Aug 25, 2020

Collection of Protocols and Guidelines for Phase 3 study of Vaccine Candidate for COVID-19

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1 Works for me dx.doi.org/10.17504/protocols.io.bj5pkq5n

Coronavirus Method Development Community

Chris Ockenhouse

ABSTRACT

This is a collection of protocols for: "Phase 3 randomized, double-blinded, placebo-controlled trial to evaluate the safety, immunogenicity, and efficacy of **Vaccine Candidate** against COVID-19 in adults > 18 years of age"

This generic Phase 3 protocol was developed by the PATH team with support of the Bill and Melinda Gates Foundation. The aim of the collection is to share recommended best practices in designing and implementing a Phase 3 study of a COVID-19 vaccine candidate. As Phase 3 trials of different Vaccine Candidates proceed around the world, following the same protocols will ensure consistency and comparability of the Phase 3 trial results.

Please note that this is an evolving document, to be versioned and updated, based on community feedback and new data.

ATTACHMENTS

Generic Phase 3 Protocol COVID-19 Vaccine - 25AUG2020-version 1.docx

DOI

dx.doi.org/10.17504/protocols.io.bj5pkq5n

COLLECTION CITATION

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COLLECTION INTEGER ID

40847

GUIDELINES

Phase 3 randomized, double-blinded, placebo-controlled trial to evaluate the safety, immunogenicity, and efficacy of [Vaccine Candidate] against COVID-19 in adults ≥ 18 years of age

Protocol Number
[XXX]

Trial Registration
[XXX]

Study Conducted By
[XXX]

<Regulatory/IND> Sponsor
[XXXX]

(Sponsor means an individual, pharmaceutical or medical device company, governmental agency, academic institution, private organization, or other organization that takes responsibility for and initiates a clinical investigation.)

Collaborating Partner/s (In Collaboration With)
[XXXX]

Pharmaceutical Support
[XXXX]

Source of funding
[SPONSOR, with funding from XXX]

Site Principal Investigator
[XXXX]

Protocol Version Number
[0.01]

Version Date
[_____2020]

Confidentiality Statement
(see example below)

"This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable regulatory authorities and independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from SPONSOR."

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Investigator's Agreement Page

1. I have read the foregoing protocol and agree to conduct the study as outlined herein.
2. I agree to follow this protocol version as approved by the Ethics Review Committee/Institutional Review Board (ERC/IRB).
3. I agree this study will be conducted in accordance and in conformity with ICH GCP, the Declaration of Helsinki, and all applicable regulations.
4. I will conduct the study in accordance with applicable ERC/IRB requirements to maintain the protection of the rights and welfare of study participants.
5. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
6. I will not modify the protocol without first obtaining permission from the sponsor, an ERC/IRB approved amendment, and new protocol version, unless modification is necessary to protect the health and welfare of study participants.
7. I will ensure the data and/or specimens are maintained in accordance with the data and/or specimen disposition outlined in the protocol. Any modifications to this plan should first be reviewed and approved by the applicable ERC/IRB.
8. I will prepare and submit continuing review reports according to established timeframes at intervals established by the IRB and a study closure report when all research activities are completed.
9. I agree to maintain adequate and accurate records in accordance with institutional policies, local laws, and regulations as applicable.
10. I certify that the statements herein are true, complete, and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept the responsibility for the scientific conduct of the project.

