

The challenge studies summarized above would represent Stage 2 type of studies (as defined subsequently in this document) that could be performed once the model has been established in Stage 1 studies. Another scenario where Stage 2 challenge studies might be particularly valuable is if the transmission of SARS-CoV-2 is drastically reduced globally by public health measures and herd immunity to the point where standard field trials would be infeasible, as happened with the Zika PHEIC.<sup>37</sup>

Whatever the results of the comparison, the volunteer model would be documenting efficacy in healthy young adults. Efficacy results could not per se be extrapolated to know how that same vaccine would perform in elderly persons and in adults with risk factors (diabetes, chronic pulmonary disease, etc.). Parenteral vaccines against influenza, another viral

---

infection spread by the respiratory route, that work well in protecting young adults, are significantly less immunogenic and less effective in older seniors and require adjuvants or higher content of hemagglutinin to enhance immunogenicity in older subjects even when the hemagglutinin in the vaccine closely matches that of circulating viruses.<sup>38,39</sup> Use of adjuvants or administration of higher doses of vaccine may similarly be needed with some COVID-19 vaccines to immunize the elderly. Immunosenescence must also be taken into account in attempting to use serological non-inferiority to compare immune responses observed in protected young adult volunteers to try and bridge by serological responses to use of the same vaccine in older and high-risk adults in the dose level and immunization schedule that was protective in young adults.

### **2.2.2. Contributions that a COVID-19 challenge model could make to eventual control of COVID-19 disease even if the model would not accelerate the time required to achieve authorized emergency use or licensure for a candidate vaccine.**

Even if an experimental challenge model of SARS-CoV-2 does not shorten the time to obtain evidence of efficacy of a specific COVID-19 vaccine that might or might not be relevant for public health decisions about use of the vaccine, such a volunteer model could still yield very important scientific insights that are not easily obtained through randomized, placebo-controlled vaccine field trials or through observational studies of vaccines that are implemented post-licensure.

These include controlled studies of whether a prior experimental clinical COVID-19 infection confers significant protection against clinical illness and shedding of virus in the “veterans” upon re-challenge ~2 months later versus primary challenge infection in a naïve control group. By extending the challenge time, this could help to estimate the degree and duration of protection, as has occasionally been done with other challenge models.<sup>40,41</sup>

The optimal design of such a study would be experimental, i.e., to randomize volunteers to be infected or not and then challenge all these study participants. Provided the sample size is large enough to ensure that randomization balances the volunteers with respect to outcome risks, such a design would enable the investigator to estimate directly the degree to which being infected with SARS-CoV-2 induces protection against SARS-CoV-2 reinfection and against COVID-19 clinical illness.

If resources for such a trial are not available or if there exist time constraints, one can compromise on the internal validity of the findings and simply challenge the veterans from dose-escalation studies and a control group consisting of naïve uninfected volunteers (who resemble the veteran volunteers when they participated in the dose-escalation studies) and compare their outcome risks.

The attack risk and virological response in the re-challenged volunteers is compared to their response upon their initial challenge as well as compared to the naïve control group. If the level of clinical and virologic protection is high, such pragmatic studies can yield highly useful information on whether natural infection induces protective immunity. There are multiple examples of such challenge/re-challenge studies providing helpful information.<sup>40,42-47</sup> Certain pathogens cause experimental clinical infections that are highly protective,<sup>40,42-47</sup> whereas other pathogens elicit less potent or shorter-lived protection.<sup>41,48</sup> This quasi-experimental study design makes such studies less suitable to estimate partially protective immunity.

If large enough, such studies, whether experimental (high quality evidence) or quasi-experimental (moderate quality evidence) can also be useful in identifying potential correlates of protection, for example, to help assess whether neutralizing antibodies or IgG anti-spike receptor binding domain (RBD) antibodies correlate with protection from being

---

infected with SARS-CoV-2 or falling ill with COVID-19. When natural infection induces a close to complete protection, even a non-randomized design may yield important information.

Such studies would be of considerable value to public health strategists and epidemiologists who are now attempting to ascertain whether mild SARS-CoV-2 infections elicit protective immunity and the relation of the immunity to the type of antibodies being measured by different simple lateral flow immunoassay serological tests, as well as by high throughput quantitative ELISAs that are being used in seroepidemiological studies. Furthermore, a volunteer challenge model would allow the kinetics of the viral infection and of the immune response, including the early innate response, to be characterized.

If one or more vaccines were already licensed and deployed when another new vaccine reaches the point needing evidence of efficacy, it may be considered unethical to perform standard placebo-controlled clinical trials to determine the efficacy of additional vaccines that might have advantages over the deployed vaccine. If the new vaccine shares an immune response that is recognized as a correlate of protection for the licensed vaccine (e.g., antibody that binds to the RBD of the S1 plus exhibits neutralizing activity), serological non-inferiority versus the licensed vaccine may be a path to licensure. Nevertheless, a COVID-19 challenge model may be the only way to obtain efficacy data on the new vaccine expeditiously. The efficacy data would be limited to young adults in a model, but it would demonstrate biological proof-of-principle.

### **2.2.3. Specific treatment for volunteers who would participate in a COVID-19 challenge model.**

The pace of generating evidence to confirm or refute the efficacy of certain anti-COVID-19 therapies (e.g., remdesivir, plasma and immunoglobulins from recovered COVID-19 patients, etc.) from well-conducted, randomized, controlled clinical trials is extremely rapid and was monitored by the Advisory Group during the weeks of its deliberations.<sup>49</sup> On April 29, 2020, preliminary results were announced that the anti-viral drug remdesivir in a randomized, placebo-controlled, double blinded, multi-center international trial supported by the U.S. National Institutes of Health demonstrated that remdesivir-treated hospitalized patients with confirmed COVID-19 disease had their hospitalization duration shortened to 11 days compared to 15 days in placebo recipients. The difference in the occurrence of this primary outcome was statistically significant. In the midst of a COVID-19 epidemic that is overwhelming the health care system such that there is a shortage of ICU beds and ventilators, shortening the length of hospitalization by four days can free up many ICU beds and increase the capacity of a teetering health care system to weather the storm through the peak of the epidemic. Thus, on May 1, 2020, the US FDA issued an Emergency Use Authorization (EUA) for use of remdesivir in hospitalized cases of COVID-10 disease. The published results of the remdesivir clinical trial also demonstrated a reduction in mortality but with the limited numbers of cases analyzed the difference was not statistically significant.<sup>50</sup>

Relevant to providing information to advise the establishment of an experimental challenge model of SARS-CoV-2 infection in healthy adult volunteers, it is expected that by July 2020 data may become available to affirm or refute the efficacy of several other new treatments in interrupting the progression of COVID-19 infection from mild or moderate illness to severe and fatal disease. Should one of these interventions (or several in combination) prove to be highly efficacious in stopping the progression from mild/moderate illness to severe COVID-19 disease, this would increase the feasibility of undertaking volunteer challenge models with wild type virus in young adults in a low-risk, narrow age group (e.g., 18-25 years of age).

---

Such a reliable “rescue treatment” would then bring a COVID-19 model closer, by comparison, to several other viral disease models. However, the ongoing therapeutic trials are not large enough and do not include a sufficient number of young individuals to determine, with adequate statistical power, if the drugs are sufficiently effective in preventing serious adverse events (including death), especially in young adults, in which such events are rare. A COVID-19 model will still have to grapple with the high transmissibility of the virulent agent and its high biocontainment needs for some steps in the clinical procedures that would be constraining. This will be particularly true during the step of instilling the infective inoculum into the upper respiratory tract of volunteers. Although constraining, the Advisory Group came up with practical solutions to address high the transmissibility of SARS-CoV-2 in a volunteer challenge setting.

### **3. Why now for an advisory group to consider the feasibility, potential value and limitations of establishing a closely monitored challenge model of experimental COVID-19 infection and illness in healthy young adult volunteers?**

The World Health Organization considered April 2020 to be a propitious time to convene a multi-disciplinary group of experts from across the world to discuss from different perspectives the concept of volunteer challenge studies with SARS-CoV-2. The Advisory Group assembled included experts with experience in:

- The design and performance of human volunteer challenge models;
- SARS-CoV-2 virology;
- Measurement of human immune responses to SARS-CoV-2 and to other viruses;
- Clinical management of COVID-19 clinical disease in different global settings;
- Regulatory considerations associated with testing and emergency use of vaccines pre-licensure and with larger-scale deployment post-licensure;
- The GMP manufacture of virulent viruses under BSL-3 containment.

Collectively, the Advisory Group, whose members are listed in **Appendix A**, was tasked to consider the feasibility, utility, realistic timelines and (in a few instances) approximate costs for the key steps to be taken to establish a closely monitored experimental challenge model in healthy adult volunteers who would be administered attenuated or fully virulent SARS-CoV-2. The Advisory Group was divided into Subgroups (and two of the Subgroups were further divided into two Teams each) for the members to address in detail specific procedures to be codified and logistical obstacles to be overcome to perform such challenge studies. The Advisory Group proposed potential practical solutions to overcome or bypass the hurdles that they identified. The Advisory Group took into account not only the safety of the volunteers but also that of the clinical research staff and support staff, and the safety of household members and other close contacts of the volunteers after their discharge.

#### **3.1. Terms of Reference**

The Advisory Group was asked to discuss specific issues to be considered in establishing a closely monitored volunteer challenge model of attenuated or fully virulent SARS-CoV-2 virus. Examples of the issues that were addressed include:

- What level of physical containment is required to minimize the risk of inadvertent escape and transmission of this highly virulent pathogen?

- If desirable, can local health authorities establish legal Quarantine of the study site facility (e.g., a physical containment Research Isolation Ward)? What is the legal basis and method for establishing Quarantine (Compulsory Isolation of the challenged volunteers) in the jurisdiction where the challenge study will take place?
- Can the baseline health status of each subject be confidently documented prior to challenge to assure that they have no known predisposing risk factors associated with progression to severe COVID-19 illness?
- Can the follow-up and post-discharge monitoring of every subject be assured?
- What is the risk to household contacts and the larger community if the pathogen were inadvertently to escape containment and be transmissible to innocent bystanders?
- How will the challenge virus be administered to the volunteers to assure delivery only to the upper respiratory tract (e.g., into the nostrils by pipette, etc.) and avoid virus reaching the lower respiratory tract?

### 3.2. Logistics, timelines and costs

(examples of some specific tasks that the Advisory Group discussed)

- Arranging manufacture of a GMP lot of virulent wild type SARS-CoV-2.
  - What SARS-CoV-2 strains (e.g., what clades and sub-clades) should be selected?
  - Where would the GMP batches of challenge viruses be prepared under BSL-3 containment?
  - Would there be a frozen liquid-in-vial formulation or a lyophilized formulation for challenge studies?
  - Where would the central repository be located for storing the vials of each GMP batch of challenge virus?
  - What would be the conditions of storage of the challenge virus vials at clinical study sites?
  - Would there be vials prepared containing the different inoculum levels to be used in a stepwise dose- escalation to minimize handling in the clinical situation?
- What clinical attack risk should the model aim to elicit and what type of clinical illness (signs and symptoms) is desired?
  - Target clinical attack risk.
  - Description of the type of clinical illness to be expected.
  - What severity of clinical illness and frequency of occurrence would be considered unacceptable?
- What are the key clinical endpoints?
- Timelines for a stepwise dose-escalation study with either fully virulent or attenuated SARS-CoV-2 virus.
  - Assuming that three different dose levels may have to be tested until a satisfactory attack risk of non-severe clinical illness is achieved, what is the timeline for performing such a dose-escalation study?
    - Consider the expected range and median incubation period from inoculation to onset of clinical illness.
    - Take into account the expected duration of clinical illness.
    - Take into account the expected range of duration of shedding.
    - What will be the clinical criteria for discharge?
    - What will be the virus shedding criteria for discharge (how many days of negative RT-PCR)?

- How much time should be set aside to prepare a summary for the Data Safety Monitoring Committee and for them to convene, review the data and provide a yes/no for proceeding to the next higher dose of virus?
- How much time is needed for disinfection and refurbishment of the Research Isolation Ward between volunteer groups at different dose levels?

### 3.3. Some uses of a model, if established

The Advisory Group will be tasked to identify some specific objectives and uses of challenge trials and to prioritize them. Examples, among others, could include:

- Does an initial experimental SARS-CoV-2 infection (due either to a fully virulent or to an attenuated virus) elicit significant protection against clinical illness following subsequent re-challenge with the same virus approximately 6-8 weeks later?
- Is shedding of SARS-CoV-2 significantly diminished following re-challenge with the SARS-CoV-2?
- If clinical protection upon re-challenge is observed, does it correlate with serum IgG or mucosal IgA antibody responses to the receptor binding domain of SARS-CoV-2 spike protein or with neutralizing antibody to the whole virus? Or with CD8 or CD4 cellular immune responses to SARS-CoV-2 antigens? Note that one of the unique opportunities offered by closely monitored experimental challenge studies in healthy adult humans is to identify immunologic correlates of protection that are not easily detectable in large-scale field trials. The uniqueness stems from the fact that not only can extensive and detailed immunologic responses be measured, but these are known at baseline and immediately prior to challenge, as well as following challenge; and these data are available for all re-challenged volunteers and for all controls.
- Should one or more candidate vaccines be tested in an experimental challenge model that utilizes either virulent SARS-CoV-2 or a partially attenuated strain as the challenge organism? If a fully virulent strain is used, protection against clinical endpoints can be assessed, as well as efficacy in diminishing shedding of virus. If an attenuated strain is used, only efficacy against shedding may be measurable.
- The challenge model might also be of value to assess therapeutic approaches, particularly with respect to curtailing the duration and quantity of shedding of SARS-CoV-2 detected by RT-PCR and by virus culture.
- The Advisory Group members cautioned that expectations should be tempered with respect to what aspects of COVID-19 disease the model can be used to address, since it is only a contrived model in a narrow age group.

### 3.4. Other related issues

The Advisory Group was instructed not to discuss in depth ethical issues related to challenges with fully virulent SARS-CoV-2, as this is being addressed by another Working Group of WHO that is considering many COVID-19 ethical issues.

### 3.5. Deliverables

- 1) The Advisory Group was asked to provide a report that addresses the points raised above, as examples, as well as additional issues and hurdles that were identified that would have to be overcome.
- 2) The Advisory Group will be expected to make recommendation on the feasibility of such a model and, if deemed feasible and appropriate, how the model should be used.

## 4. Introduction to the task

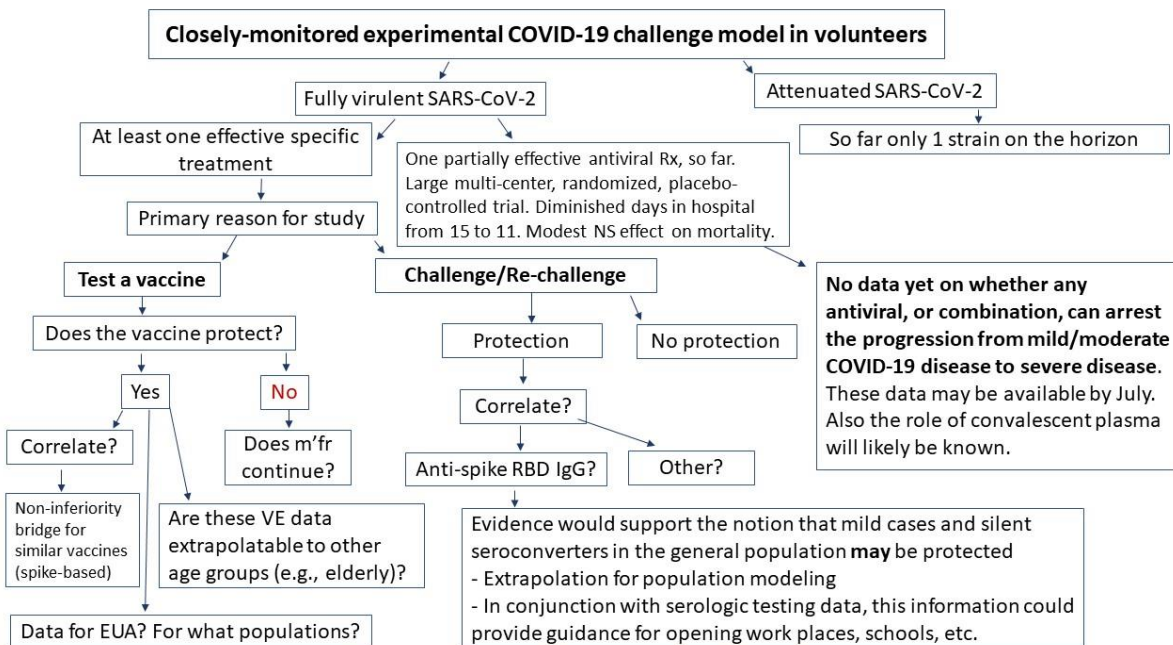


Figure 2 provides an overview of some of the strategic steps and decision trees that must be grappled with in considering the establishment of a closely monitored experimental challenge model of SARS-CoV-2 virus infection and illness in volunteers. The first would be to select whether to begin with a putatively attenuated strain of SARS-CoV-2, such as a live attenuated vaccine candidate strain, or whether to utilize fully virulent strains of SARS-CoV-2.

In practical terms this was a moot point when first discussed by the Advisory Group in April 2020, as the only attenuated vaccine strain of which the Advisory Group members were aware was an attenuating approach being pursued by Codagenix and the Serum Institute of India.

However, the Advisory Group was not aware of such a strain having progressed to the point where it could be administered in clinical trials. If such a strain were to exist and if it infected volunteers and was shed for several days (and was detectable in tissue culture) in the presence or absence of clinical signs and symptoms, a re-challenge study could be designed to determine whether subsequent exposure of the volunteers to the same attenuated strain ~6 weeks later would be followed by lower level of shedding of virus compared to a control group of naïve volunteers receiving the strain for the first time.

This pragmatic study design of comparing the “success risk” of establishing SARS-CoV-2 infection between so called veterans (who have participated in an earlier challenge study) and naïve volunteers (new recruits) may be able to reveal a very substantial or complete protection. However, for more moderate levels of protection an experimental design would be required in which an initial group of volunteers are randomized to receive or not receive an initial infection. At some period of time thereafter (e.g., 4-12 weeks) all volunteers would then be challenged with SARS-CoV-2. The latter design requires substantially more resources but could provide stronger evidence on the degree to which an initial infection with

---

SARS-CoV-2 provides protection against reinfection with the virus and, if so, against COVID-19.

In the absence of an attenuated SARS-CoV-2 virus being available for use, discussion thereafter focused on the issues associated with challenge of volunteers with a virulent SARS-CoV-2 virus. Some Advisory Group members were concerned that even as the discussions would go forth, clinical studies should not begin until there was a proven treatment shown to be efficacious in reliably arresting the progression of COVID-19 illness from a mild/moderate status to severe, complicated, potentially fatal illness among participants with the characteristics of those to be included in a vaccine challenge trial.

While that “gate” remained in the background in the discussions, the Advisory Group agreed that they would follow the progress of several therapeutic regimens that were in controlled clinical trials. One that showed some degree of efficacy in hospitalized patients with severe COVID-19 disease was the antiviral drug remdesivir which significantly reduced the days of hospitalization from 15 days to 11 days and reduced the risk of dying by ~30% (95%CI -4% to 53%) ( $p=0.056$ ).<sup>50</sup> In communities with surging epidemics of COVID-19 disease and a shortage of intensive care beds and ventilators, the ability to discharge patients after an average of 11 days rather than after 15 days frees up many hospital beds.

Although the effect on time till recovery seemed to be better among younger patients, remdesivir, with the most likely point estimate of an effect on case fatality of only 30%, does not yet offer an obvious “rescue” treatment should a challenged volunteer progress towards severe clinical illness. For that, remdesivir (or other drugs now in the pipeline to be tested), would need to be evaluated in therapeutic trials in volunteers with an age range similar to that of volunteer studies (see below) and in early clinical stages of illness. The efficacy estimates from such trials would better inform whether the drugs in question could indeed become part of early treatment or “rescue” treatment in a challenge study. The Advisory Group agreed that within several months there may appear treatments (e.g., remdesivir started earlier in the course of illness, immunoglobulins or plasma from convalescent patient donors, specific monoclonal antibodies, etc.) that could credibly serve as treatments to benefit volunteers substantially. In the meantime, there was a consensus to address the specific main tasks required to be completed to initiate a clinical trial, while simultaneously monitoring sources of information (WHO, NIH, etc.) for progress in identifying potential “rescue treatments” that may emerge from ongoing randomized controlled clinical trials.

The Advisory Group next discussed two main uses for a SARS-CoV-2 challenge model once the initial dose/escalation was completed and an acceptable, predictable challenge dose was identified that could be used to answer specific questions.

One use discussed was re-challenge of a group of volunteers who shed SARS-CoV-2 and developed mild illness on an initial challenge ~6 weeks earlier, along with a new group of naïve control volunteers. Such studies could explore whether the immune responses elicited in the re-challenged “veteran” volunteers may be reflective of protection, as evidenced by diminished shedding of SARS-CoV-2 and prevention of clinical COVID-19 illness upon re-challenge.

For considerations on the design of such studies (experimental versus pragmatic/ quasi-experimental), have been discussed earlier in this document. If substantial protection was observed it would be possible to look for an immune response (e.g., IgG anti-spike RBD or neutralizing antibodies) that could correlate with protection. Many serological tests that are used in population-based surveys to estimate from seroprevalence the proportion of the population that has already encountered the SARS-CoV-2 virus utilize assays that measure IgG antibody to the SARS-CoV-2 spike or to the RBD of the spike protein. Many COVID-19 vaccine candidates are based on stimulating immune responses to this viral surface protein by which the virus attaches to the ACE-1 receptor on human respiratory tract epithelial cells

---

and cells of other organs; and anti-spike RBD IgG exhibits virus neutralizing activity. Public health officials would benefit from seeing more direct proof in humans that infection-derived anti-spike RBD antibody is a correlate of protection against both COVID-19 disease and viral shedding.

