An International Observational Study of Outpatients with SARS-CoV-2 Infection

Short title: International SARS-CoV-2 Infection Observational Study (ICOS)

INSIGHT Protocol Number 011

Funded by the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) and
Carried out by the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT)

Sponsor: University of Minnesota

In collaboration with four International Coordinating Centers (ICCs) of the INSIGHT Network:
-Copenhagen HIV Programme (CHIP) - Copenhagen, Denmark
-Medical Research Council (MRC) Clinical Trials Unit at University College London (UCL) - London, United Kingdom
-The Kirby Institute, University of New South Wales - Sydney, Australia
-The Institute for Clinical Research at the Veterans Affairs Medical Center - Washington, D.C., USA

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1 Synopsis

Purpose
SARS-CoV-2 is a coronavirus that emerged in China in late 2019 causing a novel Corona-Virus Induced Disease (COVID-19). COVID-19 is spreading rapidly throughout the world. While a proportion of people with COVID-19 have sufficiently severe symptoms to require hospitalization at the time of initial symptom onset, in others the disease may remain mild, and in some cases there has been observed a worsening of symptoms a few days after initial presentation with relatively mild symptoms. There is an urgent need for understanding the progression of disease for individuals with SARS-CoV-2 infection/COVID-19 who do not require immediate hospitalization.

This is an international, observational cohort study of adults with SARS-CoV-2 infection/COVID-19 managed as outpatients (not hospitalised). This study will also be a platform for the enrolment of outpatients for randomized trials that will be conducted by the INSIGHT group.

Those with confirmed SARS-CoV-2 infection will form an observational cohort study and be followed for 28 days. Procedures and data collection have been streamlined to facilitate the enrolment of a large number of adults at INSIGHT sites around the world.

The general aim of this study is to estimate the rate of disease progression for adults testing positive for SARS-CoV-2. The primary endpoint for this study and the basis for sample size is hospitalization or death during the 28 day follow-up period. In some locations special facilities are being built/utilized for quarantine/public health reasons for those who are SARS-CoV-2 positive. Hospitalization is defined as a stay for at least 18 hours, irrespective of reason, at a hospital or one of these special facilities after study enrolment.

Secondary outcomes include participant-reported health status and change in severity of dyspnoea.

As the understanding of the natural history of COVID-19 improves based on this and other studies, inclusion criteria and the data collection plan, including the outcomes assessed in this protocol, may be modified.

Study Objectives
The two primary objectives of this observational study are:

Among participants testing positive for SARS-CoV-2:

1. Estimate the rate of hospitalization or death during the 28 day follow-up period.
2. Identify risk factors for hospitalization or death.

Other objectives are:

1. Compare characteristics, including demographics, co-morbid conditions or immunosuppression, and other risk factors for disease progression, including hospitalization or death, for the global cohort and by geographic region between those who have a positive test for the SARS-CoV-2 virus versus those who have a negative test.

2. Among those positive for SARS-CoV-2:

    a. Evaluate health status and the percentage reporting excellent or very good health status during follow-up.

    b. Determine the percentage reporting a return to premorbid health status during follow-up.

    c. Evaluate change in severity of dyspnoea using a standardized questionnaire during follow-up.

3. In a substudy involving selected sites, establish a repository of baseline upper respiratory and blood samples for future studies. These studies will be aimed at molecular characterization of SARS-CoV-2, and the measurement of biomarkers that predict progression of disease. Among participants co-enroling in INSIGHT 004: Genomics, DNA will be extracted for studies of host genetics to investigate the pathophysiology and host-viral interactions of COVID-19.

4. Use the data collected to inform the design of future randomized intervention studies aimed at reducing the rate of disease progression and morbidity.

Participant Selection
To be eligible for enrolment participants must be ≥ 18 years of age, not be hospitalized (outpatients), and have a signed informed consent. Participants with SARS-CoV-2 infection will be followed for 28 days from enrolment.

Study Plan
Participants who consent for the study and have SARS-CoV-2 infection/COVID-19, will be followed for 28 days in an observational cohort study.

Procedures and data collection have been streamlined to facilitate the enrolment of a large number of adults at INSIGHT sites around the world.