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XXX (PI) DateXXX

ABBREVIATIONS AND ACRONYMS

TO BE UPDATED DEPENDING UPON PRODUCT

ADE	Antibody-Dependent Enhancement
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Transaminase
AST	Aspartate Transaminase
bAb	Binding Antibody
BSC	Biological Safety Cabinet
CAPA	Corrective and Preventive Action
CBC	Complete Blood Count
CDC	Center for Disease Control
CI	Confidence Interval
CIOMS	Council for International Organization of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CoV	Coronavirus
COVID-19	Coronavirus Disease 19
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
DART	Developmental & Reproductive Toxicology
DMP	Data Management Plan
DRM	Data Review Meeting
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ELISA	Enzyme-linked Adsorbent Assay
ERC	Ethical Review Committee
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titre
HCW	Healthcare Worker
IAP	Interim Analysis Plan
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ID	Identification Number
IFN-γ	Interferon-gamma
IgG	Immunoglobulin G
IP	Investigational Product

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IRB	Institutional Review Board
ITT	Intention-to-Treat
IWRS	Interactive Web Response System
Kg	Kilogram
MERS	Middle East Respiratory Syndrome
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
mL	Milliliter
µg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
MM	Medical Monitor
mm	Millimeter
nAb	Neutralizing Antibodies
NP	Nasopharyngeal
PBS	Phosphate-buffered Saline
PI	Principal Investigator
PP	Per Protocol
PSRT	Protocol Safety Review Team
PT	Preferred Term
PTID	Participants Identification Number
RNA	Ribonucleic Acid
rRT-PCR	Real Time Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical and Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Standard Deviation
SDMC	Statistical and Data Management Center
SOC	System Organ Class
SDV	Source Data Verification
SOP	Standard Operational Procedure
SDMC	Statistical & Data Management Center
SPEAC	Safety Platform for Emergency Vaccines
VED	Vaccine-Enhanced Disease
VAERD	Vaccine-Associated Enhanced Respiratory Disease
VE	Vaccine Efficacy
VTM	Viral Transport Media
WBC	White Blood Cell
WHO	World Health Organization

KEY ROLES AND CONTACT INFORMATION

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Study Coordinator	NAME INSTITUTION ADDRESS TEL: MOBILE: FAX: EMAIL:
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Research Laboratory	NAME (Principal) INSTITUTION ADDRESS TEL: MOBILE: FAX: EMAIL:
Contract Research Organizations	**Safety Monitoring and Data Management** NAME (Principal) INSTITUTION ADDRESS TEL: MOBILE: FAX: EMAIL: **Site Monitoring** NAME INSTITUTION ADDRESS TEL: MOBILE: FAX: EMAIL:
Ethics Review Committee / Institutional Review Boards ***(for each participating institution)***	NAME INSTITUTION ADDRESS TEL: MOBILE: FAX: EMAIL: ADDITIONAL REVIEW BOARDS/ETHICS COMMITTEES TO BE ADDED

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Local Regulatory Authority ***(for each participating country)***	NAME INSTITUTION ADDRESS TEL: MOBILE: FAX: EMAIL:

PROTOCOL SUMMARY

Title	**Phase 3 randomized, double-blinded, placebo-controlled trial to evaluate the safety, immunogenicity, and efficacy of [Vaccine Candidate] against COVID-19 in adults ≥ 18 years of age**
Short Title	Phase 3 study of [Vaccine Candidate] for COVID-19
Protocol Number	[XXX]
Trial Phase	Phase 3

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Rationale	The 2019 outbreak of coronavirus disease (COVID-19)—caused by a novel coronavirus, SARS-CoV-2—has now spread to more than 210 countries and territories globally. There are no specific therapies or vaccines to prevent COVID-19 and the numbers of new cases and deaths continue to increase daily. Fast-tracked vaccine development is urgently needed. Phase 1/2 clinical trials of Vaccine Candidate, the SARS-CoV-2 vaccine candidate manufactured by Sponsor, are now being conducted in location to evaluate the vaccine candidate's safety and immunogenicity among healthy adults (Clinical Trial Registry #). Preliminary analysis from Phase 1/2 trials indicate Vaccine Candidate has an acceptable safety and immunogenicity profile. We propose to conduct a Phase 3, individually randomized, double-blind, placebo-controlled trial in location to determine the safety and efficacy of the vaccine candidate among healthy adults > 18 years of age.