A challenge model could potentially provide such useful information that would inform this discussion, as well as to identify other immune responses (mucosal anti-spike RBD antibodies, CD8 or CD4 multifunctional T-cells, etc.) that may correlate with protection. This information could also be relevant for assessing certain COVID-19 vaccines based on full spike or spike RBD protein by comparing the magnitude, quality and longevity of the immune responses elicited by vaccine in young adults with the immune responses elicited in young adult volunteers challenged with SARS-CoV-2. Evidence of protection of vaccines following challenge with virulent SARS-CoV-2 virus could set the stage for looking for correlates of protection, as the serum and mucosal antibodies and cell-mediated immune response measurements will be available from pre- and post-vaccination and immediately pre- and post-challenge. This offers an opportunity to contribute to the development of correlates of vaccine-derived protection.

If the SARS-CoV-2 challenge model proves to be associated with clinical signs and symptoms but not with severe clinical illness, and if an initial re-challenge study versus controls shows indications of protection against both clinical illness and shedding, a follow-on study could assess the results of challenging volunteers who are screened to reveal a gradation of titers of neutralizing anti-SARS-CoV-2 antibodies and IgG anti-spike RBD titers to determine if these and other (e.g., CMI) naturally-acquired immune responses are associated with protection against the artificial challenge with SARS-CoV-2. Prior to challenge, the baseline immunologic measurements of antibodies and cell-mediated immunity would be quantified to explore possible correlates of protection.

The other main use of the model discussed, once established, would be to assess preliminarily the efficacy of several different COVID-19 vaccines based on somewhat different concepts. For example, several vaccines are based on eliciting immune responses to a stabilized pre-fusion form of the SARS-CoV-2 spike protein, whether encoded by mRNA, DNA, or one of several live vectors such as attenuated chimpanzee adenovirus or uncommon serotypes of human adenovirus.

For any specific vaccine tested, challenge with SARS-CoV-2 of a group of vaccinees and of a randomly allocated arm with control volunteers who received placebo would potentially allow an assessment of the vaccine in preventing clinical illness and of diminishing shedding of wild virus. If significant protection is observed against both clinical endpoints and against virus shedding, this information would substantially contribute to the development of efficacious SARS-CoV-2 vaccines by helping to elucidate how they function and with data generated under closely monitored experimental conditions.

## 4.1. Formation of Subgroups and Teams

To pursue its work-scope with appropriate concentration and mix of expertise, the members of the Advisory Group were divided into four Subgroups, of which two Subgroups were further divided into two Teams. Each Subgroup was assigned *Lead*. Thus, the Advisory Group pursued its work through the structure shown below.

---

**Advisory Group Chair:** Prof. Myron (Mike) M. Levine

**Subgroup on Clinical Trial Issues** – Prof. Anna Durbin (Lead)

**Details of Study Design Team** – Prof. Anna Durbin (Lead), Euzebius Jamrozik, Punnee Pitisuttithum, Robert Sauerwein, Halvor Sommerfelt, John J Treanor

**Infection Control Team** – Prof. Anna Durbin (Lead), Salim Abdullah, Yaseen Arabi, Vicente Estrada, Peter Kremsner, John Treanor.

**Subgroup on Challenge Virus Strain Issues** – Prof. Kanta Subbarao (Lead)

**Challenge Virus Strain Selection Team** – Prof. Kanta Subbarao (Lead), Zheng Li Shi, Sudhanshu Vrat

**Potential Manufacturers of a GMP Batch of Challenge Virus Team** – Prof. Kanta Subbarao (Lead), Delese Mimi Darko, Deborah King, Shobana Balasingam, Stanley Plotkin, John Treanor.

**Subgroup on Measurement of Immune Responses Pre- and Post-Challenge** – Prof. Stanley Plotkin (Lead), Rosanna Lagos, Kanta Subbarao, Robert Sauerwein.

**Subgroup on Detection of SARS-CoV-2 in Clinical Specimens Post-Challenge** – Prof. Zheng Li Shi (Lead), Kanta Subbarao, Sudhanshu Vrat.

Also present in the Working Group meetings were Observers from the Wellcome Trust, UK (Deborah King, Shobana Balasingam, Charlie Weller), the Bill & Melinda Gates Foundation (Anastazia Older Aguilar), and the National Institute of Allergy and Infectious Diseases, NIH, USA (Cristina Cassetti). On certain topics and tasks some of the Observers participated actively and gathered specific information for the Advisory Group and presented the requested information to the Advisory Group.

## 4.2. A Cautious Two-Stage Approach

In the course of its deliberations, the Advisory Group concluded that following the recommendations of the Subgroup on Clinical Trials Issues, the challenge model should be developed in two distinct Stages.

**Stage 1 studies**, undertaken when there has been no previous volunteer experience with the challenge virus strains, must take place in High-Level Isolation Units and under legal Quarantine (Compulsory Isolation), not only to protect the clinical trial staff, but also to protect the household and other close contacts of the volunteers after their discharge from the Isolation Unit.

*High Level Isolation Units.* High-Level Isolation, previously referred to as “clinical biocontainment” and also as “High Level Containment Care” (HLCC),<sup>51</sup> refers to healthcare for cases or observation of patients exposed to (thus, potentially infected with) Highly Hazardous Communicable Diseases in specialized facilities specifically designed for this purpose. These specialized units provide safe, secure, high quality and appropriate care, with optimal infection containment and infection prevention and control procedures for a small number of patients (in this instance, challenged volunteers) who have (or may have) a highly infectious disease (in this instance, COVID-19). The High-Level Isolation Units must also have the capability of either providing intensive care within the unit, should that be necessary, or of easily and rapidly transporting a volunteer to an Intensive Care Unit with an appropriate infection control level to handle COVID-19 patients and with health care staff experienced in treating COVID-19 patients.

---

*Legal Quarantine (Compulsory Isolation).* By legal Quarantine, the Advisory Group refers to an action wherein health and civil authorities in the jurisdiction where the High-Level Isolation Unit is located would place the Unit under Compulsory Isolation because the individuals are or may be shedding, or were known to be exposed to, a pathogen (SARS-CoV-2) that could potentially be dangerous to certain contacts such as elderly household members or members of the community, if the quarantined individuals were allowed to leave. Public health authorities in states have powers to restrict the autonomy and liberty of individuals who pose a threat to the public health consequent to their being infected with or having been exposed to dangerous communicable diseases.<sup>52</sup> The analogy is the Compulsory Isolation in a healthcare facility of a patient with extensively drug-resistant tuberculosis or a SARS patient during the SARS PHEIC.<sup>53</sup> This is distinct from having volunteers housed in a High Isolation Unit or high containment facility but still having the option to leave the facility, albeit agreeing to be followed up thereafter, as occurred in the Poliopolis study.<sup>54</sup> The legal Compulsory Isolation assures that contacts (household, community) will be shielded from the potentially severe risks that could accrue if a volunteer shedding SARS-CoV-2 virus were to leave the unit and inadvertently transmit to an unsuspecting high risk contact. Volunteers still have the “right to leave the study” (which would entail no more venipunctures, etc.) but they cannot leave the High-Level Isolation Unit until the study officially ends. The cholera challenge studies in community volunteers carried out with *Vibrio cholerae* O1 of both classical and El Tor biotype in the 1970s and 1980s at the University of Maryland in Baltimore, Maryland, involved Quarantine as well as containment.<sup>42,55-57</sup>

**Stage 1 studies** would undertake a dose-escalation of several different virus strains to identify a suitable challenge strain, an appropriate challenge dose, and a careful assessment of the severity of clinical illness that occurs and the duration of virus shedding. To be clear, Stage 1 studies would be highly uncertain because they would involve first-in-human infection with the selected challenge viruses. It is possible that the several passages of the selected challenge viruses in tissue culture required to manufacture sufficient doses of a GMP batch will result in sufficient attenuation such that the viruses appear clinically to behave as attenuated viruses, resulting in infectivity but only mild, short-lived, coryza-like symptoms and signs, or would perhaps elicit no overt clinical illness. On the other hand, despite multiple passages needed to adapt the viruses to growth in tissue culture, the challenge virus strains may prove to retain virulence such that one or more volunteers may progress to more severe clinical forms of COVID-19 illness. Some clinical manifestations of concern would include pneumonitis, a need for supplemental oxygen to maintain a physiologic level of arterial O<sub>2</sub> saturation, and necessity for a ventilator. Highly elevated D-dimer levels accompanied by evidence of clotting in small or large blood vessels, or volunteers exhibiting highly elevated cytokine levels of pro-inflammatory cytokines and evidence of multisystem inflammatory syndrome (that is most often seen in children [MIS-C] but that has also been reported in persons 18-25 years of age). It is also possible that the two individual challenge viruses selected, representing two different clades (e.g., A and B1) may exhibit marked heterogeneity in the responses that they elicit such that one or more may be quite attenuated, whereas one or more of the others might prove to retain notable virulence. The actual clinical and virus-shedding response elicited by each challenge virus in the dose-response Stage 1 studies will only become known if and when the studies are undertaken. **The Advisory Group wanted it to be clear that their recommendation is that maximal caution should be exercised while exploring these initial first-in-human clinical research studies with the SARS-CoV-2 challenge strains.**

If performed in the proposed manner with High-Level Containment and Quarantine, such challenge studies could be conducted irrespective of whether there is ongoing COVID-19 transmission in the community. This would have particular relevance if COVID-19 transmission proves to exhibit seasonality (as do most viruses transmitted via the respiratory

---

route) and disease transmission plummets or disappears for several months. Indeed, some civil and public health authorities may be concerned about the performance of volunteer challenge studies in periods when there is an absence of ongoing natural transmission. The High-Level Isolation Units performing the Stage 1 studies could allow such studies to proceed whatever the degree of SARS-CoV-2 transmission in the community.

**Stage 2 studies.** Once the model of closely monitored SARS-CoV-2 experimental infection is established under Stage 1 conditions, the data would be reviewed to consider how one might undertake specific studies that would require larger numbers of volunteers. Such studies might include a challenge/re-challenge protocol to determine (experimental design) or give indications (pragmatic quasi-experimental design) if an initial clinical infection confers protection against illness following a second deliberate exposure (versus controls) and studies to assess the efficacy of different candidate vaccines in preventing clinical illness and/or shedding of virus.

The Advisory Group recognized that the results observed during the Stage 1 studies across a spectrum of clinical severity and virus infectivity (if virus shedding was the only endpoint) would guide the design of potentially larger Stage 2 studies that would require larger numbers of volunteers. For example, a placebo-controlled vaccine trial to assess efficacy could require approximately 48 analyzable subjects (24 vaccinees and 24 controls) to have 90% power vaccine to detect 65% (or greater) efficacy if the expected attack risk in the controls is 70% (2-tailed  $\alpha \leq 0.05$ ). For more detailed considerations of sample size see Figure 1 above.

If the selected challenge viruses, perhaps consequent to the several passages in tissue culture during manufacture, become sufficiently attenuated such that they elicit no clinical illness or cause only mild upper respiratory clinical illness, such as short-lived coryza-like symptoms and signs, but virus infectivity is documented, it might be possible to consider undertaking Stage 2 challenge studies. Studies with such attenuated challenge strains might proceed in a different type of physical and biological containment (albeit likewise under Quarantine [Compulsory Isolation]). **Nevertheless, even with a challenge model that causes little or no clinical illness in healthy young adults, and that might only be a model of virus infectivity, the step of direct intranasal inoculation of volunteers would still pose a potentially contentious issue, as it involves manipulations and procedures that could generate infectious droplets or aerosols of droplet nuclei.**

Appendix B summarizes the precautions followed, forms of containment, and Personal Protective Equipment used in Stage 2 studies to prevent infection of staff. In facilities below Tier 1, there would still have to be clear means to transport a volunteer to an intensive care facility should she/he progress to develop severe COVID-19 disease or a serious complication.

The same High-Isolation facilities that participated in the Stage 1 dose escalation studies could also participate in the Stage 2 studies, if they were joined by several other similar facilities in other parts of the same country (countries) or in other countries, as long as collectively the total number of volunteers who could participate is expanded. There are several obvious advantages to this scenario. These include that the clinical research units participating in the Stage 2 studies would include those that have the prior experience gleaned from having recruited, screened, enrolled, intranasally-challenged (under conditions that minimize generation of droplets and aerosols), and monitored the clinical, virus shedding and immunologic responses of the volunteers. Finally, the same stringent conditions that were used in the Stage 1 studies would still be required and operative but would proceed in unison within several additional High-Level Isolation Unit clinical research sites. Harmonization would be achieved through use of the same clinical protocol, challenge strain inoculum, and virus detection methods. Immunologic measurements could be

---

harmonized by designating a single reference laboratory for performance of certain specific immunologic test of high importance (e.g., serum neutralizing antibody assays; measurement of multifunctional CD8 and CD4 T cells, mucosal antibodies detected in nasal washes, etc.).

On the other hand, despite multiple passages during manufacture, the challenge virus strains may retain virulence such that one or more volunteers progress to more severe clinical forms of COVID-19 illness. Some clinical manifestations of concern would include pneumonitis, a need for supplemental oxygen to maintain a physiologic level of arterial O<sub>2</sub> saturation, need for a ventilator, highly elevated D-dimer levels accompanied by evidence of clotting in small or large blood vessels, or volunteers exhibiting highly elevated cytokine levels of pro-inflammatory cytokines and evidence of multi-organ inflammatory syndrome.

## **5. Clinical issues**

### **5.1. A Clinical Protocol Synopsis Prepared by the Subgroup on Clinical Trial Issues**

The Details of Study Design Team of the Subgroup on Clinical Trial Issues discussed key elements for the development of a SARS-CoV-2 human challenge model. The charge of the Subgroup was to carefully consider how a SARS-CoV-2 challenge study could be conducted safely: what clinical end-points should be defined so that the model can be used successfully for its intended purposes, and what are the clinical and infrastructure supports that need to be in place for the protection of subjects and third parties.

## **6. Elements of a clinical protocol**

The Advisory Group discussed elements of a clinical protocol that could be considered in drafting a protocol to perform human challenge studies. The actual protocol used may differ from that proposed here.

### **6.1. Volunteer selection**

Epidemiological data from the ongoing SARS-CoV-2 pandemic demonstrate that adults  $\geq 65$  years of age are at greatest risk for developing severe COVID-19. However, severe disease can occur in adults of any age and in children. With a lower risk of severe disease in younger age groups, adults ages 18 – 25 were deemed to be the most appropriate age group for enrollment. More epidemiologic data would be helpful to better define the risk of severe COVID-19 in healthy adults in populations and to discern more accurately differences in illness characteristics due to SARS-CoV-2 by gender. Some data suggest that women  $< 65$  years of age are at lower risk of severe COVID-19. The general inclusion criteria to be considered are discussed below.

- Healthy volunteers (exclusion of co-morbidities).
- Mental health screening (due to burden of long stay in isolation unit).

- **Age range: a consensus was reached that volunteers 18 – 25 should be enrolled.** This was done by polling the Subgroup members. Members concluded that enrolling subjects older than age 25 years would be inappropriate because older volunteers have higher risk of severe adverse events, including death.
- **Gender balance:** Some members suggested that it would be prudent to begin enrolling a greater number of women for safety reasons. Others did not support this view. There was agreement that both men and women should participate.

## 6.1.1. Inclusion/Exclusion Criteria

### 6.1.1.1. Inclusion Criteria (examples)

1. Adult male or non-pregnant female between 18 and 25 years of age, inclusive.
2. Good general health as determined by physical examination, laboratory screening, and review of medical history.
3. Available for the duration of the study.
4. Willingness to remain in the inpatient Isolation Unit until no longer infectious post-inoculation, which may be 3 weeks or longer.
  - a. The number of days spent in the Isolation Unit pre-inoculation can be shortened by testing volunteers for COVID-19 infection by RT-PCR at several time-points prior to admission to the Isolation Unit to ensure that they are not asymptotically infected. For example, they can be tested on day -14, on day -7 and at time of admission to the Isolation Unit (2 days prior to inoculation). The results of the day -2 sample would be known prior to inoculation with SARS-CoV-2. If a subject was already infected with SARS-CoV-2 during this time, they would not be enrolled in the study.
5. Sufficient understanding of the study and willingness to participate in the study as evidenced by passing a test of understanding and signing the informed consent document.
6. Females only: Female subjects of childbearing potential should be willing to use effective contraception. Reliable methods of contraception include hormonal birth control, condoms with spermicide, diaphragm with spermicide, surgical sterilization, intrauterine device, and abstinence ( $\geq 6$  months since last sexual encounter). All female subjects will be considered as having childbearing potential, except for those who have had a hysterectomy, tubal ligation, or tubal coil (at least 3 months prior to inoculation.).

### 6.1.1.2. Exclusion Criteria (examples)

A subject will be excluded from the study if any of the following criteria are met:

1. Females only: Currently pregnant, as determined by positive  $\beta$ -human choriongonadotropin (HCG) test, or breast-feeding.
2. Evidence of clinically significant neurologic, cardiac, pulmonary, hepatic, rheumatologic, autoimmune, or renal disease based on history, physical examination, and/or laboratory studies.
3. Behavioral, cognitive, or psychiatric disease that, in the opinion of the investigator, affects the subject's ability to understand and cooperate with the requirements of the study protocol.
4. Screening laboratory values of Grade 1 or above for ANC, ALT, blood glucose, and serum creatinine, as defined in this protocol.
5. Elevated hemoglobin A1c level (HA1c) above laboratory normal limits

- 
6. Any other condition that, in the opinion of the investigator, would jeopardize the safety or rights of a subject participating in the trial, or would render the subject unable to comply with the protocol.
  7. Any significant alcohol or drug abuse in the past 12 months that has caused medical, occupational, or family problems, as indicated by subject history.
  8. History of a severe allergic reaction or anaphylaxis.
  9. History of asthma
  10. History of diabetes
  11. History of arterial or venous thrombo-embolic disease
  12. HIV infection, as indicated by screening and confirmatory assays.
  13. Hepatitis C virus (HCV) infection, as indicated by screening and confirmatory assays.
  14. Hepatitis B virus (HBV) infection, as indicated by hepatitis B surface antigen (HBsAg) screening.
  15. Any known immunodeficiency syndrome.
  16. Current cigarette, electronic cigarette or cigar smoker.
  17. Current use of anticoagulant medications (this does not include anti-platelet medication such as aspirin or non-steroidal anti-inflammatory medications).
  18. Use of corticosteroids (excluding topical) or immunosuppressive drugs within 28 days prior to or following inoculation.
  19. Receipt of a live vaccine within 60 days or a killed vaccine within 30 days prior to vaccination.
  20. Asplenia
  21. Receipt of blood products within the past 6 months, including transfusions or immunoglobulin, or anticipated receipt of any blood products or immunoglobulin during the 28 days following inoculation.
  22. Anticipated receipt of any investigational agent in the 28 days before or after inoculation.
  23. Refusal to allow specimen storage for future research.
  24. Abnormal chest x-ray that indicates pulmonary disease
  25. Abnormal pulmonary function tests that indicate underlying pulmonary disease
  26. Abnormal EKG that indicates prolonged Q-T, cardiac arrhythmia, evidence of ischemia or previous infarction, or other cardiac disease that, in the opinion of the investigator affects the subject's safety in participating in the trial

## 6.2. Size of initial groups

There are numerous unknowns that must be addressed in developing a model for SARS-CoV-2. The range of clinical illness that could be induced by even the lowest dose of virus administered is unknown. Some subjects could not show any symptoms while others could become quite ill. This uncertainty mandates that dose selection in Stage 1 studies proceed with the utmost caution. For this reason, the initial challenge inoculation (proposed as  $\sim 1 \times 10^2$  Tissue Culture Infectious Dose 50 [TCID<sub>50</sub>]) should involve an initial group of few subjects (1-3) to assess safety of the challenge dose. If the safety profile is acceptable, then the next group could include more subjects (3-5) at the same dose level. If the safety profile in the first 4 – 8 subjects is acceptable, expansion of participants challenged at that dose would occur and an additional 5 – 10 subjects would be enrolled. This iterative process would continue until 20 – 25 subjects have been enrolled. Dose escalation to  $\sim 1 \times 10^3$  TCID<sub>50</sub> would proceed with increasing numbers of volunteers if the safety profile is acceptable (as determined by a review of the clinical summary by the Data Safety Monitoring Board). Dose escalation should occur to confirm the safety profiles (or lack of symptoms/shedding) and to

---

assess more accurately the incidence of symptoms/endpoints. Dose escalation should occur conservatively. Examples are provided below in **Table 2** (bottom of document).

If the sign/pre-defined symptom profile or virologic profile does not occur in a sufficient number of the 20-25 subjects, then dose escalation could occur. Before escalation (if approved by the Data Safety Monitoring Board), the challenge strain should have been evaluated in a sufficient number of subjects to: i.) be confident the dose will not achieve a desirable endpoint in a sufficient number of subjects; ii.) and to assess a risk of a serious adverse event in <5 – 10 % (<1 – 2 per 20 subjects evaluated). If, after evaluation in a sufficient number of subjects, the lowest dose does not elicit the pre-defined symptom or virologic profile, dose escalation can occur using the same type of strategy for safety purposes. During initial challenge and/or up-titration, preliminary safety endpoints can be assessed when viral loads and /or symptoms begin to regress (rather than waiting for complete resolution).

### 6.2.1. DSMB

A Data Safety Monitoring Board (DSMB) should be formed with a clear charter and a Chair with recognized leadership skills. The DSMB should include seasoned clinical investigators with experience with COVID-19 disease, performance of challenge studies, clinical virology and biostatistical expertise. After each dose, the DSMB should be convened to review the clinical safety and virologic profile data and to thereupon recommend whether or not dose escalation should proceed. This process can be expeditious.