The general aim of this study is to identify risk factors for disease progression, e.g., hospitalization or death. This information will be used to plan and rapidly enrol randomized trials of treatments for COVID-19. Protocols which are developed for the randomized trials by INSIGHT will be separate from this protocol.

2 Background and Rationale

In December 2019, the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknown cause. A novel coronavirus was rapidly identified by sequencing and named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the illness caused by infection with SARS-CoV-2 has been named Corona Virus Induced Disease 2019 (COVID-19). By February 2020 sustained community transmission outside China was apparent, and as of March 27 there are more than 500,000 cases reported in over 100 countries, with over 25,000 deaths. The World Health Organization declared the outbreak a Public Health Emergency of International Concern on 30 January 2020 and subsequently stated that the outbreak could be characterized as a pandemic on March 11, 2020.[1,2]

Over the course of the past several weeks there have been several reports describing the clinical manifestations of SARS-CoV-2 infection and factors associated with greater disease severity, mainly in hospitalized patients.[3-16] While COVID-19 may have a lower fatality rate than previous coronaviruses like MERS and SARS-CoV-1, it is more contagious.[5] Current estimates of the fatality rate range from 0.5 to 3.5% overall (versus 0.1% for seasonal influenza), and are likely higher in key risk groups including the immunocompromised.

Reports to date have focussed largely on hospitalized patients and included descriptive information on the patients as well as estimates of associations between those characteristics and disease severity. Older age has been found to be strongly related to greater severity and poorer outcome,[7,12,17] as have the presence of conditions such as hypertension, diabetes and coronary heart disease.[5,7,14] Patients with underlying cardiovascular disease who have elevated troponin T levels are at increased risk of death compared to those without elevated troponin T levels.[18] Other risk factors identified include cigarette smoking[7,12,19] and raised BMI.[10,16] Gender has not shown a consistent relationship with disease severity.[4,7] Specific symptoms at presentation that have notably been associated with greater likelihood of progression to more severe disease include shortness of breath and elevated body temperature.[7,9]

Data on the relationship between the use of routine medications for chronic conditions and COVID-19 outcomes are limited. It has been hypothesized that since the tissue receptor for SARS-CoV-2 is angiotensin-converting enzyme 2 (ACE2), and higher levels of ACE2 can protect against acute respiratory distress syndrome (ARDS), that the angiotensin receptor blockers and statins upregulate ACE2 and that these might be used to treat COVID-19.[20] On the other hand, it has also been suggested that treatment with ACE2-stimulating drugs in people with diabetes and hypertension could increase the risk of developing severe and fatal COVID-19.[21] One small study has found no association between use of an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker and risk of death in COVID-19.[10]

There is currently little data available in people with COVID-19 who are managed as outpatients. It would be useful to identify risk factors associated with progression of COVID-19 in non-hospitalized individuals leading them to require hospitalization and/or

treatment for COVID-19. This will provide critical information for clinical service planning, and further inform the development of novel therapeutics.

INSIGHT is currently enrolling hospitalized patients with COVID-19 in the INSIGHT FLU 003 Plus observational study. This observational study of outpatients with COVID-19 will complement FLU 003 Plus and address gaps in our knowledge about risk factors for disease progression that lead to hospitalization or death.

Recognizing the critical importance of maintaining front-line clinical services in responding to COVID-19 and protecting health care workers, this study is designed with minimal data collection requirements with careful attention to management of the risks of service diversion and onward disease transmission. To that end, we considered the literature reviewed above and developed a streamlined data collection plan for collection of baseline and follow-up data for adults who test positive for SARS-CoV-2. Throughout this document when referring to testing for SARS-CoV-2, this refers to a test that directly detects SARS-CoV-2 i.e. a nucleic acid test that detect the presence of viral RNA, typically a PCR test, or a viral antigen test, not an antibody test.

The data from this cohort study will be regularly summarized and may be modified based on interim results or the findings from other studies. Plans are underway for potential extension of follow-up through 5 years for the purpose of assessing long-term complications and durability of antibody response. These plans will be developed under a separate protocol or an extension to this protocol, with existing participants invited to participate.

3 Methodology

3.1 Study Design

This is an observational cohort study of outpatients with COVID-19. Enrolment will begin in June 2020 and is expected to continue for at least 12 months. Follow-up will be 28 days from enrolment in those who are positive. Those with a negative test will not be followed after enrolment or disclosure of a negative result.