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Study Products	Study vaccines:
	• Vaccine Candidate (volume mL contains xx amount of antigen and xx amount of adjuvant)
	• Control (placebo or licensed vaccine) - (i.e., no SARS-CoV-2 antigen)
Primary Study Hypotheses	• Efficacy: Vaccine Candidate will provide protection against laboratory-confirmed COVID-19 of any severity.
	• Safety: Vaccine Candidate will be safe and well-tolerated.
	• Immunogenicity: Vaccine Candidate will be immunogenic.

Primary Objectives	Primary endpoints
Efficacy	
1. To evaluate the efficacy of a full regimen of [Vaccine Candidate] against laboratory-confirmed COVID-19 of any severity.	1. Virologically confirmed COVID-19 of any severity occurring from two weeks after completion of the vaccination regimen until the time the targeted number of cases (n = XXX) has accrued.
Safety	
1. To assess Vaccine Candidate safety (i.e., severe adverse events [SAEs] or other medically attended adverse events [AEs]).	1. SAEs or other medically attended AEs occurring at any time in all study participants; SAE and medically attended AE rates will be analyzed at when the primary efficacy endpoint (XXX cases) is reached and at study end.

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2. To assess [Vaccine Candidate] post-vaccination reactogenicity in a subset of participants.	2. Solicited local and systemic reactions for seven days after each study vaccination in a subset of study participants (e.g., X,XXX).
3. To assess safety of [Vaccine Candidate] in terms of AEs > Grade 2 in all participants.	3. Vaccine related unsolicited AEs > Grade 2 occurring between vaccinations and 28 days after the final vaccination, among all study participants.
Immunogenicity	
1. To evaluate [Vaccine Candidate] immunogenicity among all study participants by ELISA-binding IgG antibodies against the [Vaccine Candidate] antigen(s).	1. IgG ELISA bAb in specimens collected before vaccination and XX days after each immunization, and at 6 and 12 months after completion of all study vaccinations.
Secondary Objectives	**Secondary Endpoints**
Efficacy	
1. To evaluate the efficacy of [Vaccine Candidate] against severe laboratory-confirmed COVID-19.	1. Virologically confirmed severe COVID-19 cases occurring from two weeks after first vaccination through 12 months of follow-up.
2. To evaluate the efficacy of [Vaccine Candidate] against laboratory-confirmed COVID-19 of any severity.	2. Virologically confirmed COVID-19 cases of any severity occurring from two weeks after first vaccination through 12 months of follow-up.

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3. To evaluate the efficacy of [Vaccine Candidate] against laboratory-confirmed COVID-19 of any severity among participants by age cohort.	3. Virologically confirmed COVID-19 cases of any severity occurring among participants 18 through 59 years of age and ≥60 years of age from two weeks after first vaccination through 12 months of follow-up.
4. To evaluate the efficacy of [Vaccine Candidate] against asymptomatic SARS CoV-2 infections detected serologically.	4. Serologically confirmed SARS-CoV-2 asymptomatic infections occurring from two weeks after first vaccination through 12 months of follow-up.
5. To evaluate the efficacy of [Vaccine Candidate] against laboratory-confirmed COVID-19 deaths.	5. Virologically confirmed COVID-19 deaths occurring from two weeks after first vaccination through 12 months of follow-up.
6. To evaluate the efficacy of [Vaccine Candidate] against deaths of any cause.	6. Deaths occurring during the study, independently of their association with COVID-19/SARS-CoV-2 infection, occurring from two weeks after first vaccination through 12 months of follow-up.
Safety	