## 6.3. Endpoints to be achieved with SARS-CoV-2 challenge model.

Whereas much discussion ensued on what would be useful endpoints of a challenge model, a consensus was not achieved. The following is a summary of the Advisory Group's discussion. Definition of the appropriate endpoints for a SARS-CoV-2 challenge model is important because it is these endpoints that will allow the model to achieve its stated purpose. The first consideration is whether different challenge models be developed for different purposes? Two such models were discussed. The first was an **infection model**. The second was an **illness model**. Some discussion points regarding the pros and cons are presented below. Ideally, the model should produce the defined endpoint in a relatively high proportion of challenged naïve subjects (**≥ 70% attack risk**) to keep the number of volunteers needed in the study to a realistic level. The primary endpoints are discussed below. There would be other secondary and exploratory endpoints as well.

### 6.3.1. Infection model:

- The primary endpoint is recovery of challenge virus from the nasopharynx or oropharynx.
- Virus would be quantified, preferably by both PCR and tissue culture.
- This model would presumably be safer and may require fewer volunteers if clinical endpoints cannot be achieved in a sufficient number of young healthy volunteers without inducing more severe disease in others.
- This model may not be able to differentiate between vaccines in terms of protection against lower respiratory tract disease.
- This model may not be able to differentiate between vaccines in terms of protection against shedding of virus if the vaccines are parenteral and by nature do not affect replication of the virus in the upper respiratory tract even though they may be effective in preventing lower respiratory tract infection.

- It is unclear how regulatory agencies would review the direct “efficacy” of vaccines that demonstrate impact on shedding of virus and/or viremia in the absence of data on prevention of endpoints of clinical illness.
- An infection model in volunteers may be useful for (i) selecting among multiple vaccines for large-scale field trials of clinical efficacy if some vaccines suppress viral replication significantly more than others, based on the assumption that reducing shedding translates to reduced transmission and possible increased indirect (herd) protection, and based on the assumption that large enough studies could be arranged to be powered to detect such a difference; (ii) investigating correlates of protection (e.g., by comparing challenge of naïve vs. recovered), even if this protection is against infection rather than against clinical illness; (iii) investigating viral dose-clinical severity relationships (presumably at lower doses); (iv) possibly helping to estimate transmission risks posed by asymptomatically infected individuals.

### 6.3.2. Illness Model

- The primary endpoint would be a constellation of clinical signs and/or symptoms that constitute a clinical “case definition”, as is used in the well-established influenza challenge model studies. The endpoint would be a type of “influenza-like” illness.
- The clinical endpoint case definition could evolve as data are collected from the first challenge studies. What signs and symptoms do subjects develop? How long do signs and symptoms last? What proportion of subjects develop signs and symptoms that could collectively define an illness end-point.
- Quantification of virus shedding would be included in the endpoints.
- Careful escalation of administered dose of virus, for example progressing from challenge with  $\sim 1 \times 10^2 \text{TCID}_{50}$  to an inoculum containing  $\sim 1 \times 10^3 \text{TCID}_{50}$  should aim to show the extent to which a spectrum of disease is predictable, at even low doses of virus inoculum. Wide variations in disease severity should prompt a pause in virus dose escalation and should attempt to decipher the reasons for increased severity.
- Advantages of this model include that it may better assess which vaccines provide direct (individual) protection and which candidates should move forward and which should not, since the comparison would be protection against clinical (albeit mild) illness. This may provide data of greater relevance for regulatory authorities. If significant protection of a specific vaccine against clinical illness was demonstrated in the model, it could also reveal one or more immunologic correlates of protection against illness rather than, or in addition to, possibly identifying a correlate of protection against infection.
- Shortcomings of this model include:
  - There may not be a dose-ranging effect with dose escalation, and it may not be possible to define a dose that induces an acceptable clinical case definition.
  - A dose of virus that is accompanied by fairly consistent clinical signs and symptoms of illness in  $\geq 70\%$  of volunteers may also raise the risk of occurrence of severe adverse events among the volunteers.
  - Unless protection against clinical disease is accompanied by protection against virus shedding, a trial with clinical disease endpoints alone does not inform the development against vaccines that can be expected to induce herd protection as well as models which use virus shedding as the endpoint,

It is important to note that in pursuing development of the volunteer challenge model, it may not be possible to achieve an “ideal” model that provides both clinical and virus shedding endpoints yet proves to be safe for volunteers. **Development of the model must proceed iteratively**, with reassessment of what type of model can be achieved consistently and

---

safely as dose ranging and dose escalation occur. There may be limitations to whatever model is developed, depending upon what questions the model is addressing.

### 6.3.3. Aims of different cohorts included in a challenge model experiment

- Naïve participants: (i) develop model of infection against which to test vaccines, passive immunoprophylactic agents (e.g., monoclonal antibody products) and other putative preventive interventions; (ii) risk of transmission (especially during asymptomatic infection).
- Previously exposed participants: risk of re-infection (shedding of virus); risk of developing clinical endpoints; identification of immunological correlates of protection (CoP) against virus shedding or against development of clinical illness following re-challenge.

### 6.4. Method of administration

There was general consensus to use droplet administration and not nasal spray or aerosol. This was to reduce the likelihood that the challenge virus would be deposited in the lower respiratory tract, which may translate to an unacceptably high risk of severe COVID-19.

### 6.5. Safety Monitoring during inpatient stay

- Safety Procedures during inpatient stay
  - At least once a day physical examination including but not limited to nose, throat, pulmonary, cardiovascular, neurological, and skin exam. The frequency would be increased if the volunteer develops clinical signs and symptoms.
  - Testing of smell and taste
  - Vital signs at least every 6 hours (if exhibiting clinical signs/symptoms) to 8 hours (no illness)
  - Continuous pulse oximetry
  - Continuous cardiac monitoring
  - Daily pulmonary ultrasound. Should an abnormality be noted, CT Scan of chest should be done
  - EKG on admission and repeated as needed
  - Safety laboratory studies to include:
    - Complete metabolic panel
    - CBC with differential (this may be checked more frequently than CMP because we would want to document lymphopenia)
    - Troponin
    - CRP
    - D-dimer
    - IL-6
    - PT/PTT

The unit should have a full crash cart on the unit, including intubation kits and easy access to ventilator treatment.

### 6.6. Discharge criteria

- Consensus that we must reduce the risk to third parties to as near zero as possible. To this end, we anticipate requiring post-challenge inpatient stays of 3 – 4 weeks.

- Three consecutive days with negative nasopharyngeal swabs by PCR (or culture)
  - Can a correlate between PCR titer and infectious (replicating) virus be established from current clinical cases? If so, discharge could occur sooner. Or if, the studies have the capability of performing virus culture, may be able to discharge the subject when replicating virus is no longer detected. This would require BSL-3 capabilities at the site and would require circa 4 additional days.
- For volunteers participating in Stage 1 SARS-CoV-2 challenge studies who change their mind and want to leave the study, a legal framework must be in place to retain them on the High-Level Isolation Unit. **To address this theoretical scenario, we strongly recommend that the Stage 1 studies to establish the challenge model be performed in High-Level Isolation Units and that, in conjunction with appropriate health and civil authorities, the Isolation Unit should be placed under legal Quarantine (Compulsory Isolation of the challenged volunteers). The Quarantine would extend from the time of inoculation of volunteers with challenge virus until the volunteers are no longer shedding virus and will no longer be a potential threat to household and community contacts. In such a situation, the subject can still withdraw from the trial and from participating in additional study-related procedures, but she/he must remain on the unit until they are no longer shedding infectious virus.** One advantage of this approach is that challenge studies with SARS-CoV-2 could proceed in geographic areas and populations where SARS-CoV-2 is no longer circulating. There is a precedent for this approach. In the 1970s and 1980s when challenge models of Classical biotype and El Tor biotype cholera were established in Baltimore, MD, USA, the studies proceeded in the confines of a 32-bed Research Isolation Unit under physical containment and under legal Quarantine. Prior to each challenge study the Baltimore City Health Department would place the Research Isolation Unit under Quarantine (Compulsory Isolation) from the date and time of challenge until all volunteers were no longer having diarrhea, had received antibiotic treatment, and all were culture negative for several days.<sup>42,55-57</sup>

## 6.7. Follow-up

- There should be an explicit plan for follow-up. For instance, monthly follow-up through 6 months then every 3 months up until 12-months following the inoculation. Key follow-up might include early post-discharge neurological examination (i.e., exclude Guillain Barre), longer term serial lung function testing +/- other organ systems if data suggest long term complications among patients. It might also include nasopharyngeal PCR during acute respiratory illness (e.g. to capture episodes of re-infection, if any).
- Follow-up should also include laboratory studies, especially serology. Recruitment for possible re-challenge at later years could be considered.
- Follow-up NP/OP swabs may be indicated to evaluate for recrudescence shedding of virus
- Should a subject become positive for SARS-CoV-2 after discharge, specific plans for how that subject will be followed must be in place. Should the subject be re-admitted to the inpatient isolation unit?

## 6.8. Laboratory studies

- Should include planned sample collection for study of disease pathogenesis, immunological response, search for correlates of protection. These assays will be discussed by the immunology working group.
- Must be done under guidelines for blood collection limits in ill patients.

---

## 6.9. Treatment protocols

- The dose-escalation challenge protocol must include criteria for the initiation of rescue drugs that have been approved for use to treat SARS-CoV-2 should they be available and deemed to be able either to interrupt the progression of COVID-19 illness from mild/moderate to severe or to prevent certain complications or fatality. A 10-day intravenous course of Remdesivir has been given Emergency Use Authorization by the FDA for the treatment of severe COVID-19 infection in hospitalized patients in the USA. “Rescue treatment” criteria will have to be revised as data emerge that identify effective therapeutic agents.
- A 10-day intravenous course of remdesivir has been given Emergency Use Authorization by the FDA for the treatment of severe COVID-19 infection in hospitalized patients in the USA. This does not mean all subjects in SARS-CoV-2 Stage 1 studies would receive remdesivir treatment. Rather, its use would be based on treatment guidelines that would be in place at the time of the challenge. Advisory Group members from European Union countries stated that the EMA is not recommending the use of remdesivir in mild COVID-19 cases.
- Should an effective treatment become available that is shown to prevent or arrest the progression from mild and moderate clinical COVID-19 illness to severe clinical illness, treatment could be initiated once a case definition has been achieved or by a certain day post-challenge if the case definition has not been met.

## 7. Isolation Units for use in a SARS-CoV-2 challenge

The Advisory Group concluded for several reasons that High-Level infection control and adequate medical support of subjects are the minimum requirements of any Isolation Unit used for SARS-CoV-2 challenge studies during Stage 1 studies and likely also during Stage 2 studies. The reasons include:

- i) The high transmissibility of SARS-CoV-2 and the risks to third parties, including staff, is best countered by performing the studies in a High-Level Isolation Unit.<sup>51,58-61</sup> A High-Level containment unit would be necessary to conduct COVID-19 human challenge studies, at least until the model or other factors have proven that such controls are not necessary. There is an increasing number of High-Level Isolation Units around the world (Appendix B). Whereas for the most part the number of beds available at each unit is small, the units would be highly suitable for Stage 1 studies.
- ii) There would be a chance of inadvertent generation of droplets and aerosols bearing virus during the critical steps of preparing the inoculum for each volunteer and the act of inoculating volunteers with the SARS-CoV-2 challenge virus material. Thus, precautions to both minimize the chance of possible generation of aerosol and conditions and actions to diminish the possible adverse consequences for clinical staff must be followed, as described in Appendix B.
- iii) The step of inoculating volunteers would involve removing vials containing frozen viral material from the secure freezer, defrosting the vials, opening the vials, transferring the appropriate volume of defrosted vial material (each vial will likely contain the target dose of virus in a volume of 1.1. ml) into either a pipette [preferred] or into a syringe. Using the pipette or syringe, 0.5 ml of inoculum would have to be instilled into each nostril of a volunteer, while her/his head is leaning backwards to minimize the chance of inoculum coming out of the nostril. With influenza challenges, many investigators used spray devices that were intended to generate a large droplet (~25-50 microns in diameter) spray so that the inoculum remained confined to the upper respiratory tract.<sup>62</sup> Nevertheless, with the devices

used, it is possible that a small percent of droplets in the spray can be small enough (<5 microns) to be able to reach the bronchioles and alveoli of the lower respiratory tract. This would be unacceptable for challenging volunteers with SARS-CoV-2, as one must avoid generation of aerosols under any circumstances for reasons of biocontainment and to avoid the possibility of very small droplets reaching the lung. Fortunately, there is also experience of volunteers in influenza challenges being given virus by installation of a 0.5 ml volume of inoculum per nostril by pipette or by needle-less syringe.

iv) Based on experiences of challenge virus administered intranasally in influenza studies, an occasional volunteer sneezes, coughs or gags. In each of these instances, an aerosol is generated. For these reasons, the step of inoculation of volunteers with SARS-CoV-2 virus is best performed in a single designated room within a High-Level Isolation Unit (Appendix A).

v) An international review of High-Level isolation units was performed by Allison Sykes in 2018. A summary of these units was derived from her report and these units are presented in Table 1. Some of these units were already in place and some were developed in response to the Ebola Zaire outbreak of 2014-2016.

In addition to the above-mentioned considerations, some authorities consulted consider that the step of administration to volunteers of an inoculum of SARS-CoV-2 from a GMP formulation of tissue culture cells infected with SARS-CoV-2 should be performed in a facility with a high level of containment against consequences of possible aerosol generation and airborne transmission.

**Table 1. Examples of High-level containment units in various countries**

Name of Unit	Hospital	# Beds	City	Country
Special Pathogens Unit	Bellevue Hospital	2+10 resp	New York	USA
Biocontainment Unit	Johns Hopkins Hospital	4 (3 rooms, 1 double)	Baltimore	USA
Serious Communicable Diseases Unit	Emory University Hospital	3+8 resp	Atlanta	USA
Biocontainment Unit	University of Nebraska Medical Center	5 doubles	Omaha	USA
NETEC conference	University of Nebraska Medical Center		Omaha	USA
High level isolation unit	Infectious Diseases Hospital Lazzaro Spallanzani	8	Rome	Italy
High level isolation unit	University Medical Centre Hamburg-Eppendorf	3 doubles	Hamburg	Germany
High level isolation unit	Charity University Medicine	4+20 resp	Berlin	Germany
High level isolation unit	Hospital La Paz Carlos 111	2 + 3	Madrid	Spain
High level isolation unit	HCDGU	7	Madrid	Spain
High level isolation unit	Newcastle Royal Victoria Infirmary High-Level Isolation Unit	4	Newcastle	United Kingdom

---

The USA has a four-tier system for the management of (Highly Contagious Infectious Diseases [HCID], Special Pathogens)

- Tier 1: Regional Biocontainment Units. There are 10 and they serve between 2-8 states.
- Tier 2: State-designated treatment centers who receive patients from their state prior to transfer to the main center and can also manage patients if the regional BCU is unable to take the patient.
- Tier 3: The Assessment Centers who can keep a suspected HCID case for up to 5 days until diagnosis can be confirmed and transfer organized.
- Tier 4: all other hospitals that can assess and isolate the patient for up to 12-24 hours until transfer.

A similar hierarchy is followed in most European countries.

## 7.1. Capabilities available on the unit

Units chosen for SARS-CoV-2 challenge studies should be high-level containment units that can house subjects in single rooms. Nursing stations should have full telemetry monitors to view vital signs, heart rhythm, and pulse oximetry. They should have the equipment and monitoring capability of an intensive care unit or step-down unit. Ideally, the challenge inoculum could be stored in a secure, locked, high security freezer in a pharmacy on the unit. If possible, the unit should have an on-site specimen processing area and point-of-care assays for some basic clinical laboratory tests. Clinical specimens will have to be sent to the central hospital laboratory for many of the tests. It is likely that some sample processing will need to be done elsewhere (such as PBMC processing).

## 7.2. Medical expertise/support care available on the unit

Close clinical monitoring of subjects is critical. Because airborne precautions will be required and will limit what can be brought on and off the unit, careful consideration should be given to what diagnostic equipment is available on the unit to minimize subject transport to and from different testing suites (radiology for example).

- Dedicated portable ultrasound with staff trained in performing the ultrasound and interpreting the results should be available on the unit.
- Oxygen and ventilatory support should be available on the unit. In addition, the site should have the clinical staff and capability to evaluate and manage other complications of SARS-CoV-2 infection such as vascular complications.
- Experienced clinicians should staff the unit at all times. The unit should have available critical care facilities and staff either as part of the unit, or transport to an ICU should be readily available.
- The clinical staff and protocols must be in place for initiating advanced care such as intubation or emergency surgery and for transfer to the ICU or other specialty service. Team members should include, in addition to the protocol PI and study team members:
  - Pulmonary / ICU specialist
  - Critical care nursing staff
  - 24-hour physician coverage on the unit (in addition to 24-hour nursing staff)
- Other support services to consider
  - Oxygen in the rooms
  - Continuous pulse oximetry, telemetry
  - Pulmonary U/S on the unit with an experience team member to perform U/S
  - EKG machine

- IV pumps and fluids
- Full crash cart including Intubation kits
- Dietary support. Meals can be prepared outside the unit and brought in daily
- Entertainment on the unit (subjects may have to remain on the unit for weeks)
- Housing: can more than 1 subject be in a room?

### 7.3. Precautions for staff/third parties

The unit should have dedicated Personal Protective Equipment (PPE) donning and doffing areas. In addition, staff should have regular serology and N-P or O-P swab collection for SARS-CoV-2 detection to detect asymptomatic infection and seroconversion (this could be a sub-study). Other requirements

- Full access to PPE
- Screening of staff to identify those who may have household members at higher risk of COVID-19. They may not be permitted to work on the unit. This would have to conform to institutional guidelines
- Protocols will need to be in place for subjects who decide they do not want to remain in the study. The subject can withdraw from the study but should remain on the isolation unit until it is confirmed that they are no longer shedding the challenge virus. These should be coordinated with local public health authorities regarding enforced quarantine (see below).

### 7.4. Measures to address volunteers who wish to leave the study before completion

Volunteers have the right to “leave the study when they wish”. However, with a virulent SARS-CoV-2 challenge they cannot be allowed to physically leave the Isolation Unit until they are no longer infectious, as they would pose a potential danger to household and other community contacts, some of whom may have risk factor for severe COVID-19 illness. This would be particularly problematic if the study were to proceed in a geographic area where there is little or no active transmission of SARS-CoV-2 at the time. The one historical method for handling potentially infectious volunteers who want to leave a study and an Isolation Unit was to have the Unit placed under health authority issued Quarantine (Compulsory Isolation) for the duration of the study from the time of inoculation. A survey taken of the Advisory Group members asking if there were local or national laws in place allowing the compulsory quarantining of subjects, even against their will, revealed that many European countries, Australia and states in the USA have public health laws that allow the establishment of legal Quarantine (Compulsory Isolation). Thus, many countries, states and municipalities have laws in place allowing for persons to be placed in Quarantine (Compulsory Isolation) if they pose a threat of disease transmission to others.<sup>52</sup> Indeed, in recent years changes in the International Health Regulations consequent to being able to deal more effectively with PHEIC infections have resulted in changes in local laws in many countries.

- This would require working with local governments to ensure that public health regulations can be adapted to allow the Isolation Unit to be placed under quarantine (Compulsory Isolation) for the duration of the study.
- The issue of Quarantine must be clearly and unequivocally stated in the consent form. The consent should include that withdrawal from the study is possible (by which is meant the volunteer no longer has to comply with procedures but that physically departing the unit is not an option. Thus, the volunteer must clearly understand that for the duration of the study she/he is forfeiting her/his autonomy to depart the Isolation Unit because they

---

constitute a potential threat to persons outside the facility who have not consented to be exposed to the SARS-CoV-2. This concept should not be foreign to motivated volunteers.

- There is a considerable experience in using this Quarantine (Compulsory Isolation) methodology from cholera challenge studies performed in the period 1977 to 1999. A key lesson from that experience is to carefully screen prospective volunteers so that they understand that they are embarking on a clinical research journey for which they must make an unusual commitment to physically remain on the Isolation Unit for the duration. The investigators must document that the volunteers understand why they are being asked to do this (to protect persons outside the facility).

## 7.5. Handling of the SARS-CoV-2 challenge virus

The inoculum is a BSL-3 product. Its formulation and presentation should be one that minimizes risk to those who prepare and administer it. Issues around the selection and production of the SARS-CoV-2 challenge virus were discussed by a Subgroup. Issues related to administration of the challenge virus include:

- Reconstitution of a lyophilized vial was deemed to present risks to those who prepare the inoculum. Thus, vials containing frozen inoculum would be preferred.
- If the frozen liquid is contained in single-dose vials, after defrosting the appropriate volume of inoculum would be withdrawn into a syringe or pipette to allow 0.5 ml to be delivered into each nostril of the volunteer. Assuming that the inoculum will reside within vials containing 1.1 ml, 0.5 ml would be dispensed into each nostril. These steps will have to be performed in appropriate containment level conditions with safeguards to minimize airborne transmission from possible generation of droplets or aerosols, as described in Appendix B.

## 7.6. Efficacy studies

Once a suitable challenge model has been established in the Stage 1 studies, larger Stage 2 studies that incorporate an increased number of volunteers could be designed. It is important to note that challenge studies undertaken to compare directly two candidate vaccines versus a control group of placebo recipients, or even to determine the efficacy of a single vaccine would require >50 to > 100 subjects to determine significant differences, depending on the risk of endpoints in the control arm of the trial and the assumptions of vaccine efficacy and the number of groups being compared. Most High-Level Isolation Units have a limited bed capacity so that such Stage 2 studies would have to be conducted in several units at the same time. This means that these Stage 2 trials must be harmonized among the sites to ensure that the results are consistent and reproducible. Otherwise major changes would have to be made in the type of Isolation Units where volunteers would be housed and the inoculation of volunteers intranasally would have to be addressed with a plausible safe scenario (Appendix B). Alternatively, one could do such vaccine challenge trials in smaller cohorts of volunteers performing block randomization with block sizes corresponding to the capacity of the research units.