3.2 Study Objectives

The two primary objectives of this observational study are:

Among those who are positive for SARS-CoV-2:

1. Estimate the rate of hospitalization or death during the 28 day follow-up period.

2. Identify risk factors for hospitalization or death.

Other objectives are:

1. Compare characteristics, including demographics, co-morbid conditions or immunosuppression, and other risk factors for disease progression, including hospitalization or death, for the global cohort and by geographic region between those who test positive for the SARS-CoV-2 virus versus those who test negative.

2. Among those who are positive for SARS-CoV-2

    a. Evaluate health status and the percentage reporting excellent or very good health status during follow-up.

    b. Determine the percentage reporting a return to premorbid health status during follow-up.

    c. Evaluate change in severity of dyspnoea using a standardized questionnaire[22] during follow-up.

3. In a substudy involving selected sites, establish a repository of baseline upper respiratory and blood samples for future studies. These studies will be aimed at molecular characterization of SARS-CoV-2, and the measurement of biomarkers that predict progression of disease. Among participants co-enroling in INSIGHT 004: Genomics, DNA will be extracted for studies of host genetics to investigate the pathophysiology and host-viral interactions of COVID-19.

4. Use the data collected to inform the design of future randomized intervention studies aimed at reducing the rate of disease progression and morbidity.

3.3 Endpoints

The primary endpoint is hospitalization or death during the 28 day follow-up period. Special facilities are being built for the care of COVID-19 patients requiring medical care. Hospitalization is defined as a stay for at least 18 hours, irrespective of reason, at a hospital or one of these special facilities after study enrolment.

Key secondary outcomes include:

- Participant-reported evaluation of health status
- Change in severity of dyspnoea.

3.4 Sample Size

Sample size is open-ended for this observational study. We estimate that several hundred sites will participate and will enrol approximately 10,000 adults with SARS-CoV-2 infection. Sites in diverse geographic locations on several continents will participate.

For participants with COVID-19, statistical considerations are summarized below. Information on rates of a composite outcome of hospitalization or death for the target

population is scarce, and rates are expected to vary across geographic locations, and possibly over time. Therefore, initial analyses will be descriptive, and sample size estimates will be updated based on the observed event rates, prevalence of risk factors, and newly emerging research questions.

For power calculations, we conservatively assume that 500 out of 10,000 (5%) participants will experience the composite outcome of hospitalization or death by day 28. This is based on the expectation that persons with mild symptoms will be discouraged from seeking SARS-CoV-2 testing at the height of the pandemic, while persons presenting with severe symptoms would not be eligible for this protocol.

Table 1 below summarizes the sizes of the associations of risk factors (dichotomized) with hospitalization or death (odds ratios) that can be detected with 80% and 90% power, using 2-sided tests with significance level of 0.05, assuming 500 or 100 events. For example, with 500 events, an odds ratio of 1.51 can be detected with 80% power for a risk factor with 10% prevalence. For analyses within subgroups, e.g., by age, event numbers may be smaller. With 100 events, an odds ratio of 2.32 can be detected with 80% power for a risk factor with 10% prevalence.

Prevalence of Risk Factor	500 events		100 events	
	80% Power	90% Power	80% Power	90% Power
5%	1.73	1.85	2.99	3.31
10%	1.51	1.59	2.32	2.55
25%	1.34	1.40	1.86	2.02
50%	1.30	1.35	1.76	1.93

Table 1. Odds ratios that can be detected with 80% and 90% power, assuming 500 or 100 persons are hospitalized or die.

For continuous risk factors, odds ratios are expressed per unit increase in the risk factor. Table 2 summarizes the odds ratios per 1 standard deviation higher levels of the risk factor that can be detected with power of 80% or 90% if the association with outcomes is positive (odds ratio > 1) or negative (odds ratio < 1). For example, with 500 events, an odds ratio of 1.17 per 1 standard deviation higher levels of the risk factor can be detected with 90% power. Calculations assume that the risk factor has a normal distribution.