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1. To assess [Vaccine Candidate] safety in terms of vaccine-enhanced disease (VED) and adverse events of special interest (AESI).	1. Vaccine enhanced disease (VED) events occurring among participants with symptomatic, virologically confirmed COVID-19 over the entire duration of the study; adverse event of special interest (AESI) events observed among all study participants over the entire duration of the study.
Immunogenicity	
1. To evaluate immunogenicity of [Vaccine Candidate] by neutralizing antibody (nAb) assay against SARS-CoV-2.	1. nAb titers measured by neutralization assay against SARS-CoV-2 will be measured in a random subset of participants in specimens collected before the first and XX weeks after the final immunization.
2. To evaluate persistence of vaccine-induced ELISA binding IgG antibodies against the vaccine antigen.	2. IgG ELISA bAb in specimens collected at 6 and 12 months after vaccination in a random subset of participants. Geometric mean ELISA units will be reported.
Exploratory Objectives	**Exploratory Endpoints**
Efficacy	
1. To evaluate the efficacy of [Vaccine Candidate] against laboratory-confirmed COVID-19 of any severity categorized by sex.	1. Virologically confirmed COVID-19 cases of any severity occurring from two weeks after first vaccination through study end categorized by sex.

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2. To evaluate the efficacy of Vaccine Candidate against laboratory-confirmed COVID-19 of any severity stratified by disease severity grades.	2. Virologically confirmed COVID-19 cases of any severity occurring from two weeks after first vaccination through study end stratified by disease severity according to WHO Clinical Progression Scale.
3. To evaluate the efficacy of [Vaccine Candidate] against laboratory-confirmed COVID-19 of any severity among participants who were virologically or serologically positive for SARS-CoV-2 at time of enrollment.	3. Virologically confirmed COVID-19 cases of any severity occurring from two weeks after first vaccination through study end in participants who were virologically or serologically SARS-CoV-2 positive at the time of enrollment.
4. To evaluate the efficacy of [Vaccine Candidate] against laboratory-confirmed COVID-19 of any severity among participants who were virologically and serologically negative for SARS-CoV-2 at time of enrollment.	4. Virologically confirmed COVID-19 cases of any severity occurring from two weeks after first vaccination through study end in participants who were virologically and serologically SARS-CoV-2 negative at the time of enrollment.

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5. To evaluate the efficacy of Vaccine Candidate against laboratory-confirmed COVID-19 of any severity among individuals who previously presented with a symptomatic COVID-19 infection of any severity.	5. Virologically confirmed COVID-19 cases of any severity occurring from two weeks after first vaccination through study end. Includes only participants who were virologically or serologically positive at enrollment as well as participants who developed symptomatic SARS-CoV-2 infection of any severity during the follow-up.
6. To evaluate the efficacy of [Vaccine Candidate] against laboratory-confirmed COVID-19 of any severity within subgroups defined by randomization across sites	6. Virologically confirmed COVID-19 of any severity occurring from two weeks after completion of the vaccination regimen through study end for each clinical site independently.
7. To investigate disease severity as measured by hospitalization or mechanical ventilation.	7. Count and frequency of COVID-19 cases that require hospitalization or mechanical ventilation.
Safety	
1. To evaluate COVID-19 cases of any severity with specialized assays to discern potential differences between breakthrough cases detected among [Vaccine Candidate] recipients vs. those in the placebo/control group.	1. Exploratory tests to be defined, e.g., IL-6, inflammation markers, Th1/Th2 markers (IgG subclasses, cytokines), etc. Frequency count and rate of positive tests will be reported.
Immunogenicity	

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1. To evaluate early infection serum samples and convalescent serum samples (~15 days after infection resolution), as well as baseline and post-vaccination serum samples from COVID-19 cases.	1. IgG ELISA bAb in specimens collected before vaccination and XX days after each immunization, as well as at 6 and 12 months after vaccination, from participants who develop COVID-19 of any severity. Acute and convalescent sera will also be collected. Geometric mean ELISA units, geometric mean fold rise, and seroconversion rates (proportion of participants with XX-fold rises in ELISA units between pre-vaccination and XX days after final vaccination) will be reported. Geometric mean ELISA units for sera collected at 6 and 12 months will be reported.
2. To evaluate additional serological assays in samples from COVID-19 cases (and appropriate controls) in an effort to identify immune correlates of protection or risk (e.g., antibody affinity, ADCC, complement fixation, novel assays to be developed).	2. Test results, positivity rates, and mean titers will be reported.
Clinical	