The Advisory Group did not address in any depth the details of performance of Stage 2 studies, as it would be speculative without knowing the results of the Stage 1 studies that established the model through testing different SARS-CoV-2 strains in different doses, observing the clinical responses, the kinetics of virus shedding and the immunologic responses. The Advisory Group's assessment is that the step of administering virulent SARS-CoV-2 will always need to be done with utmost care, basically translating to using a high containment environment and precautions to prevent airborne transmission during preparation of challenge inoculum and the act of challenge of volunteers intranasally. However, it is conceivable that after that initial intranasal inoculation step, the remainder of

---

the period of observation of volunteers participating in a Stage 2 study could theoretically be conducted with the subjects confined in a Research Isolation Facility that is secure but not meeting High-Level Isolation criteria. Staff caring for the volunteers would still need to use PPE and the infection control protocols would have to be compatible with avoiding nosocomial transmission of SARS-CoV-2.

## 8. Consent Form

The Subgroup on Clinical Trials Issues worked extensively to craft a draft Consent Form that they deemed to be appropriate for the Stage 1 dose-escalation viruses, representing the first times that volunteers would be given SARS-CoV-2 viruses. All members of the Subgroup participated, after which other members of the Advisory Group and from other Subgroups had an opportunity to provide their input. An attempt was made to craft a Consent Form that would, with relatively minor edits, be usable in potential study sites in the USA, Europe, Australia, Asia and other countries where the infrastructure of suitable High Isolation Units existed. This draft Consent Form is attached as **Appendix C**.

## 9. Volunteer comprehension test

The Subgroup on Clinical Trials Issues, which includes a number of clinical investigators who collectively have established and undertaken a number of different types of challenge studies over many decades concluded that prospective volunteers should be given a test containing multiple choice and true/false questions to document in an objective manner that they have understood the purpose of the challenge studies, the risks entailed, the procedures they will have to undergo and why, the timeline, the specifics of the Quarantine of the Isolation Unit during the study period, the number and purpose of the follow-up visits, etc. A draft Volunteer Comprehension Test is attached as **Appendix D**. The test will contain approximately 30 questions and volunteers will have to attain a grade of 80% or better to be enrolled into the study.

**Table 2. Timetable if challenge virus #1 elicits mild upper respiratory clinical illness at dose level 1**

Site	Cohort	SARS-CoV-2 test virus	Dose level	No. of subjects	Days of acclimation on ward pre-challenge	Study day of virus administration	Estimated maximal days of clinical observation post-challenge	Estimated maximal days of RT-PCR positivity if subjects become infected	Days of Isolation Ward cleaning and disinfection	Cumulative overall study days at a single site with rapid step-wise progression
#1	1	#1	1	1 - 3	(-2, -1)	0	21 <sup>1</sup>	21 <sup>2</sup>	3	~49
#1	2	#1	1	3 - 5	(-2, -1)	50	21	21	3	~99
#1	3	#1	1	5 - 10	(-2, -1)	100	21	21	3	~148
#1	4	#1	1	10 - 15	(-2, -1)	149	21	21	3	~199
<b>Timetable for dose level 2 if challenge virus #1 does not elicit mild upper respiratory clinical illness at dose level 1</b>										
#1	1	#1	2	1 - 3	(-2, -1)	0	21 <sup>1</sup>	21 <sup>2</sup>	3	
#1	2	#1	2	3 - 5	(-2, -1)	50	21	21	3	
#1	3	#1	2	5 - 10	(-2, -1)	100	21	21	3	
#1	4	#1	2	10 - 15	(-2, -1)	149	21	21	3	
<b>Timetable for dose level 3 if challenge virus #1 does not elicit mild upper respiratory clinical illness at dose level 2</b>										
#1	1	#1	3	1 - 3	(-2, -1)	0	21 <sup>1</sup>	21 <sup>2</sup>	3	
#1	2	#1	3	3 - 5	(-2, -1)	50	21	21	3	
#1	3	#1	3	5 - 10	(-2, -1)	100	21	21	3	
#1	4	#1	3	10 - 15	(-2, -1)	149	21	21	3	
<b>Timetable for dose level 1 with challenge virus #2 if virus #1 does not elicit mild upper respiratory clinical illness at dose level 3</b>										
#1	1	#2	Dose level 1	1 - 3	(-2, -1)	0	21 <sup>1</sup>	21 <sup>2</sup>	3	
#1	2	#2	Dose level 1	3 - 5	(-2, -1)	50	21	21	3	
#1	3	#2	Dose level 1	5 - 10	(-2, -1)	100	21	21	3	
#1	4	#2	Dose level 1	10 - 15	(-2, -1)	149	21	21	3	

<sup>1</sup> The mean incubation period of COVID-19 illness is ~5.5 days and >98% of cases occur within ≤12 days. However, occasional cases have an incubation as long as 13 or 14 days. The maximal 21-day clinical observation period shown is based on an incubation as long as 14 days and 7 days for evolution of the clinical illness. If no clinical illness occurs but there is infectivity, the period of clinical observation could be shortened and the days until eligibility for discharge would then be dictated by the length of shedding of virus by the volunteer in the cohort who has the longest RT-PCR positivity. If the low dose and/or middle dose level result in neither clinical illness nor infectivity, the volunteers may be on the Isolation Unit for a much shorter period that could be as short as circa 17 days.

<sup>2</sup> Most symptomatic individuals infected with SARS-CoV-2 shed virus for no more than 10-14 days. However, some centers are reporting RT-PCR positive shedding for 21 – 28 days post-onset of clinical signs/symptoms.

---

## 10. Selection of viruses to be used in challenge studies

### 10.1. Points to consider in selecting a SARS-CoV-2 challenge virus strain

#### 10.1.1. Background:

There are two main lineages of SARS-CoV-2 (A and B) that can then be subdivided into a number of component lineages. The bulk of the infections currently worldwide (June 2020) are derived from the B.1 lineage which is associated with the large European outbreak. Currently, most cases across the USA are lineage B.1 following multiple introductions from Europe.

Coronaviruses acquire genetic variation by mutation and recombination. It is important to recognize that mutations can emerge as a consequence of passage in cell culture, as would occur in the preparation of a GMP batch of a SARS-CoV-2 strain for use in challenge studies.

#### 10.1.2. Options for selection of a challenge virus strain.

There are two options for selection of a challenge virus strain:

1. Although documenting the clinical history of the patient whose virus isolate is selected is not a regulatory requirement, the Advisory Group opined that ideally the biological isolate should be obtained from a relatively young subject with non-fatal COVID-19 illness who does not have known risk factors (e.g., age <45 years, no history of diabetes, hypertension, cardiovascular disease, renal or hepatic disease). The Advisory Group took the view that when informed consent is obtained and the consent form is discussed by the investigators with the prospective volunteer, it will be comforting to the prospective volunteer to know that the virus isolate did not derive from a fatal case. Each selected strain will have to be isolated or plaque purified in a qualified cell line, plaque-purified three times, and manufactured and tested to meet regulatory standards in at least one jurisdiction. (If clinical or virus passage history of the strain is undocumented, plaque purification could address potential concerns regarding adventitious agents. However, as mentioned, the Advisory Group prefers to have an isolate that comes accompanied by a clinical history).
2. Alternatively, using reverse-genetics, a potential challenge virus can be derived that is rescued in qualified cells. The advantage of this approach is that a genetic tag can be introduced into the challenge virus and this it can be tracked. There are a few laboratories globally with expertise to employ this technology. However, the resultant virus will be a genetically-modified organism (a “GMO”), the use of which may be problematic for use in some countries.<sup>63</sup> Therefore, some members of the Advisory Group were less enthusiastic over this option. Nevertheless, there was broad agreement that this option should be included in the report as it was discussed, and it would be an attractive option for use in some settings.

#### 10.1.3. Criteria in selecting a virus.

- Select two viruses from each of the dominant clades (currently A and B.1).

- Each selected virus should represent, as closely as possible, a consensus sequence for its clade.
- It is not important to select a virus that has been used in animal models. Rather, it would be preferable to confirm virulence in animal models after the selected virus has been isolated, plaque purified and sequenced.

#### 10.1.4. Advice from experts.

- The B.1 lineage has a mutation in the spike protein (D614G) that is generally thought to be a significant mutation from the molecular perspective but there is debate as to its importance in terms of its effect on pathogenesis and transmissibility. Viruses at the base of the B.1 lineage can be selected that harbor the D614G mutation but that exhibit few other mutations.
- If two variants of SARS-CoV-2 are to be manufactured as potential challenge viruses, the Subgroup on Challenge Virus Issues proposed that one should be a B.1 lineage virus, which is the representative dominant lineage in circulation, while the other challenge strain could be representative of the original A clade viruses (which would not have the D614G mutation). The original A genotype is apparently diminishing in frequency but there are still cases in Europe and the USA (plus many other parts of the world).
- The goal would be to manufacture candidate B.1 and A challenge viruses from two different B.1 and A clinical isolates each, as one or another individual virus may exhibit lower yields than its counterpart clade virus after several passages in tissue culture.
- A number of research groups have observed a notable deletion in the spike protein that accompanies culture in Vero cells. This deletion removes the furin cleavage site. One expert consultant suggested that viruses with the deletion of the furin cleavage site should be avoided. However, another expert advised choosing a purified plaque of S1/S2 deletion mutant that is stable on multiple passages in Vero cells as the challenge virus on the assumption that such a virus might be safer for the unvaccinated control volunteers. A third expert's opinion was that deletions in the spike protein are inevitable after passage in Vero cells and that the stability on serial passage and characterization of the challenge virus pool in an animal model were important considerations.

#### 10.1.5. A list of specific sequenced viruses.

Prof. Kanta Subbarao, *Lead* for the Subgroup on Challenge Virus Strain Issues, consulted with Prof. Andrew Rambaut (Institute of Evolutionary Biology, University of Edinburgh, UK) and Prof. Edward Holmes (School of Life & Environmental Sciences and School of Medical Sciences, University of Sydney, Sydney, Australia), requesting that they provide some SARS-CoV-2 strain designations for representative viruses at the base of the B.1 lineage that have the D614G mutation and also A lineage viruses that are close to the base. Their list is shown below as **Table 3**. Some viruses have a few differences at the beginning and end that may be due to sequencing errors.

**Table 3. A List of potential SARS-CoV-2 challenge virus candidates of Clade B.1 (“European epidemic” clade) and Clade A (“Chinese epidemic” clade)**

Lineage B.1	Lineage A
Italy/INMI3/2020/B.1 Italy 1.65 2020-03-01	China/WF0018/2020/EPI_ISL_413748 China 2020-02
Australia/NSW39/2020/B.1 Australia 1.65 2020-03-11	China/WF0016/2020/EPI_ISL_413746 China 2020-02
Netherlands/Gelderland_6/2020/B.1 Netherlands 1.65 2020-03-09	China/WF0020/2020/EPI_ISL_413750 China 2020-02
USA/WI-151/2020/B.1 USA 1.65 2020-04-08	Taiwan/NTU01/2020/EPI_ISL_408489 Taiwan Taipei 2020-01-31
USA/WI-134/2020/B.1 USA 1.65 2020-04-13	China/WF0015/2020/EPI_ISL_413729 China 2020-02
USA/NY-PV08426/2020/B.1 USA 1.65 2020-03-18	Belgium/GHB-03021/2020/EPI_ISL_407976 Belgium Leuven 2020-02-03
USA/WI-UW-265/2020/B.1 USA 1.65 2020-04-08	Hangzhou/ZJU-02/2020/EPI_ISL_416042 China Hangzhou 2020-01-26
Scotland/CVR131/2020/B.1 UK 1.65 2020-03-12	Shanghai/SH0043/2020/EPI_ISL_416352 China Shanghai 2020-01-30
Scotland/CVR62/2020/B.1 UK 1.65 2020-03-12	Shanghai/SH0013/2020/EPI_ISL_416326 China Shanghai 2020-01-30
Scotland/CVR54/2020/B.1 UK 1.65 2020-03-13	Guangzhou/GZMU0044/2020/EPI_ISL_414689 China Guangdong Guangzhou 2020-02-25
Scotland/CVR247/2020/B.1 UK 1.65 2020-03-19	Guangzhou/GZMU0048/2020/EPI_ISL_414691 China Guangdong Guangzhou 2020-02-25
Netherlands/Zeevolde_1365080/2020/B.1 Netherlands 1.65 2020-03-02	Guangzhou/GZMU0016/2020/EPI_ISL_414663 China Guangdong Guangzhou 2020-02-25
Netherlands/Blaricum_1364780/2020/B.1 Netherlands 1.65 2020-03-02	Wuhan/HBDC-03/2020/EPI_ISL_412979 China Hubei Wuhan 2020-01-18
Netherlands/Utrecht_11/2020/B.1 Netherlands 1.65 2020-03-03	China/WF0001/2020/EPI_ISL_413691 China 2020-01
Czech_Republic/IAB_18/2020/B.1 Czech_Republic 1.65 2020-03-27	Taiwan/3/2020/EPI_ISL_411926 Taiwan Taipei 2020-01-24
Belgium/BG-030551/2020/B.1 Belgium 1.65 2020-03-05	Australia/NSW01/2020/EPI_ISL_407893 Australia New_South_Wales Sydney 2020-01-24
Belgium/VDLH-030548/2020/B.1 Belgium 1.65 2020-03-05	Wuhan/WH04/2020/EPI_ISL_406801 China Hubei
Belgium/RS-030677/2020/B.1 Belgium 1.65 2020-03-06	
Belgium/WAM-030676/2020/B.1 Belgium 1.65 2020-03-06	
Belgium/HL-030771/2020/B.1 Belgium 1.65 2020-03-07	
Belgium/GE-030573/2020/B.1 Belgium 1.65 2020-03-05	
Belgium/DLDJ-030569/2020/B.1 Belgium 1.65 2020-03-05	
Belgium/DCB-0324163/2020/B.1 Belgium 1.65 2020-03-24	
Belgium/CJE-0325178/2020/B.1 Belgium 1.65 2020-03-25	
Italy/INMI6/2020/B.1 Italy 1.65 2020-03-23	
Italy/UniMI03/2020/B.1 Italy 1.65 2020-02-24	
Australia/VIC136/2020/B.1 Australia 1.65 2020-03-22	
Georgia/Tb-477/2020/B.1 Georgia 1.65 2020-03-10	
Australia/VIC174/2020/B.1 Australia 1.65 2020-03-18	
Czech_Republic/IAB_21/2020/B.1 Czech_Republic 1.65 2020-03-27	
Australia/VIC853/2020/B.1 Australia 1.65 2020-04-04	
Denmark/SSI-09/2020/B.1 Denmark 1.65 2020-03-03	
Australia/VIC843/2020/B.1 Australia 1.65 2020-04-04	
USA/NY-NYUMC69/2020/B.1 USA 1.65 2020-03-18	
Australia/QLDID920/2020/B.1 Australia 1.65 2020-03-11	
Brazil/SPBR-06/2020/B.1 Brazil 1.65 2020-02-29	
Singapore/49/2020/B.1 Singapore 1.65 2020-03-08	
Australia/VIC92/2020/B.1 Australia 1.65 2020-03-15	
Iceland/111/2020/B.1 Iceland 1.65 2020-03-11	
Canada/ON_PHL4088/2020/B.1 Canada 1.65 2020-03-15	
Brazil/SPBR-09/2020/B.1 Brazil 1.65 2020-03-04	
Italy/FVG-ICGEB_S1/2020/B.1 Italy 1.65 2020-03-01	
Russia/StPetersburg-RII4326S/2020/B.1 Russia 1.65 2020-03-25	
Brazil/SPBR-05/2020/B.1 Brazil 1.65 2020-02-29	
USA/IA_6390/2020/B.1 USA 1.65 2020-03-07	
Brazil/SPBR-01/2020/B.1 Brazil 1.65 2020-02-25	
USA/IA_6399/2020/B.1 USA 1.65 2020-03-08	
USA/IA_6401/2020/B.1 USA 1.65 2020-03-08	
USA/IA_6396/2020/B.1 USA 1.65 2020-03-08	
Luxembourg/LNS2334563/2020/B.1 Luxembourg 1.65 2020-03-17	
USA/AZ-TG268281/2020/B.1 USA 1.65 2020-03-17	
USA/AZ-TG268657/2020/B.1 USA 1.65 2020-03-17	
USA/NY-NYUMC4/2020/B.1 USA 1.65 2020-03-16	
Russia/StPetersburg-RII3992/2020/B.1 Russia 1.65 2020-03-18	
Russia/Samara-73406/2020/B.1 Russia 1.65 2020-03-20	
India/GMC-KN318/2020/B.1 India 1.65 2020-03-11	
Sweden/20-05627/2020/B.1 Sweden 1.65 2020-03-13	
Sweden/20-05856/2020/B.1 Sweden 1.65 2020-03-17	
Sweden/20-06468/2020/B.1 Sweden 1.65 2020-03-25	
Saudi_Arabia/KAUST-Jeddah61/2020/B.1 Saudi_Arabia 1.65 2020-04-01	
USA/NY-WCMP2D04P/2020/B.1 USA 1.65 2020-03-12	
Greece/127_HPI/2020/B.1 Greece 1.65 2020-02-29	
Italy/CDG1/2020/B.1 Italy 1.65 2020-02-20	
Italy/FVG-ICGEB_S8/2020/B.1 Italy 1.65 2020-03-01	
Luxembourg/LNS2580723/2020/B.1 Luxembourg 1.65 2020-03-22	
France/GE1973/2020/B.1 France 1.65 2020-03-04	
England/20132081104/2020/B.1 UK 1.65 2020-03-24	
Italy/FVG-ICGEB_S9/2020/B.1 Italy 1.65 2020-03-01	
Wales/PHWC-27C1E/2020/B.1 UK 1.65 2020-03-31	
Australia/VIC141/2020/B.1 Australia 1.65 2020-03-16	
Scotland/CVR56/2020/B.1 UK 1.65 2020-03-12	
Russia/StPetersburg-RII4936S/2020/B.1 Russia 1.65 2020-04-08	
Iceland/214/2020/B.1 Iceland 1.65 2020-03-16	
England/BRIS-123B05/2020/B.1 UK 1.65 2020-04-07	
England/20109047803/2020/B.1 UK 1.65 2020-03-07	
Australia/VIC652/2020/B.1 Australia 1.65 2020-03-28	
Australia/VIC198/2020/B.1 Australia 1.65 2020-03-19	
Australia/VIC682/2020/B.1 Australia 1.65 2020-03-29	
England/20104007503/2020/B.1 UK 1.65 2020-03-03	
USA/MI-MDHS-SC20173/2020/B.1 USA 1.65 2020-03-17	
USA/MI-MDHS-SC20142/2020/B.1 USA 1.65 2020-03-24	
USA/MI-MDHS-SC20134/2020/B.1 USA 1.65 2020-03-24	
Wales/PHWC-29E07/2020/B.1 UK 1.65 2020-04-04	
Wales/PHWC-27267/2020/B.1 UK 1.65 2020-03-31	
Germany/BAV-MVP0015/2020/B.1 Germany 1.65 2020-04-09	
Wales/PHWC-2B04B/2020/B.1 UK 1.65 2020-04-08	
Germany/BAV-MVP0082/2020/B.1 Germany 1.65 2020-03-30	
Japan/SMU-0311S3/2020/B.1 Japan 1.65 2020-03-11	

---

### 10.1.6. What will be needed to obtain and ship the candidate challenge viruses and to characterize them before and after manufacture of the GMP batches.

- Original clinical material from which the virus was isolated/sequenced will be necessary if it is desired to re-isolate the virus in qualified cells instead of plaque-purifying the virus.
- If re-isolation of the virus is desired, public health officials will have to track back from the list of possible candidate viruses to determine:
  - Whether original clinical material from which these sequences were derived is still available;
  - If desired, that the clinical history of the patients from whom these viruses were identified meet the criteria listed above;
  - That the laboratory that has the material is able to share it (appropriate consent, MTA, etc.).
- If the accompanying clinical and virological information is in a language different from languages read, written, and spoken by key staff in the BSL-3 manufacturer, it is recommended that an official translation should accompany the clinical information and the virological data along with Certificates of Translation to document accuracy.
- Each selected virus isolate intended to undergo GMP manufacture for use in volunteer challenge studies will have to be plaque-purified three times prior to manufacture.
- Plaque purification must occur in qualified cells under conditions that address the potential for introduction of new adventitious agents.
- It will be critical to establish the genetic sequence of each virus strain by New Generation Sequencing (NGS) both at the commencement and at the completion of the manufacturing process for each strain. This will allow the appearance of mutations to be identified, characterized and documented.
- The Advisory Group opined that each virus strain should be tested for adventitious agents by the rapid NGS method as well as by conventional methods.

## 11. Manufacture of GMP batches of SARS-CoV virus strains for volunteer challenge studies

### 11.1. Points to consider in identifying manufacturers for a GMP batch of SARS-CoV-2 challenge virus

#### 11.1.1. Background:

Manufacture of a SARS-CoV-2 challenge virus pool will require a BSL3 manufacturing facility. The type of formulation and the dosing in the vials should be selected to minimize handling.

#### 11.1.2. Assumptions related to manufacture of GMP Batches of challenge viruses.

- The manufacturer of the challenge virus batches should perform plaque purification X3 in their GMP facility using qualified cells.
- Each challenge virus pool will have to be generated under cGMP conditions in a BSL-3 facility.
- Two viruses of each clade should be tested by the manufacturer in case growth or yield differs.