Association	500 events		100 events	
	80% Power	90% Power	80% Power	90% Power
Positive (OR>1)	1.14	1.17	1.33	1.39
Negative (OR<1)	0.88	0.85	0.75	0.72

Table 2. Odds ratios per 1 SD higher levels of a continuous risk factor that can be detected with 80% and 90% power, assuming 500 or 100 events.

3.5 Participant Selection

This study intends to target enrolment at research sites that can recruit a large number of individuals with SARS-CoV-2. Thus, each participating site will be asked to describe the approach they plan to take for enroling individuals. Sites may be asked to change their approach to enrolment if the expected percentage positive for SARS-CoV-2 is too low. Enrollment at registered sites may be paused if there are too few positive individuals being enroled.

The inclusion and exclusion criteria for enrolment are given below.

3.5.1 Inclusion Criteria

- ≥ 18 years of age
- Not hospitalized
- Signed informed consent.

3.5.2 Exclusion Criteria

- Persons with a known positive SARS-CoV-2 test > 28 days ago.

Those who are negative for SARS-CoV-2 at enrolment will not be followed further in the observational cohort. If the test result is indeterminate, re-testing may be carried out according to local standards.

Individuals who have previously been tested
Individuals with a previous positive test for SARS-CoV-2 within 3 days of enrollment may be enrolled without the need for a repeat test at enrollment. If the positive test was > 3 days and < 28 days before enrollment the test will need to be repeated at enrollment.

3.5.3 Study Sites

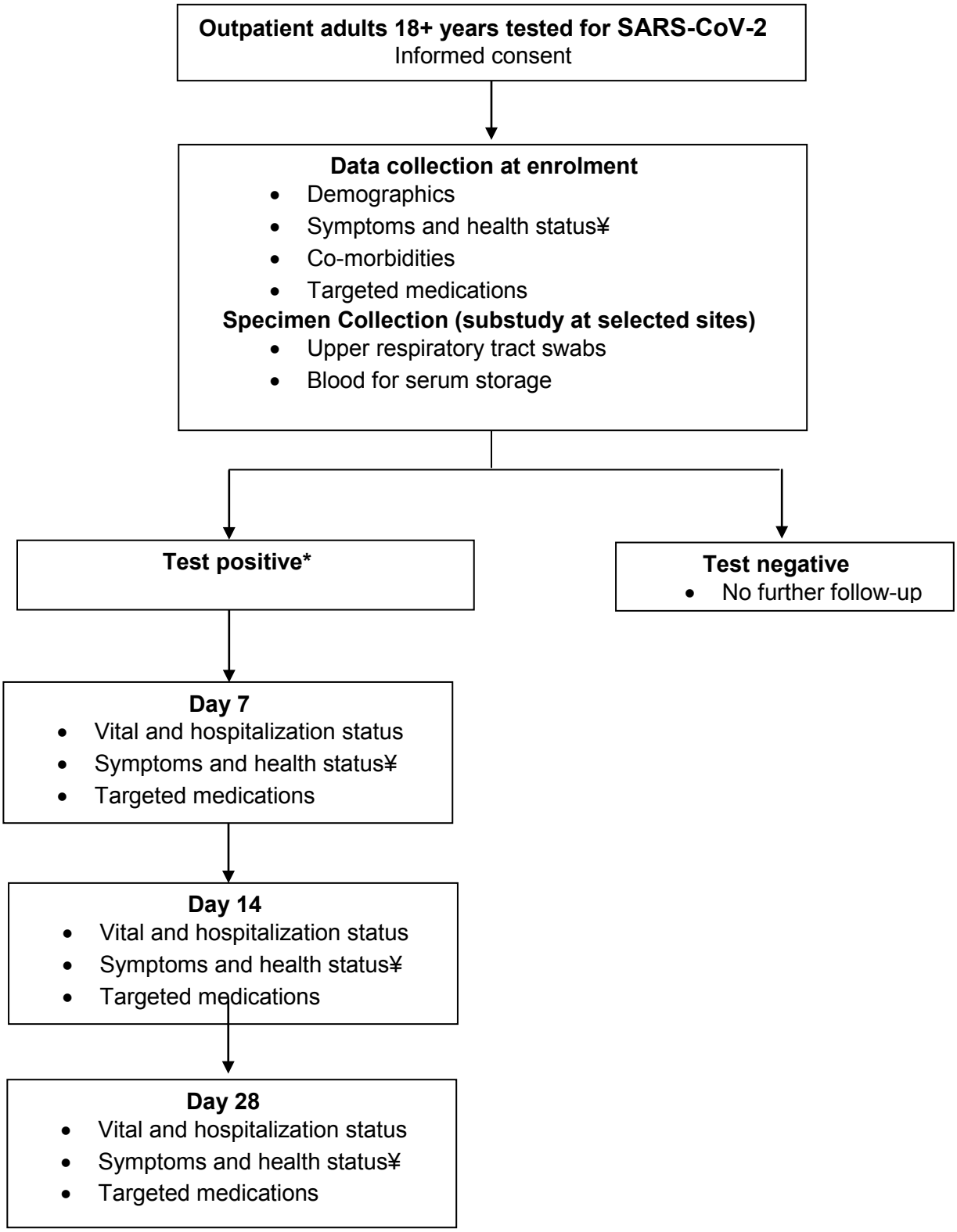
This study will be conducted in geographic locations where the incidence of COVID-19 is high. To avoid enrolling a large number of individuals testing negative to SARS-CoV-2, participation of sites that are registered to conduct this study may be paused depending on the prevalence of positive test results for SARS-CoV-2 in their area.