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1. To evaluate COVID-19 symptoms in [Vaccine Candidate] vs. placebo recipients and to investigate the relationship between COVID-19 symptoms and disease severity, in an effort to develop a severity score that can be used in future COVID-19 studies.	1. Tabulate the range of symptoms presented among COVID-19 cases in [Vaccine Candidate] vs. placebo recipients and examine the relationship of symptoms with disease severity. Counts and rate of individual systems will be presented categorized by vaccine / placebo treatment and by disease severity according to the WHO Clinical Progression Scale.
Virological	
1. To evaluate and compare sequences of breakthrough infection viruses in [Vaccine Candidate] vs. placebo recipients, and vs. the strain source of the vaccine antigen.	1. Attempt to isolate/cultivate viruses from COVID-19 cases. Viral sequence comparisons between strains isolated from study participants and the vaccine strain from which the vaccine was derived.
2. To confirm SARS-CoV-2 infection either by virologic or serologic methods, or by evaluating antibodies to SARS-CoV-2 antigens not included in the vaccine.	2. Frequency and counts of seroresponses to non-vaccine SARS-CoV-2 antigens that may be indicative of infection in samples collected at the time of infection and after a COVID-19 infection.
Study Design	A case-driven, randomized, double-blind, placebo-controlled, adaptive, group-sequential Phase 3 clinical trial will be conducted to assess the efficacy, safety,

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		and immunogenicity of [Vaccine Candidate]. Men and women 18 years and older will be enrolled and stratified by age (< 60 years and ≥ 60 years). Note: Pregnant and breastfeeding women, as well as those intending to become pregnant within the three months after vaccination, will not be permitted to participate, unless data from developmental and reproductive toxicology (DART) and Phase 1/2 studies and a benefit/risk analysis are supportive). No pre-screening at time of enrollment to exclude seropositive or RT-PCR positive participants will be conducted. Participants will be randomized among X number of sites in X countries. Solicited AEs will be recorded in a subset of participants for seven days following each immunization and unsolicited AEs grade ≥2 will be recorded for all participants in between vaccinations and 28 days following the last vaccination. SAEs and medically attended AEs will be

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monitored throughout the study duration. For immunogenicity evaluations, blood samples will be taken from all participants before and XX weeks after each vaccination, and at 6 and 12 months. Antibody titers of IgG against SARS-CoV-2 will be measured in all participants pre-vaccination and XX days following the last vaccination. Neutralizing antibody titers will be measured in a subset of participants, with samples retained from all participants for future use to identify immune correlates of protection and/or risk. Attempts will be made to obtain acute (i.e., obtained at time of diagnosis) and convalescent (~2 weeks after recovery) serum from any participant that develops COVID-19 during the follow-up period.

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Participants will be monitored over 12 months for signs of COVID-19 infection. The study is end point driven. If the rate of detection of primary COVID-19 endpoints indicates that XX number of primary endpoints (i.e., laboratory-confirmed COVID-19 of any severity) has been accrued among fully vaccinated participants eligible for the primary analysis are not likely to be detected within 6 months of initiating surveillance, additional sites and/or countries may be enrolled. Enrollment at some sites may be closed due to low disease incidence, and total sample size may be increased or decreased based on blinded data. For safety determination for AESI or VED, whether Vaccine-Associated Enhanced Respiratory Disease (VAERD) or Antibody-Dependent Enhancement (ADE), an extended follow-up period may be necessary. The study will include interim analyses for safety, as well as formal early efficacy or futility analysis.