- Each virus will likely be passaged about 5-10 times in the manufacturing process.
- The proposed three initial dose levels to be used in the clinical challenge studies will be  $\sim 1 \times 10^2$  TCID<sub>50</sub>,  $\sim 1 \times 10^3$  TCID<sub>50</sub>, and  $\sim 1 \times 10^4$  TCID<sub>50</sub>. It is possible that a higher dose level ( $\sim 1 \times 10^5$  TCID<sub>50</sub>) may be needed for one or more of the strains.
- The titer and volume for the initial dose response studies should be predefined based on the estimated number of volunteers expected to participate in challenge studies and who will receive dose level 1 ( $\sim 1 \times 10^2$  TCID<sub>50</sub>), dose level 2 ( $\sim 1 \times 10^3$  TCID<sub>50</sub>) or dose level 3 ( $\sim 1 \times 10^4$  TCID<sub>50</sub>). One assumption may be that the middle dose may be the most likely to provide the best balance of infectivity and acceptable clinical signs/symptoms. This is only a guess.
- An engineered virulent SARS-CoV-2 derived by reverse genetics and containing a genetic “bar code” to identify the virus offers theoretical attractions. Such a “GMO” virus might evoke regulatory constraints in some countries,<sup>63</sup> whereas in other it would not. This type of strain would be most attractive if the GMP manufacturing facility and one or more High-Level Isolation clinical testing units reside within the same country and the national regulatory agency is one that does not have major issues per se with GMOs.

### 11.1.3. What will be needed.

- Genetic sequence data by NGS at the start and end of the manufacturing process to document whether mutations have appeared.
- A decision on whether the formulation of the virus will consist of frozen liquid or lyophilized material and the presentation for the final drug product, e.g., specific dose levels in vials or in pre-filled syringes. Note – The Advisory Group concluded that use of lyophilate would be inadvisable as it would require a reconstitution step with diluent which would increase biocontainment risk even in a High-Level Isolation Unit clinical arena. Fortunately, the potential manufacturers contacted preferred to prepare the frozen liquid formulation.
- Information from prospective manufacturers on how long it will take to manufacture the challenge virus pools.
- Information from prospective manufacturers on how long it will take to fill and finish the challenge material to prepare it as a clinical study-ready form as either vials or pre-filled syringes containing the challenge viruses in frozen liquid at “low” ( $\sim 1 \times 10^2$  TCID<sub>50</sub>), “medium” ( $\sim 1 \times 10^3$  TCID<sub>50</sub>), and “high” ( $\sim 1 \times 10^4$  TCID<sub>50</sub>) dose levels. Note -- The three potential manufacturers contacted all declined to prepare pre-filled syringes but were all ready and able to fill single-dose vials (or two-dose vials) with the desired dose levels.

### 11.1.4. Questions to ask potential manufacturers:

- Will the manufacturer’s insurance provide indemnification (product liability) for the product or will product liability insurance costs have to be carried by the sponsor?
- Total cost for manufacture of the virus challenge drug product.
- An estimate from the manufacturer on how long it will take to manufacture the virus challenge drug product including taking into consideration any preparatory administrative or regulatory paperwork.

### 11.1.5. A stability plan to monitor challenge virus potency over time

- In order to assure that there is no substantial loss of viability of the virus in the GMP batches over time, vials containing the final “drug product” (DP) for each virus will have to

---

undergo periodic testing to monitor the virus titer (TCID<sub>50</sub> or PFU) of the DP on an agreed upon schedule.

- The stability testing will initially have to be done at the same frequency for all three dose levels of each virus used in the Stage 1 challenge studies. However, once a specific challenge dose level is identified for each challenge virus from the Stage 1 dose-escalation studies, whereas the close monitoring must continue for the chosen challenge dose level, it may be possible to diminish the frequency of stability testing of the other dose levels.

#### 11.1.6. How to bring the challenge virus “drug product” out of BSL3

- A well-known global courier was contacted to explore possibilities for this service to perform the tasks and to learn of constraints.
  - It was noted that it is likely that a SARS-CoV-2 virus shipment will need to be flagged with management for approval.
  - The courier would provide a customs invoice for the shipper to fill in and would assist in getting export/import licenses where needed. They would consult with local offices, which will be the rate limiting step. For shipments from a manufacturing site to one or more clinical sites within the US there would likely be no need for paperwork.
- The needed export/import licenses and regulatory agency letters needed to transport the challenge virus drug product across international borders would be investigated on a case-by-case basis. In exploring such cross international border scenarios, the receiving facility would need to contact the relevant national regulatory agencies, as required.
- Shipping -- Once approval to ship has been given, the courier will provide the 650 packaging, assuming the virus is UN3373-compliant and will supply the dry ice along with the dry ice box. The courier can add in a temperature data logger and will top up the dry ice every 24 hours (or at shorter intervals if required). There is likely to be a cost for the additional dry ice. There shouldn't be a limit to the number of vials/boxes shipped but this would need to be confirmed at time of booking.
- Cost – A shipment from US to Europe or US to Australia is estimated to be approximately £1000.
- The size of the dry ice box will not impact cost, neither should the number boxes but this will need to be confirmed with the courier at the time of booking the shipment.
- How long it will take to manufacture and release challenge virus drug product and to get it transported to study sites – This estimate is impacted by two major factors, the manufacturer-specific agenda that the manufacturer largely (but not entirely) controls and specifics of shipping (that in great part depend on the site of manufacture and the site of the clinical trials and the import/export and regulatory rules to be addressed).

#### 11.2. Criteria for selection of a manufacturer of the challenge agents

Below are listed a set of criteria to be used in choosing a manufacturer to produce a GMP lot of each of the selected challenge viruses (which may require up to four separate GMP batches if all four viruses grow equally well).

- BSL-3 containment facilities for manufacture, finish and fill
- GMP production facility
- Previous experience of producing challenge inoculum desirable
- Validated cell line and assays as required

- Validated release testing assays
- QP release
- Dossier listing full documentation of production
- Stability testing plan

Previous communication with three potential manufacturers has indicated that the timeframe for producing four batches (lots) of challenge inoculum under GMP conditions is approximately 3-4 months. Contract negotiations, production of any pilot batches (“engineering runs”), etc., may need additional lead time. It is highly recommended that manufacturers are consulted early enough to ensure availability in the facility.

Assuming that the final formulation of challenge virus will be frozen liquid, aliquoted liquid will have to be filled into vials, as none of the three manufacturers contacted would be able to fill the final drug product into syringes prior to freezing.

### 11.3. Some Advisory Group suggestions to be discussed with the manufacturer

- Any strain that does not grow well would not be considered for further development.
- Any virus strain that grows well after multiple passages in tissue culture but that, upon sequencing, reveals one or more mutations of concern, will be winnowed from consideration for further development.
- Strains that grow well and that do not reveal problematic mutations will undergo bulk manufacture to prepare a “Drug Substance” for that virus strain. The titer of the bulk would likely have to be  $\geq 10^7$  TCID<sub>50</sub>/ml, as there will be some loss during freeze/thaw steps.
- Two strains will be selected for vialing, of which at least one must be a clade B1 strain.
- The vials of finished ‘Drug Product’ will contain either  $\geq 10^2$  TCID<sub>50</sub>/ml,  $\geq 10^3$  TCID<sub>50</sub>/ml, or  $\geq 10^4$  TCID<sub>50</sub>/ml, the initial three dose levels to be tested clinically. Only a limited number of vials should be manufactured for the early dose-escalation studies, perhaps 100-200 per strain dose, in order to avoid wastage until the suitable dose level is identified. Additional vials will have to be set aside for the stability plan that will monitor the dose levels in the vials over time.
- If one of the initial dose levels proves to be suitable, additional vials of that strain at the successful dose level can be requested for Stage 2 studies in larger numbers of volunteers.
- If the initial dose levels prove to be incorrect, the bulk Drug Substance for the strains will be re-accessed by the manufacturer to formulate a one-log higher dose for further dose-escalation studies.
- Strains and dose levels that are discarded from consideration presumably do need not to have continuing stability testing.
- It will be important to establish an early dialog and interactive relationship with the manufacturer so that these suggested points can be discussed with the manufacturer to have their input and feedback and to gain from their experience.

---

## 12. Report of the subgroup on measurement of immune responses pre- and post-challenge

### 12.1. Background

The Subgroup discussed which tests should be done to evaluate immune responses in volunteers experimentally exposed to SARS-CoV-2 (attenuated or fully virulent) under closely monitored conditions, as well as immune responses to specific vaccines administered prior to volunteers who may then participate in a challenge study. A range of (semi)-innate, humoral and cellular functions were discussed to characterize immune responses and are listed in Table 5, but the subgroup members are fully aware that additional assays may be considered by lead investigators at challenge study sites. The idea would be to characterize both antibody and cellular responses that could be associated with efficacy, as shown by resistance to challenge. Those responses that appear to be associated with efficacy could then be followed to determine duration of immune memory.

The vaccines to be tested in challenge studies would be prototype vaccines that have already demonstrated preliminary safety and immunogenicity in phase 1 or 2 clinical trials and are available for testing. These may include inactivated virus, purified subunit, mRNA, DNA, and live vector vaccines as prototypes. Candidate vaccines may be those given in one or two doses. In the latter case, the interval between doses will be four weeks and the challenge would be given circa four weeks after the second dose. The protective effect of convalescent plasma and monoclonal antibodies could also be assessed in parallel in challenge studies.

### 12.2. Principles of immunologic study of volunteer challenges with SARS-CoV-2

#### 12.2.1. Specific volunteer groups to be included in challenge studies:

- Volunteers who lack antibodies to SARS-CoV-2 (seronegatives).
- Volunteers who have antibodies to SARS-CoV-2 (seropositives) consequent to prior natural exposure or to closely monitored experimental infection.
- Volunteers immunized with candidate COVID-19 vaccines.

#### 12.2.2. Time Points Post-Challenge

Clinical specimens to measure immune responses will be collected on Days 0, 1, 3, 5, 7, 10, 14, 21, 28 days, 6 months and 12 months, and possibly at later time points to monitor the longevity of the immune responses. See **Table 4** for which tests will be performed on which days.

#### 12.2.3. Blood volume constraints

The total volume of blood to be collected *for all purposes* within the study cannot exceed a total of 500/ml per 8-week period of time. So, the various immunologic assays will have to be prioritized to remain within that volume constraint and efforts will have to be taken to minimize the volumes and to optimize the testing. For example, if certain antibody tests on certain timepoints can be performed with plasma, the same sample can provide peripheral blood mononuclear cells (PBMCs) for measurement of cellular responses, while the plasma from that specimen can be utilized for antibody measurements.

---

#### 12.2.4. Following exposure, protected and infected subjects can be studied for humoral and innate responses:

- Induced (semi)-Innate responses in circulation and/or airways
- Induction and duration of humoral responses in circulation and/or airways:
- Specific antibodies (specificity, affinity, isotype, functionality by *in vitro* assays)
- Composition/activation of B cell populations (blasts, memory, atypicals)

#### 12.2.5. Induction and duration of cellular responses in circulation and/or airways:

- Composition/activation of T (subset) cell populations including regulatory T cell network
- Functionality *ex vivo* of induced T (subset) populations (cytotoxicity, cytokines)
- Specificity of induced T (subset) populations
- RNA-seq

#### 12.2.6. Pathology of Cellular Responses

Induced (semi)-Innate responses in relation to viral load and clinical signs/symptoms

- Soluble markers of inflammation in circulation and/or airways
- Composition, activation (surface markers) of innate cell populations (e.g., mono (subsets), NK (T) cells, gamma delta T cells, ILC's) in circulation and/or airways
- *Ex vivo* production of inflammatory markers
  - RNA-seq in identified subsets

### 12.3. The volunteer challenge model can contribute to identification of

#### 12.3.1. Immune mechanisms / immune correlate signatures for:

- Pathology
- Exposure
- Protection
- Disease enhancement

The theoretical concern that some types of COVID-19 vaccines in humans might inadvertently be associated with disease enhancement has been flagged by several authorities.<sup>64,65</sup> Other Advisory Groups have reviewed available preclinical animal data and have discussed the theoretical possibility of such events occurring.<sup>66</sup> Accordingly, this Subgroup did not delve into this area.

#### 12.3.2. Longevity of immune responses

- Duration of induced immune responses
- Induction and duration of immune memory
- Identification of immune targets for clinical vaccine development
- Immune regulation: Induction of immune evasion/suppression/immunopathology

Table 4. Immune functions to be evaluated during Human Challenge Studies						
Immune Effector	Clinical Specimen	Antigen (source)	Measure	Assay	Timepoints	Include in studies to address
Antibodies	Serum	RBD on S1	Binding	IgG, IgM and IgA ELISA (Krammer)	Baseline, days 7, 14, 21 and 28	Pathology Exposure/protection Disease enhancement
Antibodies	Serum	S1 protein	Binding	IgG, IgM and IgA ELISA commercial or CDC/NIH (Natalie Thornberg/ Barney Graham ELISA	Baseline, days 7, 14, 21 and 28	Pathology Exposure/protection Disease enhancement
Antibodies	Serum	S1 protein	Binding	IgG subclasses	Baseline, days 7, 14, 21 and 28	Pathology Exposure/protection
Antibodies	Serum		Neutralizing Ab	Live virus in BSL3 Surrogate sVNT (Linfa Wang/Genscript) in BSL2 Identification of the epitopes inducing neutralizing antibodies	Baseline, days 7, 14, 21 and 28	Pathology Exposure/protection Disease enhancement
Antibodies	Serum		Neutralizing Ab	Pseudovirion approach (which would be amenable in a BSL-2 lab) reagents are available under MTA from VRC, NIH (Barney Graham) Must be accompanied by neutralization assays using infectious virus	Baseline, days 7, 14, 21 and 28	Pathology Exposure/protection
Antibodies	Serum	Spike protein	Dimeric IgA	David Anderson, Burnet Instt, Melbourne	Baseline, days 7, 14	Exposure/protection
Antibodies	Serum		ADCC Ab	Promega kit	Baseline, days 7, 14, 21 and 28	Pathology Exposure/protection Disease enhancement
Antibodies	Nasal washes (to detect mucosal antibodies)	S1?	IgA subclasses; IgG	ELISA		Pathology Exposure/protection
Cellular	Peripheral blood mononuclear cells (PBMC)		Counts of B and T (CD4 <sup>+</sup> and CD8 <sup>+</sup> ) cells		Baseline, days 7, 14, 21 and 28	Pathology Exposure/protection Disease enhancement
Cellular	PBMC	Stimulation with specific peptides/ inactivated virus?	T cells: cTfh	CD4+CXCR5+ICOS+PD-1+ Thevarajan Nat Med 2020 <sup>67</sup>	Baseline, days 7, 14, 21 and 28	Pathology Exposure/protection Disease enhancement
Cellular	PBMC	Stimulation with specific peptides/ inactivated virus	Activated CD8 <sup>+</sup> T cells	CD38+HLA-DR+ CD8+ Thevarajan Nat Med 2020 <sup>67</sup>	Baseline, days 7, 14, 21 and 28	Pathology Exposure/protection Disease enhancement
Cellular	PBMC	S1/ inactivated virus/peptides	B cells: Antibody secreting cells (ASC)	CD3–CD19+CD27hiCD38hi Thevarajan Nat Med 2020 <sup>67</sup>	Baseline, days 7	Pathology Exposure/protection
Cellular	PBMC	S1/ inactivated virus/	B cells: Antibody secreting cells (ASC)	IgG, IGA and IgM ASC by ELISPOT	Baseline, days 7, 14, 21 and 28	Pathology Exposure/protection
Immune Effector	Clinical Specimen	Antigen (source)	Measure	Assay	Timepoints	Include in studies to address

Cellular	PBMC	S1 and RBD	memory B cells	IgG and IgA Bm cells CD3(-)CD19(+)IgD(-) CD27(+)).	Baseline, days 7, 14, 21 and 28	Pathology Exposure/protection
Cellular	PBMC	S1/ inactivated virus/peptides	Th 1/2 orientation	Which cytokines?	Baseline, days 7, 14, 21 and 28	Pathology Exposure/protection Disease enhancement
Cellular	PBMC	S1/ inactivated virus/peptides	Th17 cells and IL-17 production		Baseline, days 7, 14, 21 and 28	Pathology Exposure/protection Disease enhancement
Cellular	PBMC and serum	S1/ inactivated virus/peptides	Cytokines, especially IL-6		Baseline and every other day	Pathology Exposure/protection
Innate immune system	Serum		CRP protein level		Baseline and Day 1 and 3 minimum	Pathology Exposure/protection Disease enhancement
Transcriptomics	Whole blood PAXgene tubes		Transcriptomics		Baseline and every other day	Pathology Exposure/protection Disease enhancement

---

## 13. Subgroup on detection of SARS-CoV-2 in clinical specimens post-challenge

### 13.1. Nucleic acid assay

#### 13.1.1 Sampling

Upper respiratory tract sampling of every challenged volunteer will take place every day until 14 days after challenge. Recognizing that nasopharyngeal swabs may be both uncomfortable and traumatic to nasal mucosa, these swabs may be interspersed with saliva or oral fluid samples.

Whereas most persons infected with SARS-CoV-2 shed virus for only up to 14 days, it is well recognized that a small proportion of infected individuals may have positive RT-PCR tests for up to 25-28 days. Therefore, we suggest daily sampling until three consecutive negative PCR samples, at least two days apart, are obtained, to indicate that the virus is cleared.

#### 13.1.2. Sample types

##### 13.1.2.1. Clinical specimens to be tested will include:

- Induced sputum of the lower respiratory tract (preferred);
- Nasopharyngeal swabs (preferred);
- Bronchoalveolar lavage (BAL) (for any patient that developed severe illness).

##### 13.1.2.2. Detection methods:

- Quantitative PCR targeting at least 2 genes (RdRp and E/N) and with the internal control of a housekeeping gene to monitor the quality of the sample.
- Detection of virus by culture
  - Virus isolation in Vero E6 or Vero cells determined by CPE;
  - Confirmation by IFA or PCR (without CPE)
  - Virus titer quantified by TCID<sub>50</sub> or PFU.
  - Successful isolation of virus will be correlated with the Ct value from PCR detection.
  - Sequencing of the initial subject's virus obtained by culture and of the last positive virus culture by next generation sequencing.

## Selected references

1. Lurie N, Saville M, Hatchett R, Halton J. Developing Covid-19 Vaccines at Pandemic Speed. *N.Engl.J Med.* 2020:10.
2. Gsell PS, Camacho A, Kucharski AJ, Watson CH, Bagayoko A, Nadlaou SD et al. Ring vaccination with rVSV-ZEBOV under expanded access in response to an outbreak of Ebola virus disease in Guinea, 2016: an operational and vaccine safety report. *Lancet Infect.Dis.* 2017; **17**:1276-84.
3. Wells CR, Pandey A, Parpia AS, Fitzpatrick MC, Meyers LA, Singer BH et al. Ebola vaccination in the Democratic Republic of the Congo. *Proc.Natl.Acad.Sci.U.S.A.* 2019; **116**:10178-83.
4. FDA. FDA News Release -- First FDA-approved vaccine for the prevention of Ebola virus disease, marking a critical milestone in public health preparedness and response. 12-19-2019. US Food and Drug Administration. 12-19-2019.  
Ref Type: Report
5. Callaway E. 'Make Ebola a thing of the past': first vaccine against deadly virus approved. *Nature.* 2019; **575**:425-6.

6. Cohen J. The Truest Test. *Science*. 2016; **20**;352:882-5.
7. Chen WH, Cohen MB, Kirkpatrick BD, Brady RC, Galloway D, Gurwith M et al. Single-Dose Live Oral Cholera Vaccine CVD 103-HgR Protects Against Human Experimental Infection with *Vibrio cholerae* O1 El Tor. *Clin.Infect Dis*. 2016; **62**:1329-35.
8. Levine MM, Chen WH, Kaper JB, Lock M, Danzig L, Gurwith M. PaxVax CVD 103-HgR single-dose live oral cholera vaccine. *Expert.Rev.Vaccines*. 2017; **16**:197-213.
9. Stoute JA, Slaoui M, Heppner DG, Momin P, Kester KE, Desmons P et al. A preliminary evaluation of a recombinant circumsporozoite protein vaccine against Plasmodium falciparum malaria. RTS,S Malaria Vaccine Evaluation Group. *N.Engl.J.Med*. 1997; **336**:86-91.
10. Lyke KE, Ishizuka AS, Berry AA, Chakravarty S, DeZure A, Enama ME et al. Attenuated PfSPZ Vaccine induces strain-transcending T cells and durable protection against heterologous controlled human malaria infection. *Proc.Natl.Acad.Sci.U.S.A.* 2017; **114**:2711-6.
11. Treanor JJ, Kotloff K, Betts RF, Belshe R, Newman F, Iacuzio D et al. Evaluation of trivalent, live, cold-adapted (CAIV-T) and inactivated (TIV) influenza vaccines in prevention of virus infection and illness following challenge of adults with wild-type influenza A (H1N1), A (H3N2), and B viruses. *Vaccine*. 1999; **18**:899-906.
12. Larsen CP, Whitehead SS, Durbin AP. Dengue human infection models to advance dengue vaccine development. *Vaccine*. 2015; **33**:7075-82.
13. Gomez-Perez GP, Legarda A, Munoz J, Sim BK, Ballester MR, Dobano C et al. Controlled human malaria infection by intramuscular and direct venous inoculation of cryopreserved Plasmodium falciparum sporozoites in malaria-naïve volunteers: effect of injection volume and dose on infectivity rates. *Malar.J.* 2015; **14**:306. doi: 10.1186/s12936-015-0817-x.306-0817.
14. Jin C, Gibani MM, Moore M, Juel HB, Jones E, Meiring J et al. Efficacy and immunogenicity of a Vi-tetanus toxoid conjugate vaccine in the prevention of typhoid fever using a controlled human infection model of Salmonella Typhi: a randomised controlled, phase 2b trial. *Lancet*. 2017;10:6736.
15. Levine MM, Barry EM, Chen WH. A roadmap for enterotoxigenic Escherichia coli vaccine development based on volunteer challenge studies. *Hum.Vaccin.Immunother*. 2019:1-22.
16. Sauerwein RW, Roestenberg M, Moorthy VS. Experimental human challenge infections can accelerate clinical malaria vaccine development. *Nat.Rev.Immunol*. 2011; **11**:57-64.
17. Yap XZ, McCall MBB, Sauerwein RW. Fast and fierce versus slow and smooth: Heterogeneity in immune responses to Plasmodium in the controlled human malaria infection model. *Immunol.Rev*. 2020; **293**:253-69.
18. Black RE, Levine MM, Clements ML, Losonsky G, Herrington D, Berman S et al. Prevention of shigellosis by a *Salmonella typhi*-*Shigella sonnei* bivalent vaccine. *J.Infect.Dis*. 1987; **155**:1260-5.
19. Atmar RL, Bernstein DI, Harro CD, Al-Ibrahim MS, Chen WH, Ferreira J et al. Norovirus vaccine against experimental human Norwalk Virus illness. *N.Engl.J.Med*. 2011; **365**:2178-87.
20. Tao T, Skiadopoulos MH, Durbin AP, Davoodi F, Collins PL, Murphy BR. A live attenuated chimeric recombinant parainfluenza virus (PIV) encoding the internal proteins of PIV type 3 and the surface glycoproteins of PIV type 1 induces complete resistance to PIV1 challenge and partial resistance to PIV3 challenge. *Vaccine*. 1999; **17**:1100-8.
21. Roestenberg M, Mordmüller B, Ockenhouse C, Mo A, Yazdanbakhsh M, Kremsner PG. The frontline of controlled human malaria infections: A report from the controlled human infection models Workshop in Leiden University Medical Centre 5 May 2016. *Vaccine*. 2017; **35**:7065-9.
22. Eyal N, Lipsitch M, Smith PG. Human challenge studies to accelerate coronavirus vaccine licensure. *J Infect.Dis*. 2020:5814216.
23. Cohen J. Infect volunteers to speed a coronavirus vaccine? *Science*. 2020; **368**:16.
24. Plotkin, S. A. and Caplan, A. Extraordinary diseases require extraordinary solutions. *Vaccine* . 2020.
- Ref Type: In Press
25. Jongo SA, Shekalaghe SA, Church LWP, Ruben AJ, Schindler T, Zenklusen I et al. Safety, Immunogenicity, and Protective Efficacy against Controlled Human Malaria Infection of Plasmodium falciparum Sporozoite Vaccine in Tanzanian Adults. *Am.J Trop.Med.Hyg*. 2018; **99**:338-49.
26. van DN, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN et al. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. *N.Engl.J Med*. 2020; **382**:1564-7.