Since the handling of clinical specimens may be problematic at many testing locations, the collection of study specimens will be limited to a substudy involving selected sites (see Appendix F).

3.6 Study Plan

The study plan is depicted in Figure 1.

Figure 1: Study plan for participants undergoing SARS-CoV-2 testing and consenting to participation in this observational study.



Footnote
*on the day of enrolment or test done within 3 days before enrolment
¥ includes COVID-19 related out-patient treatments

Enrolment

Outpatient testing for SARS-CoV-2 may be performed in a variety of ways and for a variety of reasons. To avoid risk to health care workers, in many locations, special facilities are being identified for rapid identification of those with COVID-19. We refer to these as “testing stations”. Since the testing stations are likely to be overwhelmed with people seeking testing, we anticipate that separate areas will have to be identified to consent participants for this research study and to collect the required data. We refer to these as “research stations”. Collaborations between the testing and research stations will be important.

For participants who consent to the study, permission to release medical records will be sought and reasons for hospitalization and events during hospitalization will be requested. Information regarding demographics; medical history, including co-morbidities; onset date of symptoms; targeted symptoms, including difficulty breathing; smoking; and targeted medications will be obtained. Contact information for one or two persons who know(s) the participant’s whereabouts will also be recorded.

At the time of enrolment, selected sites participating in a substudy (see Appendix F) will be asked to obtain separate consent for the swabs from the upper respiratory tract and a blood sample sufficient for 4mL of serum to be shipped to a central repository for future respiratory virus research; and 2) co-enrolment in the INSIGHT Genomics Study (INSIGHT 004) where a blood sample sufficient for obtaining 6mL whole blood will be collected and stored. These specimens will be sent to a central repository in the United States for storage.

Proposed research utilizing stored specimens collected per this protocol will be reviewed and approved by the Protocol Team, the INSIGHT Scientific Steering Committee, and NIAID.

Disclosure of SARS-CoV-2 Test Result

Participants already known SARS-CoV-2 positive within 28 days of enrollment are eligible. If the documented positive test was within 3 days of enrolment they do not need to be retested at enrolment, and will be followed for 28 days. For others being tested at enrolment, results may not be available on the day of enrolment. When the test results become available, participants will be contacted with the test result. If positive for SARS-CoV-2, these participants will be followed for 28 days.

Participants who do not have a positive test result for SARS-CoV-2 at enrolment will not be followed. Repeat testing can be carried out following local guidelines.

Follow-up of SARS-CoV-2 positive participants

During the follow-up period, the status of each participant will be assessed at 7, 14 and 28 days following enrolment. Status may be checked by telephone or by means other than face-to-face visits (e.g., text messages).

Follow-up assessments at 7, 14 and 28 days will include:

- Vital status
- Hospitalization status
- Specific symptoms, including difficulty breathing
- General health status
- COVID-19 related out-patient treatments
- Targeted medications

Participants hospitalized during the 28 day follow-up period may be invited to participate in FLU 003 Plus, if the location of their hospitalization is a FLU 003 Plus site.