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Study Population	Adults (male and female) ≥ 18 years old at enrollment
Participating Sites	[Sponsor] will initiate a Phase 3 trial in the following location(s): XXX.
Study Duration	Participants will be followed for 12 months following first vaccination. Time until primary efficacy analysis will be based on accumulation of primary endpoints which is expected to be approximately 6-12 months duration. With an anticipated enrolment period per site of 6 months, the study is anticipated to last for ~18 months.

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Additional Resources:

COVID-19 specific:

- National Institutes of Health, Office of Science Policy. Clinical Trial E. Protocol Tool and Template Documents. https://osp.od.nih.gov/clinical-research/clinical-trials/https://osp.od.nih.gov/clinical-research/clinical-trials/
- Naming the coronavirus disease (COVID-19) and the virus that causes it. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it
- The Brighton Collaboration standardized template for collection of key information for benefit-risk assessment of protein vaccines. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7343648/
- WHO Target Product Profiles for COVID-19 Vaccines. https://www.who.int/publications/m/item/who-target-product-profiles-for-covid-19-vaccines
- WHO HO Working Group – Core Protocol for vaccines against COVID-19. https://www.who.int/publications/m/item/who-working-group-core-protocol-for-vaccines-against-covid-19

General:

Code of Federal Regulations (CFR)
21 CFR Part 11: Electronic Records, Electronic Signatures

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21 CFR Part 50: Protection of Human Subjects
21 CFR Part 312: Investigational New Drug Application
45 CFR Part 46: Protection of Human Subjects Research

Food and Drug Administration (FDA)
FDA Regulations Relating to Good Clinical Practice and Clinical Trials
Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs – Improving Human Subject Protection
Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees
Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance
Guidance for Industry: Multiple Endpoints in Clinical Trials
Guidance for Industry: Safety Assessment for IND Safety Reporting

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
Guidance for Industry, E6 (R2) Good Clinical Practice: Consolidated Guidance
Guidance for Industry, M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

FILES

PATH Background and Rationale (Part 1 of Phase 3 study of Vaccine Candidate for COVID-19)
by Chris Ockenhouse

PATH Hypotheses, Objectives, Endpoints, and Case Definitions (Part 2 of Phase 3 study of Vaccine Candidate for COVID-19)
by Chris Ockenhouse

PATH Study Design (Part 3 of Phase 3 study of Vaccine Candidate for COVID-19)
by Chris Ockenhouse

PATH Study Population (Part 4 of Phase 3 study of Vaccine Candidate for COVID-19)
by Chris Ockenhouse

PATH Study Vaccine (Part 5 of Phase 3 study of Vaccine Candidate for COVID-19)
by Chris Ockenhouse

PATH Study Procedures (Part 6 of Phase 3 study of Vaccine Candidate for COVID-19)
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Safety Assessment and Reporting (Part 7 of Phase 3 study of Vaccine Candidate for COVID-19)
by Chris Ockenhouse

Data Handling and Recordkeeping (Part 8 of Phase 3 study of Vaccine Candidate for COVID-19)
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Statistical Considerations (Part 9 of Phase 3 study of Vaccine Candidate for COVID-19)
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Quality Assurance and Quality Control (Part 10 of Phase 3 study of Vaccine Candidate for COVID-19)
by Chris Ockenhouse

Ethical Considerations and Informed Consent (Part 11 of Phase 3 study of Vaccine Candidate for COVID-19)
by Chris Ockenhouse

Financing and Insurance (Part 12 of Phase 3 study of Vaccine Candidate for COVID-19)
by Chris Ockenhouse

Publication and Data Sharing Policy (Part 13 of Phase 3 study of Vaccine Candidate for COVID-19)
by Chris Ockenhouse

Schedule of Study Visits and Evaluations (Appendix A of Phase 3 study of Vaccine Candidate for COVID-19)
by Chris Ockenhouse

Severity Grading Table (Appendix B of Phase 3 study of Vaccine Candidate for COVID-19)
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Sample Informed Consent Form Template (Appendix C of Phase 3 study of Vaccine Candidate for COVID-19)
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