- 
27. Levine MM, Campbell JD, Kotloff KL. Overview of vaccines and immunisation. *British Medical Bulletin* 2002; **62**:1-13.
28. Levine MM, Chen WH. How are vaccines assessed in clinical trials? In: Bloom BR, Lambert PH, editors. Second ed. Philadelphia: Academic Press; 2016.
29. Schaffer DS, Pudalov NJ, Fu LY. Planning for a COVID-19 Vaccination Program. *JAMA*. 2020:10.
30. Henao-Restrepo AM, Longini IM, Egger M, Dean NE, Edmunds WJ, Camacho A et al. Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial. *Lancet*. 2015:10-6736.
31. Gunther S, Feldmann H, Geisbert TW, Hensley LE, Rollin PE, Nichol ST et al. Management of accidental exposure to Ebola virus in the biosafety level 4 laboratory, Hamburg, Germany. *J.Infect.Dis.* 2011; **204 Suppl 3:S785-90**. doi: **10.1093/infdis/jir298**.:S785-S790.
32. Agnandji ST, Huttner A, Zinser ME, Njuguna P, Dahlke C, Fernandes JF et al. Phase 1 Trials of rVSV Ebola Vaccine in Africa and Europe - Preliminary Report. *N.Engl.J.Med.* 2015; DOI: **10.1056/NEJMoa1502924**.
33. Regules JA, Beigel JH, Paolino KM, Voell J, Castellano AR, Hu Z et al. A Recombinant Vesicular Stomatitis Virus Ebola Vaccine. *N.Engl.J Med.* 2017; **376**:330-41.
34. Tapia MD, Doumbia M, Dembele R, Ball K, N'Diaye B, Amadou H et al. Arranging good clinical practices training and trial monitoring for a vaccine efficacy study during a public health emergency of international concern. *Vaccine*. 2020:10.
35. Hossmann S, Haynes AG, Spoerri A, Diatta ID, Aboubacar B, Egger M et al. Data management of clinical trials during an outbreak of Ebola virus disease. *Vaccine*. 2019; **37**:7183-9.
36. Dean NE, Gsell PS, Brookmeyer R, De G, V, Donnelly CA, Halloran ME et al. Design of vaccine efficacy trials during public health emergencies. *Sci.Transl.Med.* 2019; **11**:eaat0360.
37. Vannice KS, Cassetti MC, Eisinger RW, Hombach J, Knezevic I, Marston HD et al. Demonstrating vaccine effectiveness during a waning epidemic: A WHO/NIH meeting report on approaches to development and licensure of Zika vaccine candidates. *Vaccine*. 2019; **37**:863-8.
38. Smetana J, Chlibek R, Shaw J, Splino M, Prymula R. Influenza vaccination in the elderly. *Hum.Vaccin.Immunother.* 2018; **14**:540-9.
39. Weinberger B, Herndler-Brandstetter D, Schwanninger A, Weiskopf D, Grubeck-Loebenstien B. Biology of immune responses to vaccines in elderly persons. *Clin.Infect.Dis.* 2008; **46**:1078-84.
40. Levine MM, Black RE, Clements ML, Cisneros L, Nalin DR, Young CR. Duration of infection-derived immunity to cholera. *J.Infect.Dis.* 1981; **143**:818-20.
41. Memoli MJ, Han A, Walters KA, Czajkowski L, Reed S, Athota R et al. Influenza A Reinfection in Sequential Human Challenge: Implications for Protective Immunity and "Universal" Vaccine Development. *Clin.Infect.Dis.* 2020; **70**:748-53.
42. Levine MM, Nalin DR, Craig JP, Hoover D, Bergquist EJ, Waterman D et al. Immunity of cholera in man: relative role of antibacterial versus antitoxic immunity. *Trans.R.Soc.Trop.Med.Hyg.* 1979; **73**:3-9.
43. Harro C, Chakraborty S, Feller A, Denearing B, Cage A, Ram M et al. Refinement of a human challenge model for evaluation of enterotoxigenic Escherichia coli vaccines. *Clin.Vaccine Immunol.* 2011; **18**:1719-27.
44. Chakraborty S, Harro C, Denearing B, Ram M, Feller A, Cage A et al. Characterization of Mucosal Immune Responses to Enterotoxigenic Escherichia coli Vaccine Antigens in a Human Challenge Model: Response Profiles after Primary Infection and Homologous Rechallenge with Strain H10407. *Clin.Vaccine Immunol.* 2015; **23**:55-64.
45. Herrington DA, Van de Verg L, Formal SB, Hale TL, Tall BD, Cryz SJ et al. Studies in volunteers to evaluate candidate Shigella vaccines: further experience with a bivalent *Salmonella typhi-Shigella sonnei* vaccine and protection conferred by previous *Shigella sonnei* disease. *Vaccine* 1990; **8**:353-7.
46. Kotloff KL, Nataro JP, Losonsky GA, Wasserman SS, Hale TL, Taylor DN et al. A modified Shigella volunteer challenge model in which the inoculum is administered with bicarbonate buffer: clinical experience and implications for Shigella infectivity. *Vaccine* 1995; **13**:1488-94.
47. Black RE, Levine MM, Clements ML, Hughes TP, Blaser MJ. Experimental Campylobacter jejuni infection in humans. *J.Infect.Dis.* 1988; **157**:472-9.

- 
48. Callow KA, Parry HF, Sergeant M, Tyrrell DA. The time course of the immune response to experimental coronavirus infection of man. *Epidemiol.Infect.* 1990; **105**:435-46.
49. Kupferschmidt K, Cohen J. Race to find COVID-19 treatments accelerates. *Science.* 2020; **367**:1412-3.
50. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC et al. Remdesivir for the Treatment of Covid-19 - Preliminary Report. *N.Engl.J Med.* 2020:10.
51. Cieslak TJ, Kortepeter MG. A Brief History of Biocontainment. *Curr.Treat.Options.Infect.Dis.* 2016; **8**:251-8.
52. Fidler DP, Gostin LO, Markel H. Through the quarantine looking glass: drug-resistant tuberculosis and public health governance, law, and ethics. *J Law Med.Ethics.* 2007; **35**:616-28, 512.
53. Markel H, Gostin LO, Fidler DP. Extensively drug-resistant tuberculosis: an isolation order, public health powers, and a global crisis. *JAMA.* 2007; **298**:83-6.
54. Van DP, Coster I, Bandyopadhyay AS, Suykens L, Rudelsheim P, Neels P et al. Poliopolis: pushing boundaries of scientific innovations for disease eradication. *Future.Microbiol.* 2019; **14**:1321-1330. doi: 10.2217/fmb-2019-0196. Epub;2019 Sep 4.:1321-30.
55. Nalin DR, Levine MM, Hornick RB, Bergquist EJ, Hoover D, Holley HP et al. The problem of emesis during oral glucose-electrolytes therapy given from the onset of severe cholera. *Trans.R.Soc.Trop.Med.Hyg.* 1979; **73**:10-4.
56. Levine MM, Black RE, Clements ML, Lanata C, Sears S, Honda T et al. Evaluation in humans of attenuated *Vibrio cholerae* El Tor Ogawa strain Texas Star-SR as a live oral vaccine. *Infect.Immun.* 1984; **43**:515-22.
57. Levine MM, Kaper JB, Herrington D, Ketley J, Losonsky G, Tacket CO et al. Safety, immunogenicity, and efficacy of recombinant live oral cholera vaccines, CVD 103 and CVD 103-HgR. *Lancet* 1988; **2**:467-70.
58. Bannister B, Puro V, Fusco FM, Heptonstall J, Ippolito G. Framework for the design and operation of high-level isolation units: consensus of the European Network of Infectious Diseases. *Lancet Infect.Dis.* 2009; **9**:45-56.
59. Brouqui P, Puro V, Fusco FM, Bannister B, Schilling S, Follin P et al. Infection control in the management of highly pathogenic infectious diseases: consensus of the European Network of Infectious Disease. *Lancet Infect.Dis.* 2009; **9**:301-11.
60. Andonian J, Galusha KE, Maragakis LL, Garibaldi BT. The Impact of High-Level Isolation Units Beyond High-Consequence Pathogen Preparedness. *Health Secur.* 2019; **17**:69-73.
61. Garibaldi BT, Kelen GD, Brower RG, Bova G, Ernst N, Reimers M et al. The Creation of a Biocontainment Unit at a Tertiary Care Hospital. The Johns Hopkins Medicine Experience. *Ann.Am.Thorac.Soc.* 2016; **13**:600-8.
62. Memoli MJ, Czajkowski L, Reed S, Athota R, Bristol T, Proudfoot K et al. Validation of the wild-type influenza A human challenge model H1N1pdMIST: an A(H1N1)pdm09 dose-finding investigational new drug study. *Clin.Infect.Dis.* 2015; **60**:693-702.
63. Jamrozik E, Selgelid MJ. Human challenge studies in endemic settings: ethical and regulatory issues. Springer Briefs in Ethics. Springer; 2020.
64. Graham BS. Rapid COVID-19 vaccine development. *Science.* 2020; **368**:945-6.
65. Peeples L. News Feature: Avoiding pitfalls in the pursuit of a COVID-19 vaccine. *Proc.Natl.Acad.Sci.U.S.A.* 2020; **117**:8218-21.
66. Lambert PH, Ambrosino DM, Andersen SR, Baric RS, Black SB, Chen RT et al. Consensus summary report for CEPI/BC March 12-13, 2020 meeting: Assessment of risk of disease enhancement with COVID-19 vaccines. *Vaccine.* 2020:10.
67. Thevarajan I, Nguyen THO, Koutsakos M, Druce J, Caly L, van de Sandt CE et al. Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19. *Nat.Med.* 2020; **26**:453-5.

---

## APPENDIX A

### Members of the Advisory Group

Chair: Prof. Myron (Mike) M. Levine  
Prof. Salim Abdullah  
Prof Yaseen Arabi  
Mrs. Delese Mimi Darko  
Prof Vicente Estrada  
Prof Anna Durbin  
Dr. Euzebiusz Jamrozik  
Prof Peter Kremsner  
Dr. Rosanna Lagos  
Prof Punnee Pitisuttithum  
Prof Stanley Plotkin  
Prof Robert Sauerwein  
Prof Zheng-Li Shi  
Prof Halvor Sommerfelt  
Prof Kanta Subbarao  
Prof John J Treanor  
Prof Sudhanshu Vrat

Observers: Wellcome Trust (Dr. Debbie King, Dr. Shobana Balasingam, Dr. Charlie Weller)  
Bill & Melinda Gates Foundation (Anastazia Older Alguilar)  
NIAID, NIH (Dr. Cristina Cassetti), Dr. Philip Krause (FDA)

WHO: Secretariat: Dr. Ana Maria Henao Restrepo,

WHO Support: Dr. Pierre Gsell, Ximena Riveros, Neddy Mafunga

---

## APPENDIX B

### **A Short Overview of High-Level Isolation Units in the USA and Similar Containment Units in Europe and a Brief Description of Laboratory Biosafety Levels and their Relevance for Facilities and Practices in High-Level Isolation Units for Clinical Care and Clinical Research**

To conduct COVID-19 human challenge studies with a minimal risk of transmission to staff or other persons, these studies should be performed in High-Level Isolation Units (HLIU). The WHO Advisory Group judged that this guidance should be strictly followed during Stage 1 challenge studies that try to establish the model and when candidate challenge virus strains are being assessed in careful dose escalation studies and when there are no data or only minimal data on the clinical and virus shedding responses to challenge. If a potentially safe model should become successfully established and Stage 2 studies (involving a large number of volunteers than Stage 1) are being considered, if those studies are planned to proceed in a geographic site where at the time there is no evidence of active transmission of SARS-CoV-2 in the community, the Advisory Group recommendation is for those Stage 3 studies also to be restricted to performance in HLIU units.

Following the Ebola outbreak of 2016, HLIUs were developed in Europe, the United States, and other parts of the world with the anticipation that patients may be transported to different regions for care. As an example, the description of these units in the USA that is provided below is taken from the Assistant Secretary for Preparedness and Response's report that describes the Regional Treatment Network for Ebola and other Special Pathogens released in November, 2017.<sup>1</sup> The descriptions of the tiered network is applicable to HLIUs found in Europe and other regions of the world that have set up similar networks. The hospitals that make up the tiered network serve different purposes depending on their capabilities (see Table I), although an institution can perform more than one of the functions described below.

The tiered isolation units in the USA and their functions are summarized in Table 1, below. Tiers 1 and 2 are considered High-Level Isolation Units. Tier 1 centers were designated as regional Ebola and special pathogens centers. They have some requirements above those of the Tier 2 Treatment centers. Ten hospitals listed in Table 2 were designated as Tier 1 Regional Ebola and Special Pathogens Treatment Centers (RESPTC). There are 63 Tier 2 units in the USA and several in Europe that are specially designed High-level Isolation Units equipped with infrastructure, laboratory capabilities, and trained staff to minimize transmission risks while caring for patients with highly hazardous communicable diseases (HHCD) such as hemorrhagic fever viruses, Avian influenza virus, SARS, MERS, and COVID-19. These units have the stringent infection control measures, the ability to process laboratory specimens safely, the possibility of point-of-care clinical laboratory testing, and specialized specimen transport.

**Tier 1 and Tier 2 level units are able to care for patients under precautions to prevent contact, droplet, and/or airborne transmission.** The infrastructure contains single patient rooms under negative pressure. However, many of the units do not have dedicated PPE donning and doffing areas or one-way flow of personnel on and off the unit. Personnel must use N95 masks with a face shield or a PAPR in the "warm zones" which are outside of the patient rooms but within the unit. This would include the nurses' station, hallway, storage rooms, etc. The capabilities of the units are described in the table below. The WHO Advisory Group strongly advises that COVID-19 human challenge model development (Stage 1 studies) should be performed in Tier 1 or 2 High Level Isolation Units, as described above, to ensure that sufficient infection control procedures were in place.

To reduce the risk of exposure to others, the challenge virus should be stored under appropriate highly secure conditions on the HLIU. Of special concern is preparation of the challenge inoculum and the inoculation procedure itself because these pose a high risk of transmission to staff. Preparation and administration of the inoculum should be considered procedures that are likely to

generate infectious droplets or aerosols. Tier 1 units have biosafety cabinets within the unit in which the inoculum could be drawn into a syringe or pipet and then taken directly to the subject's room for administration. The inoculum should be given by a person in full contact, droplet, and airborne precaution PPE. The syringe or pipet would be disposed of as hazardous waste and treated per the standard procedures on the unit. Tier 2 units, in general, do not have biosafety cabinets on the unit. In this case, the inoculum should be prepared in the subject's room by personnel wearing full contact, droplet, and aerosol precaution PPE.

<b>Table I. Different tiered containment levels in the USA</b>		
<b>Tier</b>	<b>N</b>	<b>Role and Capabilities Required</b>
<b>Tier 4:</b> Frontline Healthcare Facility	4,845 in USA	<ul style="list-style-type: none"> <li>• Quickly identifies and isolates patients</li> <li>• Notifies facility infection control and state and local public health officials</li> <li>• Has enough PPE for at least 12-24 hours of care</li> </ul>
<b>Tier 3:</b> Assessment hospital (N=217)	217 in USA	<ul style="list-style-type: none"> <li>• Safely receives and Isolates a patient with possible highly hazardous communicable disease (HHCD)</li> <li>• Provides immediate laboratory evaluation and coordinates Ebola virus disease (EVD) or other HHCD testing</li> <li>• Provides immediate laboratory evaluation and coordinates EVD or other HHCD testing</li> <li>• Cares for a patient for up to 96 hours until disease is confirmed or ruled out</li> <li>• Secured services of waste management vendor capable of managing and transporting Category A infectious substances</li> <li>• Coordinates transport of the patient to an Ebola Treatment Center (ETC) depending on the status of the patient and the capacity of the Ebola assessment hospital</li> </ul>
<b>Tier 2:</b> Treatment centers	US = 63 EU = 23 (EU, Table III)	<ul style="list-style-type: none"> <li>• Safely receives and isolates a patient with confirmed EVD or other HHCD</li> <li>• Cares for patients for duration of illness</li> <li>• Has enough PPE for at least 7 days of care (will restock as needed)</li> <li>• Has sustainable staffing plan to manage several weeks of care</li> <li>• Secure the services of a waste management vendor capable of managing and transporting Category A infectious substances</li> <li>• CDC experts are ready to deploy to provide assistance as needed</li> </ul>
<b>Tier 1:</b> Regional Ebola and special pathogens treatment centers (Table 2)	16	<p>These hospitals are part of the network of Ebola treatment centers across the country but have "enhanced capabilities". They are required to:</p> <ul style="list-style-type: none"> <li>• Accept patients within 8 hours of notification</li> <li>• Be able to treat simultaneously at least 2 EVD patients for duration of illness</li> <li>• Have respiratory infectious disease isolation capacity or negative pressure rooms for at least 10 patients</li> <li>• Conduct trainings and exercises each quarter</li> <li>• Be able to treat pediatric patients with EVD or another highly infectious disease or partner with a nearby facility to do so</li> <li>• Be able to safely handle waste from such patients</li> <li>• Receive annual readiness assessment from the National Ebola Training and Education Center</li> </ul>

<b>Table II. Regional Ebola and Special Pathogens Treatment Centers worldwide (Tier 1).</b>		
<b>Name of Unit</b>	<b>City</b>	<b>Country/State</b>
<b>Europe</b>		

Infectious Diseases Hospital Lazzaro Spallanzani	Rome	Italy
University Medical Centre Hamburg-Eppendorf	Hamburg	Germany
Charity University Medicine	Berlin	Germany
Hospital La Paz Carlos 111	Madrid	Spain
HCDGU	Madrid	Spain
Newcastle Royal Victoria Infirmary High-Level Isolation Unit	Newcastle	United Kingdom
<b>USA</b>		
Massachusetts General Hospital	Boston	Massachusetts
NYC Health and hospitals Bellevue	New York City	New York
Johns Hopkins Hospital*	Baltimore	Maryland
Emory University and Children's healthcare of Atlanta	Atlanta	Georgia
University of Minnesota Medical Center	Minneapolis	Minnesota
University of Nebraska*	Omaha	Nebraska
University of Texas Medical branch at Galveston	Galveston	Texas
Denver Health Medical Center	Denver	Colorado
Cedars-Sinai Hospital	Los Angeles	California
Providence Sacred Heart Medical Center and Children's Hospital	Seattle	Washington State
* These facilities have the capability of converting normal patient care rooms/floors to biomode (Tier 2)		

<b>Table III. High Level Isolation Units (HLIU) in Europe (Tier 2)<sup>2</sup></b>	
<b>Country</b>	<b>No. Units</b>
Finland	1
France	5
Germany	6
Greece	1
Ireland	1
Italy	2
Norway	1
Spain	5
United Kingdom	1

Many of these units have a limited number of beds (see Table 1 in the body of the report). The Tier 2 hospitals potentially have more beds that can be converted to HLIUs. However, these are not free-standing clinical research units; they were designed for care of hospitalized patients. It would therefore be difficult to enroll more than ~ 10 subjects per unit for a COVID-19 challenge study. Until the transmissibility of the SARS-CoV-2 strain used in human challenge studies has been characterized, these studies should be performed on a HILU. Should the challenge strain be less transmissible and infection control experts agree, future studies may be done on units with their own HVAC system under droplet isolation but this would have to be determined after expert review.

### **Laboratory Biosafety Levels and Guidelines and their Relevance for Mitigating to Risks in Clinical Challenge Studies with Highly Infectious Agents**

---

The US government has recommendations and guidelines in place for laboratory work with microbiological agents in vitro and in animals (BMBL).<sup>3</sup> The primary risk criteria used to define the four ascending levels of containment, referred to as biosafety levels 1 through 4, are: infectivity; severity of disease; transmissibility; and the nature of the work being conducted. Another important risk factor for agents that cause moderate to severe disease is the origin of the agent, whether indigenous or exotic. Each level of containment describes the microbiological practices, safety equipment and facility safeguards for the corresponding level of risk associated with handling a particular agent. These basic practices and equipment are appropriate for protocols common to most research and clinical laboratories. The facility safeguards help protect non-laboratory occupants of the building and the public health and environment.

Biosafety level 1 (BSL-1) is the basic level of protection and is appropriate for agents that are not known to cause disease in normal, healthy humans.

Biosafety level 2 (BSL-2) is appropriate for handling moderate-risk agents that cause human disease of varying severity by ingestion or through percutaneous or mucous membrane exposure.

Biosafety level 3 (BSL-3) is appropriate for agents with a known potential for aerosol transmission, for agents that may cause serious and potentially lethal infections and that are indigenous or exotic in origin.

Biosafety level 4 addresses exotic agents that pose a high individual risk of life-threatening disease by infectious aerosols and for which no treatment is available. Work with such agents are restricted to high containment laboratories that meet biosafety level 4 (BSL-4) standards.<sup>3</sup>

Facility safeguards help prevent the accidental release of an agent from the laboratory. Their use is particularly important at BSL-3 and BSL-4 because the agents assigned to those levels can transmit disease by the inhalation route or can cause life-threatening disease. For example, one facility safeguard is directional airflow. This safeguard helps to prevent aerosol transmission from a laboratory into other areas of the building. Directional airflow is dependent on the operational integrity of the laboratory's heating, ventilation, and air conditioning (HVAC) system. HVAC systems require careful monitoring and periodic maintenance to sustain operational integrity. Loss of directional airflow compromises safe laboratory operation.

---

## APPENDIX C

### ADULT INFORMED CONSENT - EXAMPLE

**Principal Investigator:**

**Study Title:** Evaluation of SARS-CoV-2 virus strains for use in a closely-monitored COVID-19 human challenge model

**Ethics Committee No.:**

**Sponsor:**

**Principal Investigator Version Date:**

#### Key Information about the Study

We are asking you to volunteer for a research study to investigate the virus, SARS-CoV-2, that causes COVID-19 illness. We want to give you the COVID-19 virus to see if you develop mild symptoms and signs of COVID-19, something called a COVID-19 human challenge model. We hope we can use a COVID-19 human challenge model to better understand COVID-19, to see if an initial episode of mild COVID-19 illness stimulates immunity (protection) against a subsequent challenge, and to test new vaccines to prevent COVID-19.

- You do not have to join the study; it is your choice and there is no penalty for not joining. Ask as many questions as you need to help you make your decision. If you decide to join the study, you may change your mind and drop out later. Please review the details outlined in the rest of this consent document before deciding.
- You may be eligible for this study because you are a healthy adult 18-25 years old who does not have any underlying medical problems.
- If you join, you will have one or more screening visits (2-3 hours) to see if you are eligible up to XX days before getting the COVID-19 virus. If you are healthy and your labs are normal, you will be invited to enroll in the study – meaning you will be admitted to an isolation unit and given the COVID-19 virus in your nose.
- You will stay in an inpatient research isolation unit for approximately 2.5-3 weeks if you do not become infected with the virus and for up to 5-6 weeks (or longer) if you do become infected. Because you might be contagious with COVID-19 virus, you cannot leave the unit during the inpatient period until your tests for virus are negative on three consecutive days. We will use a nasal swab each day to test for the virus.
- You will also have 8 (30-60 minutes) outpatient visits (3 visits before you come into the isolation unit and 5 visits after your discharge from the unit. Some of the visits may include a brief medical history and physical, review pregnancy prevention, have bloodwork done, and collection of saliva (drool), a swab from your nose, urine and other bodily fluids.
- Most people who have symptoms of COVID-19 have fever, chills, headache, cough, sore throat, body aches, diarrhea, and loss of smell or taste.
- You may develop an immune response that damages your heart and blood vessels. This is more common in children and young adults and could possibly cause a stroke or very rarely, death.
- Approximately 10% of people who have COVID-19 get hospitalized. They have shortness of breath, infection in their lungs, and can have blood clotting problems that lead to stroke. Some people need to be put on a breathing machine. Some people develop shock. Most of these people are older than 65 and have other health problems. **Approximately X% of hospitalized patients 18-25 years of age die from COVID-19.**
- If you join the study, you will not personally benefit from this research. We hope that the information we gather from this study can be used to help learn more about COVID-19 and how to prevent it.
- This study will last approximately 12 months (360 days), which will include the follow-up visits to collect blood and to follow your health for months after your discharge from the isolation unit.
- There will be no costs to you for being in this study. If you get sick with acute COVID-19 illness in this study, you will be treated at no cost to you.
- Study doctors will be available at all times while you are in the study to check on you and treat you for any medical care resulting from you taking part in this research study. You will be compensated for your time and travel.

- 
- For taking part in this research, you may be compensated up to a total of \$XXXX. A detailed breakdown is provided below.

### **Why is this research being done?**

This research study is being done to develop a human challenge model for COVID-19. We want to find a dose of the COVID-19 virus that gives some symptoms of illness but doesn't make people very sick. However, we cannot guarantee that the dose we give you will only cause only mild illness. A COVID-19 human challenge model could be used in the future to test vaccines and drugs against COVID-19. The use of the COVID-19 virus in this research study is investigational. The word "investigational" means that the COVID-19 virus not approved for this use by the national regulatory agency (Food and Drug Administration [FDA] in USA; European Medicines Agency [EMA] in many European countries; Medicines and Healthcare products Regulatory Agency [MHRA] in the UK; Therapeutic Goods Administration [TGA] in Australia); The national regulatory agency is allowing the use of the COVID-19 virus in this study.

During the study, we will frequently check you for side effects and illness. We will check your nose, blood, saliva, and urine for COVID-19 virus. We will also study how your immune system responds to COVID-19. To do this, we will measure disease fighting proteins (antibodies) in your blood and collect different blood cells. We will also collect cells & fluid from your nose and mouth with a swab. We hope that this study will also help us learn more about signs and symptoms of COVID-19 infection and how to treat it.

### **Background Information:**

#### *Information about COVID-19*

COVID-19 is an illness caused by the SARS-CoV-2 virus. In December 2019, China reported that people were becoming sick from a new infection. This infection was later found to be caused by the SARS-CoV-2 virus and the clinical illness was named COVID-19. Since then, COVID-19 has spread around the world causing a pandemic. During the pandemic more than 5,600,000 people are thought to have gotten COVID-19 and more than 350,000 people have died (Johns Hopkins Coronavirus Resource Center, [Coronavirus tracker](#), accessed May 27, 2020). The COVID-19 virus (SARS-CoV-2) causes flu-like symptoms including; fever, headache, cough, sore throat, diarrhea, and body aches. About 10% of people who get COVID-19 get severe disease. People who developed severe cases of COVID-19 had trouble breathing and developed an infection in their lungs (pneumonia). They had to be put on a breathing machine (a ventilator). COVID-19 also can cause blood clots, stroke (loss of ability to move parts of your body), and shock. Most people who develop severe illness from COVID-19 are older and have some health problems like diabetes, heart disease, and obesity, but even young healthy adults have gotten severe COVID-19 and a small number have died. In young children, COVID-19 can cause the immune system to become over-active causing lung, liver, kidney, and skin problems. Most of these children get better but a small number have died.

### **Who can join this study?**

Healthy male and non-pregnant females 18-25 years old who do not smoke are eligible to screen for the study. Before entering the study, you will have blood and urine tests to see if you are healthy. The overall visit is called the "screening visit" and may occur over one or more visits.

To find out about your health, you will have:

- A complete medical history
- A physical examination
- An EKG
- A chest x-ray
- Lung function tests
- Several laboratory tests, including:
  - A complete blood count (CBC)
  - A blood clotting test (PT/PTT)
  - Blood chemistries (including tests of your kidneys, liver, and muscle)
  - A test for diabetes
  - Pregnancy test(s) and pregnancy prevention counseling.
  - A urinalysis

- A urine drug screen
- HIV test (a test for the virus that causes AIDS)
- Hepatitis B test (a test for a virus that hurts the liver)
- Hepatitis C test (a test for another virus that hurts the liver)
- There may be additional blood tests if the doctor judges they are needed

You will be told of any abnormal results that may require you to follow up with your personal doctor. Based on the results of these screening tests, you may be invited to join the study. There may be reasons why you cannot take part in this study.

If your tests show that you have HIV, the study doctor may have to notify the local health department. A separate HIV testing education form explains how positive results are reported to the local health department. Counseling will also be made available to you to discuss your positive HIV test and to receive information on how to get treatment for HIV if you do not have a regular doctor.

If your tests show that you have hepatitis B or hepatitis C virus, the study doctor may have to notify the health department. If so, the health department will be notified in writing of the following information: laboratory test date, type of test, result of test, your name, age, sex, and address. We will also provide information to you to follow up with a doctor if you do not have a regular doctor.

**We encourage questions.** If you have any questions or concerns about this, please talk to the research staff.

Because we do not know how COVID-19 affects an unborn baby, you cannot be in the study if you are pregnant. If you become pregnant during the study, tell the staff right away. We may ask you to continue to come in for regular study visits and/or ask you to agree to let us keep checking on you until the end of your pregnancy. If you do not have your own doctor to care for you during your pregnancy, we will refer you to an obstetrician (OB) to care for you. We will ask you to sign a medical information release form so that we can learn about your pregnancy and, if applicable, your baby's health at birth. If the study ends prior to your delivery, we may ask you to return for one or more visits until you deliver and/or call you on the phone.

#### **What will happen if you join this study?**

If you are invited to enroll in this study, you will be asked to participate in all of the following study visits. Below is a detailed description of what will occur before, during the inpatient stay, and follow up visits after you are discharged from the unit. If you have any questions, please discuss them with research staff. A total of up to XX subjects may be enrolled in this study.

**Study Day -14:** You will have nasal swab test to see if you are silently infected with the COVID-19 virus.

**Study Day -7:** You will have nasal swab test to see if you are silently infected with the COVID-19 virus.

**Study Day -2:** You will come to the inpatient isolation unit on Day -2 (two days before you get the COVID-19 virus) and be admitted. You will have nasal swab test to see if you are silently infected with the COVID-19 virus or another respiratory virus. The isolation unit is a smoke-free hospital-like setting where you will be confined to a hospital room. It is important that you know:

- Visitors are not allowed.
- You will be asked to stay on the isolation unit 24 hours per day so you will not be able to come and go from your room or from the unit.

Once you are admitted to the inpatient unit, you will need to stay in the unit for 3 – 4 weeks or longer. You will not be allowed to leave the isolation unit until you are no longer positive for COVID-19 virus in your nose.

**It is important that you stay in the unit until we tell you it is OK to leave (be discharged). We want to be sure that if you get symptoms of COVID-19 infection, we can monitor you and give you**

---

**treatment if necessary. We also want to be sure that you cannot spread COVID-19 to other people. You need to be available and willing to stay in the unit for at least 3-4 weeks. You should make plans for childcare needs or emergencies that may occur during the study. *If you do not think you can stay in the inpatient unit you should not join the study.***

**Challenge Day (Study Day 0):**

On study day 0, you will have your blood drawn, discuss your medical history, receive a physical examination, have blood taken, saliva collected, urine collected, and a swab taken from your nose.

You will then get the dose of COVID-19 virus (SARS-CoV-2) in your nose. The COVID-19 virus will be given by drops in both sides of your nose (both nostrils). After receiving the nose drops, you will be monitored for at least 30 minutes to check if you feel sick or have any side effects.

You will stay in the inpatient isolation unit until for approximately 3 weeks if you do not become infected or for 5 – 6 weeks if you do develop infection. In natural COVID-19 infection the virus takes from as short as only 2 days to as long as 12 days to start showing up in your nose in 99% of cases, with most cases taking a period of 5 days. Once infected, you may shed virus from your nose or mouth for 3-4 weeks through talking, shouting and singing even though you are on longer sniffing, sneezing or coughing. Therefore, you cannot be released until you have had negative tests for shedding virus for three consecutive days.

Each day you are in the isolation unit, you will have a history and physical exam, and vital signs taken (pulse, breathing rate, blood pressure and temperature) at least three times daily. You will wear a device on your finger that tells us how much oxygen is in your blood. Each day a swab will be placed in your nose to test for the COVID-19 virus. On specified days, you will also be required to give blood, urine, and saliva. These samples will be used to check your health and to see if you have developed an immune response to the COVID-19 virus and if it can be found in urine and saliva.

**Follow-up Visits:**

Here is a schedule of what you will be asked to do each day if you agree to be part of this study. In addition to the table below, other blood tests can be done any time during the study if the doctor thinks it's needed for your health and safety. The procedures we will do are listed in the table below (Table 1).

**Table 1: Procedures during the study**

Procedure	Inpatient Isolation Unit Stay																		
Study Day	-14	-7	-2	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	29-37
COVID-19 virus given				X															
Admitted to isolation unit			X																
Medical history			X	X															
Symptom review			X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>
Physical exam			X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>
Vital signs			X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>
Pregnancy test			X	X								X						X	X
Blood Draw			X <sup>4</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sample				X			X			X			X			X		X	X
N-P Swab	X	X	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>
Saliva sample				X				X		X		X		X		X		X	X
Discharge from inpatient unit																		X <sup>6</sup>	X <sup>7</sup>
Review Pregnancy Prevention			X	X														X	

1. Symptom review will be performed each day the volunteer is confined to the isolation unit, every other day is listed to fit in in the table.
2. Physical examination will be performed each day the volunteer is confined to the isolation unit, every other day is listed to fit in in the table.
3. Vital signs will be taken three times daily and more frequently as indicated every day the volunteer is on the isolation unit. Every other day is listed to fit in in the table.
4. A blood draw is needed for the pregnancy test on Study Day -2. The blood draws represented here are for clinical laboratory studies and research studies. It is anticipated that blood draws will be required on most of these days but will be finalized in the protocol.
5. An N-P swab will be taken every day. Every other day is listed to fit in in the table.
6. Discharge may occur sooner (or later) depending when the N-P becomes negative for COVID-19 virus by PCR
7. Represents the longest potential stay in the inpatient isolation unit

### **Follow-up Visits after discharge:**

You will have monthly follow-up visits for the first 5 months after discharge and then a follow-up visit at month 9 and month 12 (1 year after being given the COVID-19 virus). Each follow-up visit will take approximately 30-60 minutes. At each visit we will perform some or all of the following:

- Ask you questions about how you are feeling and if you have been sick
- Review your temperature card
- Pregnancy test and pregnancy prevention counseling
- Draw your blood
- Collect an NP swab
- Give you a physical examination
- Check your vitals (blood pressure, pulse, temperature, respiration rate)

Prior to discharge, you will receive education regarding the proper use of a thermometer, the signs and symptoms of potential side effects, and how and when to contact study staff. We will give you a thermometer. You will be told how to take your temperature and how often to write it down for record-keeping purposes. If you test positive for the COVID-19 virus, we will ask you to come to the isolation unit for evaluation. You may be asked to come back into the unit until you are not positive for the virus again or we may ask you to self-quarantine at home.

We will test up to 3 different doses of the COVID-19 viruses. We will start testing a low dose of the virus and then test higher doses if needed. You will know which dose group (cohort) you are in. **You will only get one dose of the COVID-19 virus.** Each dose will be studied in up to 20 – 25 volunteers. A total of up to 75 people will be enrolled in this trial. Each dose cohort will be divided into approximately 4 different groups of volunteers (Table 2). As shown below in Table 1, the first group will consist of only 1 – 3 volunteers. If the COVID-19 virus doesn't cause symptoms or causes only mild symptoms in the first few volunteers, the next group of volunteers will be increased to 3 – 5 and will be given the same dose as per the table below. The group sizes will be increased until the first dose of COVID-19 virus has been given up to a total of 20 - 25 volunteers. Depending on the signs and symptoms induced by this dose of COVID-19 virus, a higher dose may be studied. It would be studied in the same manner as shown for the low dose in Table 1.

**Table 2: Dose Schedule for Dose Cohort 1**

Group	No. of Subjects <sup>1</sup>	Dose
1	1-3	Lowest dose COVID-19 virus
2	3-5	Lowest dose COVID-19 virus
3	5-10	Lowest dose COVID-19 virus
4	10-15	Lowest dose COVID-19 virus

---

**Blood Sample Collection:** You will have blood drawn while you are in the isolation unit and at most study visit(s). Each time we will take less than 5 tablespoons of blood. The total amount of blood to be taken from you during the 12-month study is a little more than 1 ½ pints.

The blood we draw at your visits will be tested to:

- Check on your health after receiving the COVID-19 virus
- Look for COVID-19 virus in your blood
- See if your body has made antibodies (germ fighters) against COVID-19
- Test markers on your white blood cells and genes and look for proteins in your blood that may be important for your body to fight COVID-19 infection

**In addition:**

- A study doctor can be reached 24 hours a day during the study
- If you become ill during the study, additional tests (for example blood tests, nasal swab, or x-rays) may be done. You will not be charged for these tests. Any risks associated with these tests will be explained to you before they are performed. You may refuse to have these tests done if you do not want them.
- We will contact you to remind you of study visits and to check on you if you miss a study visit. We may contact you by one or more of the following means:
  - Telephone call
  - Text message
  - Electronic media (Twitter, Facebook, etc.)
  - Email message
  - Card mailed by Postal Service
  - Ask one of the people you provided as a contact to remind you to come to the clinic
  - We will contact you to remind you about the study and discuss pregnancy prevention approximately every 30 days

**What are my responsibilities if I take part in this research?**

If you take part in this research, you will be responsible to:

- Tell the staff if you become sick or feel bad. We may ask you to come to the clinic after discharge so that we can check on you.
- Because COVID-19 is spread by droplets in the air, ***you will not be able to leave the unit until you are medically discharged.*** See “Risks of Transmission” below for more details.
- Contact the staff or study doctor before taking medication or receiving any vaccines. This includes medicines that you buy without a prescription like herbal or over-the-counter medicines, such as Advil; and medicines that affect the immune system, such as prednisone.
- Not getting any live vaccines 60 days before you come on the isolation unit, not getting any killed (inactivated) vaccines 30 days before you come on the unit and waiting to get either a live or killed vaccine until after you are discharged. This may put you at more risk for illness such as the flu. Depending on the time of year, we may offer you a flu vaccine prior to admission on the inpatient unit [within acceptable time constraints].
- We will ask you to tell us if you do get a licensed vaccine anytime during the study.
- Not donate any blood products.
- Tell the staff if you receive any blood products.
- Women who are of childbearing potential must use a reliable form of birth control (hormonal birth control, surgical sterilization or intrauterine device). Exception: women who only have sex with women and women who are postmenopausal (no period for at least 1 year).
- If you become pregnant during the study, tell the staff right away.

---

### **Will clinical care test results be shared with you?**

We will share all results related to your care with you while you are on the isolation unit. These will include your blood count results, tests of liver and kidney function, blood clotting tests, any ultrasound of the lungs, or chest x-ray results. We will also share the results of any other tests that are done as part of the care of your COVID-19 infection.

### **Will research test results be shared with you?**

The research tests we perform are not like routine medical tests and may not relate directly to your medical care, so we may not put future test results in your medical record.

### **New Findings**

The study doctor or staff will share with you any new findings that may develop while you are participating in this study that might change your decision to be in this study. You may be asked to sign a revised consent form if this occurs.

### **How long will you be in the study?**

As stated above, your participation in this study will last for approximately 12 months from when you are given the COVID-19 infection. Screening visits occur within 60 days before you get the shot.

In the event that you become sick during the study and it has not resolved by the end of the study, you may be followed somewhat longer, typically until the issue is resolved or stabilized.

It is very important for you to come to all of your study visits. If you are unable to return to the center for study visits, you may be asked to have blood drawn at a local clinical lab so that we can follow you for safety. It is very important that you understand the requirements of the study before you decide to sign this consent form and join the study.

### **What happens to data and biospecimens that are collected in the study?**

Biospecimens may include any of the following: blood, tissue, saliva, urine, cells, etc. Most biospecimens contain DNA, which is the genetic code for each person. The biospecimens we collect during this study will be tested as outlined above in the section “**What will happen if you join this study?**”

### **What will happen to my unused samples?**

We will store any unused blood, urine, and N-P swab samples once this study is finished. Your samples will be used only for research. We may use these samples to learn more about COVID-19 and other diseases. The blood samples may be used for tests to detect:

- Immune responses to the test virus (immunology)
- How long COVID-19 can be found in the body
- How COVID-19 makes people sick
- How COVID-19 and your immune response to COVID-19 affects other viral infections
- Genetic differences in responses to COVID-19 or other viral infections (samples will be used anonymously)

Your samples will not be sold. Your samples will not be used to make commercial products. If researchers use them to create a new product or idea, including those that may have commercial value, you will not benefit financially from these efforts. We will label your stored samples with a code that only the study team can link to you. We will keep any information that can be traced back to you private to the extent permitted by law. In some cases, institutional review board (IRB) will review new research proposals that would like to use your samples. The IRB is a group of people who perform independent review of research.

Your data and/or biospecimens may be shared:

- directly with research collaborators, other researchers, sponsors, government agencies, publishers of papers and other research partners
- through government or other databases/repositories

Data/biospecimen sharing could change over time and may continue after the study ends. Generally, if we share your data/biospecimens without identifiers (such as your name, address, date of birth) new uses of the data/biospecimens do not need further review and approval by an IRB.

Reports about research with your samples will be kept with the study records only. There will be no direct benefit to you. From studying your samples, we may learn more about how to prevent, treat, or cure COVID-19 disease or other diseases. Results from research using your samples may be presented in publications and meetings but your name will not be used.

#### Genetic Information Nondiscrimination Act (GINA)

This study involves genetic testing on samples that you provide. There are risks associated with a loss of confidentiality of your health information and genetic testing results. Information about genetic test results may affect your employment, insurance, or family relationships. The sponsor cannot be certain that your genetic test results could never be linked to you.

The Genetic Information Nondiscrimination Act (GINA) is a federal law that helps reduce the risk of discrimination by health insurers or employers based on your genetic information. GINA does not protect you from discrimination if you apply for other types of insurance (such as life, disability or long-term care). GINA also does not protect you against discrimination based on an already-diagnosed genetic condition or disease.

Genetic information is unique to you and your family. Even without your name or other identifiers, it may be possible to identify you or other members of your family with your genetic information.

The doctors doing this study follow procedures so that people who work with your DNA information for research cannot discover it belongs to you, unless you have given consent. However, new techniques may be developed that in the future make it easier to link your genetic data to you, so we cannot promise that your genetic information will never be linked to you.

***You must agree to the use of your samples for future research if you want to join the study. If you do not want your unused samples used for future research, you should not join this study.***

If you agree to the future use of specimens, you have the right to change your mind at any time after you have joined the study. If you do change your mind, write the study doctor to make this request. Then your samples will no longer be made available for research. Your samples will be destroyed.

#### **What are the risks or discomforts of the study?**

In this study, you will be intentionally exposed to the virus that causes COVID-19. This virus is currently causing a world-wide pandemic of severe respiratory disease with frequent disease in other parts of the body. Humans have only experienced infections with this virus over the last 4 to 6 months, and the complete spectrum of disease caused by COVID-19 virus is not fully known. Although most severe cases of COVID-19 disease are usually seen in the elderly (over 65 years of age) and those with pre-existing conditions, severe COVID-19 disease can occur in young, healthy adults. The factors that might increase the risk of such events in young persons are unknown and may not have been detected in the screening process that you underwent before entering the study. Therefore, at present it is not possible to predict accurately and completely the risks to you from participating in this study. The potential risks of participation, based on available information as of this date, are described below.

---

### **Potential risks due to infection with COVID-19-**

Common risks from the COVID-19 infection: One or more of these symptoms are seen in almost all identified cases:

- You may have a flu-like symptoms. These include fever, headache, sore throat, runny nose, cough, and body aches.
- You could lose your sense of smell and/or sense of taste.
- You could have diarrhea

Less common and more serious risks from COVID-19 infection are listed below. It is not possible to predict at this time what your risks of developing these complications are. However, based on current knowledge they appear to occur in fewer than 1 in 10 cases, and mostly, but not only, in older adults. If you develop severe disease you may need to be transferred to an intensive care unit or receive intensive care on the isolation unit.

- You may develop a newly described complication in which the body's immune system turns against your body's tissues, destroying blood vessels, the skin, and other organs. ***This syndrome is seen primarily in children and young adults and can very rarely be fatal.***
- You may develop shortness of breath.
- You may develop pneumonia. The pneumonia may be severe, and you may need to receive supplemental oxygen by mask or by placing small tubes near your nose.
- You may become so short of breath that you cannot breathe on your own. In this case, you will need to be placed on a ventilator (a mechanical breathing machine). About one-half of patients who reach this state of severity will die.
- You may develop blood clots. These could cause swelling in your legs, or they could lead to a stroke. A stroke is a clinical event that occurs when a blood vessel that brings oxygen and nutrients to your brain becomes blocked by a clot, or the blood vessel ruptures. A stroke may be minor, or it may be more serious, leading to paralysis of one side of your body, inability to speak, or other serious nervous system problems. These outcomes from a stroke could be long lasting or even permanent. If you have a stroke you could be permanently disabled or you could never recover your full strength, or, in a few instances, you may die.
- Although the risk is small, you could develop low blood pressure or shock. If this happens you will be given medication and other support to maintain your blood pressure. Treatments for shock in COVID-19 are not always successful, and death is in such circumstances regrettably common.
- You could develop kidney disease (your kidneys do not work as well). This could be permanent. Permanent kidney failure may require use of an artificial kidney system (dialysis) or may require that you receive a kidney transplant.
- You could develop liver disease (your liver will not work as well). This could be permanent. Severe liver disease can be fatal or could require a liver transplant.
- You could develop painful swelling of your toes ("COVID toes"). This usually lasts 3 – 4 weeks.

The FDA, EMA, MHRA and TGA have not approved any drugs to treat COVID-19. Should you become ill with COVID-19, you will be given the current recommended treatments to help you get better. These may include giving you oxygen, putting you on a breathing machine, giving you medications to help your blood pressure, or other treatments that are not yet known. The best available treatment, whatever its cost, will be made available for you and at no cost to you.

---

There is a very small risk that you could die if you develop COVID-19 illness during this trial. If you die due to COVID-19, it is important for us to know how COVID-19 caused your death. We would like permission to perform an autopsy (study your body after you have died) to find out how COVID-19 caused your death. An autopsy may be required by medical authorities. If you don't want an autopsy done, you should not join the study.

### **Risks of Transmission**

- COVID-19 can be spread by an infected person's coughing, singing, speaking, or by her/his touching things (writing utensils, packages, door handles, elevator [lift] buttons, etc.). A susceptible contact person who is near a COVID-19-infected individual who has coughed, sneezed, spoken or sang or who touches objects previously touched by the infected individual can, in turn, become infected. The susceptible person becomes infected by breathing air contaminated by the infected person. The susceptible person can also be infected by rubbing their eyes, picking their nose or putting fingers into their mouth after touching objects contaminated by the infected person. The virus that causes COVID-19 is **very** contagious. By agreeing to participate in this study, you are agreeing to stay in the unit/hospital for 3 – 5 weeks or longer after you are admitted. You will be tested for the presence of the COVID-19 virus on a daily basis while in the research facility.
- While you are in the study unit/hospital, you must remain in your room, unless accompanied by study staff for study procedures, and you are not allowed to have visitors. Friends and relatives may leave things for you at the study unit but are not allowed to enter. You are not allowed to send materials, such as mail or packages, while you are in the research isolation unit.
- You will not be allowed to leave the research isolation unit until you have been shown to be no longer contagious. Early studies of challenge with COVID-19 virus are expected to be carried out under a legal QUARANTINE. Quarantine will extend in duration from the day you receive the challenge virus until you no longer have evidence of infection, as evidenced by three days of negative tests for the virus. You may "leave the study" at any time, which is one of your rights as a volunteer. However, even if you decline to participate further in the study, you are legally bound to remain on the research isolation unit until the end of the Quarantine. Depending on local health ordinances you will be committing a crime by trying to leave the Quarantined unit and each attempt to do so will be considered a separate offence. The reason for this severe restriction is to protect other individuals in your home and in the community with whom you may have contact from acquiring COVID-19 from you. Whereas you have volunteered to enter this study and to be exposed to the highly contagious virus that causes COVID-19, others have not. To repeat, once you have been challenged with the COVID-19 virus and the research isolation unit is in Quarantine, you will have to remain until you are no longer capable of spread COVID-19, to others outside, that is until you and the others have been shown no longer to harbor the virus on repeated testing.

### **Risks from blood drawing**

- Taking blood may cause minor, momentary pain, bruising where the needle enters the body, a lump called a hematoma, or (very rarely) infection at the place where blood is taken. To ease the discomfort, a cream may be spread on the skin over the vein where your blood will be collected to diminish the feeling of the prick of the needle, if both you and the health professional drawing your blood agree to its use.
- In the occasional adult the act of drawing blood can cause you to feel lightheaded or result in fainting. Such a drop in blood pressure is never dangerous but to minimize the chance of this happening and the discomfort that ensues, we can

---

draw your blood specimens while you are lying down.

- Some individuals bleed a bit from the site of blood draw. Putting on a small bandage and applying pressure for some minutes prevents this.

**Discomfort of N-P swab sample collection.** We will take a sample from your nose with a swab called a nasopharyngeal or N-P swab. The swab will be placed in your nose and will be moved back until the tip of the swab is in the back of the throat. This can cause discomfort and may cause a gagging sensation.

**Local risks of getting the COVID-19 virus placed in your nostrils**

- You may experience a runny or stuffy nose immediately after drops containing the virus that causes COVID-19 are put into your nostrils.

**Other risks.**

- We will ask you to wait to get a routine, licensed vaccines like the flu shot or nasal spray flu vaccine from before 30 days prior (killed vaccine) or 60 days prior (live vaccine) to the COVID-19 challenge. This may put you at more risk for illness such as the flu.
- You may become anxious, lonely or depressed by being confined to the isolation unit for 3 – 4 weeks without being able to see family or friends
- Your personal private space will be limited and you will be visited frequently by study staff to check on you
- There may be psychological or social risks that result from taking part in the study, such as concern about being tested for HIV. Disclosure of a positive test may result in discrimination by friends, family, employers, insurance companies and others.
- Risks occasionally associated with the use of topical anesthetic cream include temporary skin discoloration, skin irritation, rash, hives, and rarely, dizziness or drowsiness.
- If you become pregnant while you are in the study, you must tell your study doctor. You must also inform your obstetrician, midwife, or seek the care of an obstetrician or midwife, if you do not have one.

***There may be other side effects and risks that we don't know about yet.***

If we learn about any new side effects or risks while you are in the study, we will tell you and you can decide if you want to continue in the study.

**Interviews or questionnaires**

You may get tired or bored when we are asking you questions about your medical history, sexual history or pregnancy prevention information. Some questions may make you feel embarrassed or uncomfortable. Let us know if you feel distressed. You do not have to answer any question you do not want to answer.

**Personal Privacy**

Research staff will work to protect your personal privacy throughout the study. Sensitive questions regarding your medical history, sexual history and pregnancy prevention will be asked in a private area. All forms where personal information is recorded will be kept securely stored at the study site in a locked area. Please discuss any concerns you have about protecting your personal privacy with research staff.

**Identifiable private information**

There is a risk that information about you may become known to people outside this study. We will protect your information to reduce the chance of this happening. We

---

assign you a study ID number upon screening to minimize use of identifying information on forms, documents and specimens.

All study-related information will be stored securely at the study site in a locked area with limited access. All laboratory specimens, reports, study data collection, and administrative forms will be identified by coded number to maintain your confidentiality. All local databases will be secured with password-protected access systems.

### **How will the confidentiality of your data be protected?**

The Sponsor of this study has given us a **Certificate of Confidentiality** for this study. This Certificate does not mean that the local, state or federal government approves or disapproves of this study. This Certificate adds special protection for research information that identifies you. It allows us, in some circumstances, to refuse to give out study information about you without your consent when it is sought in a legal action. Still, we may disclose identifying information about you if, for example, you need medical help. We may also give out information about you if the government audits us. The research team will also give information to local or state authorities:

- if they suspect abuse or neglect of a child or a dependent adult;
- if certain infectious/communicable diseases are present; and
- if the team learns that you plan to harm someone. In this case, the team also may warn the person who is at risk
- if you need medical help

A description of this clinical trial will be available on <https://ClinicalTrials.gov/>, as required by federal laws. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this website at any time.

Information from this study will be given to the Sponsor. The Sponsor is the organization responsible for financing and overseeing this study. The Sponsors of this study are XXXX. "Sponsor" includes any persons, institutions, companies or foundations that are contracted by the sponsor to have access to the research information during and after the study. Information about side effects of the challenge virus will also be given to the national regulatory agency (in the USA this is the Food and Drug Administration [FDA]; in many European countries this is the European Medicines Agency [EMA]; in UK this is the Medicines and Healthcare products Regulatory Agency [MHRA]). It may be given to governmental agencies in other countries where the challenge viruses may be considered for approval.

Medical records which identify you, including photographs, and the consent form signed by you will be looked at and/or copied for research or regulatory purposes by the sponsor, and may be looked at and/or copied for research or regulatory purposes by:

- The regulatory agency providing oversight) (e.g., US FDA, EMA for many European countries, MHRA for UK, Australian TGA, National Medical Products Administration [NMPA] for China, etc.)
- Governmental agencies to whom certain diseases must be reported
- Governmental agencies in other countries
- The Hospital or institution where the research isolation unit is located
- University or academic institutions affiliated with the research isolation unit

Absolute confidentiality cannot be guaranteed because of the need to give information to these parties. The results of this research study may be

---

presented at scientific and public health meetings or in publications. **Your identity will not be disclosed in those presentations.**

Data or specimens collected in this research might be deidentified and used for future research or distributed to another investigator for future research without your consent

Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that you make yourself are also not protected.

**What are the potential benefits to being in the study?**

There are no known direct benefits to you for participating in this study. We hope that the information we gather from this study will lead to a COVID-19 vaccine that could help many people around the world. There is a chance you could develop antibodies against COVID-19. We don't know if you will develop antibodies or if those antibodies would protect you against another COVID-19 infection.

**What are your options if you do not want to be in the study?**

This research is not designed to diagnose or treat any disease. Your alternative is to decline to participate in the study.

If you do not join, your care at XXXX hospital or clinic will not be affected.

If you do not join, your employment/education at will not be affected.

**Will it cost you anything to be in this study?**

There will be no costs to you for being in this study. Ask your study doctor (provider) to discuss the costs of treating possible side effects. Otherwise, you might have unexpected expenses from being in this study.

**Will you be compensated if you join this study?**

For taking part in this research, you may be compensated up to a total of \$XXXX (€XXXX, etc.). Your compensation will be broken down as follows:

- You will receive a voucher for parking or public transportation tokens, as needed, for the days that you screen or have study visits.
- You will be compensated \$XX (€XX, etc.) for your screening visit *only* if you are enrolled in the study. compensate
- You will be compensated \$XX (€XX, etc.) for each inpatient day (Study Days -2 to 28, or longer)
- If you are an alternate, you will be admitted on Study Day -2 and stay on the inpatient unit overnight. If you are not given the COVID19 challenge, you will be compensated \$XXX (€XXX, etc.) for your time and discharged on Study Day 0. If you receive the COVID-19 challenge virus you will be enrolled in the study.
- You will be compensated \$XX (€XX, etc.) for each of the 9 out-patient clinic visits.
- If you complete all study visits on time and adhere to all inpatient policies, you will be given a \$XXX (€XXX, etc.) bonus. You may only receive a portion of the bonus if not all study visits are completed on time or for failure to follow inpatient policies
- If you choose to withdraw (dropout) before the study is completed, you will only receive payment for the number of visits that you have completed.

Compensation will be distributed by check or credit card according to the following schedule:

- Insert schedule when known

---

You may be required to provide your social security number or national identity number to get compensation for taking part in this study. Tax laws of some countries require that you report your research payments when you file your taxes. If your total payments from XXXXX institution exceed \$XXX or €XXX per year, XXXXX institution will report these payments to the government tax office and you will receive a form from us.

### Can you leave the study early?

- Your participation in this study is voluntary.
- You can agree to be in the study now and change your mind later.
- If you wish to stop, please tell us right away.
- ***You may leave the study at any time, but you cannot physically leave the unit until the period of legal Quarantine is discontinued.*** Please see the section on Risk of Transmission above.
- If you “leave the study” early you will not have to have additional study procedures, but you will have to stay on the research isolation unit while the Quarantine is still active.
- Leaving this study early will not stop you from getting regular medical care. If you are ill with COVID-19 and leave the study early but are still on the research isolation unit, we will still take care of you and give you the medical treatment you need.
- Leaving this study early will not affect your employment/education.

If you leave the study early, the investigators and the Sponsors of the study may use or share your health information that it has already collected if the information is needed for this study or any follow-up activities.

Your decision not take part or to withdraw from the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to leave the study, the samples that have been collected will be used as described in this consent form. If you do not wish us to use these samples after you leave the study, you may request that we destroy them and they will be destroyed. You should ask the study doctor listed below any questions you may have about this research study. You may ask questions in the future if you do not understand something that is being done.

We will tell you about any new information that may affect your health, welfare, or choice to stay in this research.

### Why might we take you out of the study early?

You may be taken out of the study (withdrawn) at any time by the study doctor or the sponsor without your consent if:

- Staying in the study would be harmful.
- You need treatment not allowed in the study.
- You have a side effect that requires stopping the research
- You become pregnant.
- The study is cancelled.
- The study staff or the study sponsor decides to discontinue your participation for any reason.
- You do not follow instructions from the staff or do not keep appointments.
- The Data and Safety Monitoring Board (a scientific review board that monitors clinical research studies) concludes that the study should be stopped.
- The regulatory agency providing oversight of the study, the institution in which the research isolation unit is located, or the Sponsors decide that the study should be stopped.
- If new information becomes available regarding the safety of the challenge virus.
- You do not consent to continue in the study after being told of changes in

- 
- the research that may affect you.
  - There may be other reasons to take you out of the study that we do not know at this time.

If you are taken out of the study early, the investigators and the Sponsor may use or give out your health information that it has already collected if the information is needed for this study or any follow-up activities.

**Will the study require any of your other health care providers to share your health information with the researchers of this study?**

As a part of this study, the researchers may ask to see your health care records from your other health care providers.

**What information is being collected, used, or shared?**

To do this research, we will need to collect, use, and share your private health information. By signing this document, you agree that your health care providers may release your private health information to us, and that we may use any and all of your information that the study team believes it needs to conduct the study. Your private information may include things learned from the procedures described in this consent form, as well as information from your medical record (which may include information such as HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment). Prior to contacting your health care provider to release your health information, we will discuss with you what records we will be requesting and why.

**Who will see, use or share the information?**

The people who may request, receive or use your private health information include the researchers and their staff. Additionally, we may share your information with other health professionals at the hospital in which the research isolation unit is located, for example, if needed for your clinical care or study oversight. To improve coordination of your research and clinical care, some information about the study you join will be included in your electronic medical record. By signing this form, you give permission to the research team to share your information with others outside of the institution where the research isolation unit is located. This may include the sponsor of the study and its agents or contractors, outside providers, study safety monitors, government agencies, other sites in the study, data managers and other agents and contractors used by the study team. We try to make sure that everyone who sees your information keeps it confidential, but we cannot guarantee that your information will not be shared with others. If your information is disclosed by your health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

**Do you have to sign this Authorization?**

You do if you wish to participate in the study. If you do not sign, you may not join the study.

**How long will your information be used or shared?**

Your Authorization for the collection, use, and sharing of your information does not expire. Additionally, you agree that your information may be used for similar or related future research studies.

**What if you change your mind?**

You may change your mind and cancel this Authorization at any time. If you cancel, you must contact the Principal Investigator in writing to let them know by using the contact information provided in this consent form. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization.

---

**What treatment costs will be paid if you are injured in this study?****For potential US research isolation unit study sites:**

A study doctor will be available at all times while you are in the study to check on you and treat you for any short-term medical care resulting from you taking part in this research study. You are a young adult and therefore at a lower risk to get severe COVID-19 illness. If you, despite of this small chance you do become seriously ill, the services at the hospitals affiliated with the research isolation unit will be available to you at no cost to you. Medical care will be given while you are on the isolation unit. If you require movement to an intensive care unit, this will be provided including, provision of a ventilator, if necessary, to help you to breathe. You will also be provided with any available drug against the infection, at whatever its cost. Should you require long-term care for illness suffered as part of this study, long-term medical care or financial compensation for research-related injuries will be offered by the institutions affiliated with the research isolation unit, the Sponsor, or the state or federal government. The study will also provide a financial settlement to your beneficiaries should you die from COVID-19 infection as a result of being in the study and your life insurance company does not cover provide coverage.

By signing this form, you will not give up any rights you have to seek compensation for injury.

**For potential European or U.K. sites:**

If you are injured as part of this study, your medical care will be provided by the government. In addition, the study will also provide a financial settlement to your beneficiaries should you die from COVID-19 infection as a result of being in the study and your life insurance company does not cover provide coverage.

**What other things should you know about this research study?**

If you would like to review the information for this study, or a summary of the results, ask the study team doctor for the ClinicalTrials.gov study registration number.

During this study, you will not have access to certain medical information and test results collected for study purposes. If an emergency occurs while you are in the study, medical information needed for your treatment can be made available to your study doctor and other physicians who treat you. When the study is completed, all the information in your medical record will be available to you.

During the study, we will tell you if we learn any new information that might affect whether you wish to continue to participate.

**What is the Ethical Committee and how does it protect you?**

This study has been reviewed by an Ethical Committee (EC), a group of people including scientists and community people, that reviews human research studies. The EC can help you if you have questions about your rights as a research participant or if you have other questions, concerns or complaints about this research study. You may contact the EC at [insert phone number] or [insert email address].

[insert all contact information, name, address, etc]

**What should you do if you have questions about the study, or are injured or ill as a result of being in this study?**

Contact the principal investigator, [Name], at the phone numbers or address listed below.

[List name, address, affiliation, phone number  
and email address]

---

If the principal investigator is unavailable, you can call you study coordinator at the contact number provided to you. If you wish, you may contact the principal investigator by letter. The address is on page one of this consent form. If you cannot reach the principal investigator or study coordinator or wish to talk to someone else, call the EC office at [insert phone number].

If you have an urgent medical problem or think you are injured or ill because of this study, call 911 or go to your local emergency department. You should also call the [insert name of PI] at **[insert phone number]**.

**What does your signature on this consent form mean?**

Your signature on this form means that you have reviewed the information in this form, you have had a chance to ask questions, and you agree to join the study. You will not give up any legal rights by signing this consent form.

**WE WILL GIVE YOU A COPY OF THIS SIGNED AND DATED CONSENT FORM**

---

Signature of Participant  
Date/Time

(Print Name)

---

Signature of Person Obtaining Consent

(Print Name)

Date/Time

**NOTE: A COPY OF THE SIGNED, DATED CONSENT FORM MUST BE KEPT BY THE PRINCIPAL INVESTIGATOR; A COPY MUST BE GIVEN TO THE PARTICIPANT.**

---

**WHO Headquarters in Geneva**  
**Avenue Appia 20**  
**1202 Geneva**  
**Telephone: +41-22-7912111**



**R&D Blueprint**  
Powering research  
to prevent epidemics