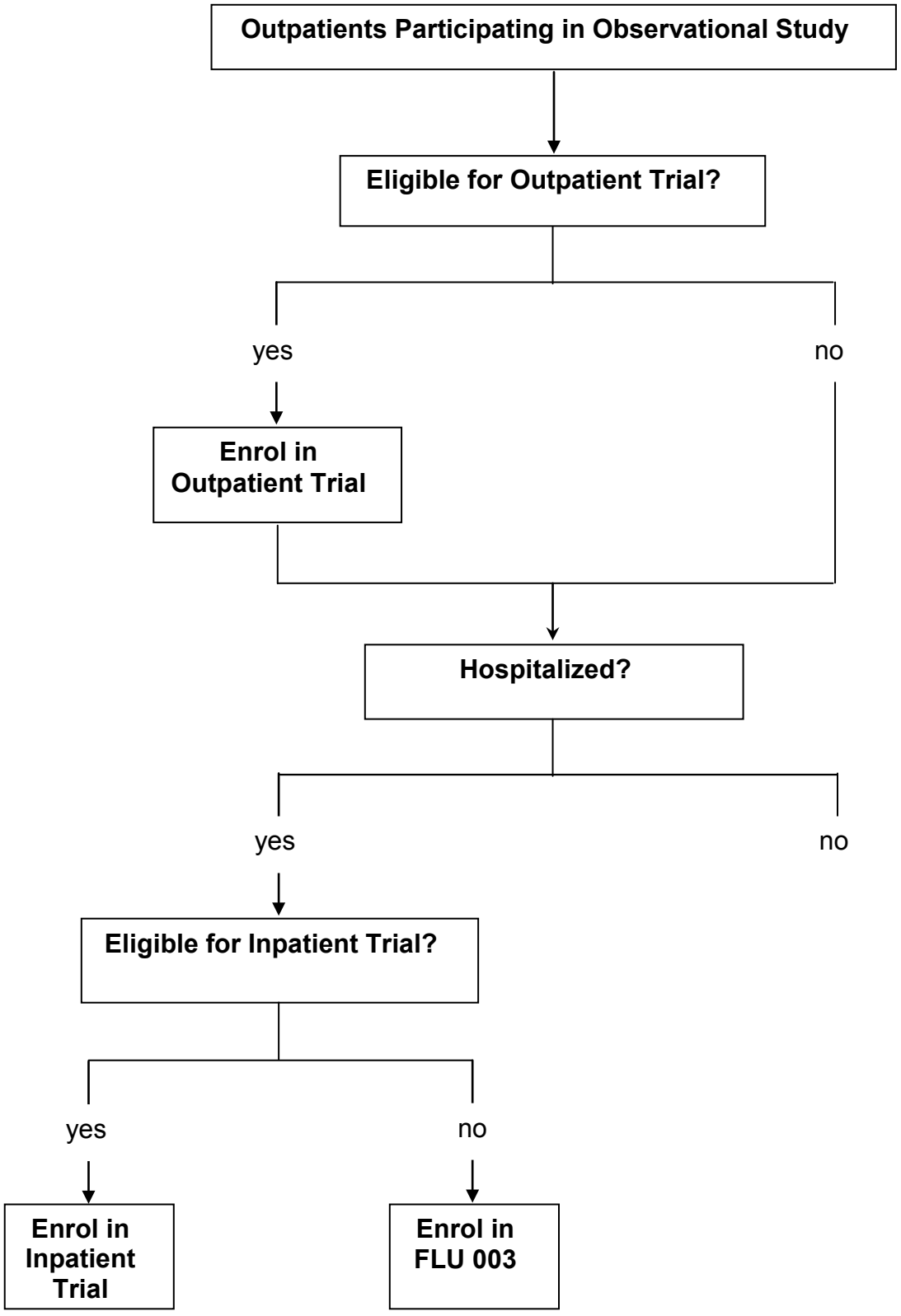
In summary, there are 4 time points at which data are collected for this observational study:

1) enrolment (in person),
2) at day 7 (may be by telephone or other means),
3) at day 14 (may be by telephone or other means) and
4) at day 28 (may be by telephone or other means).

Follow-up will continue through day 28 for all participants regardless of enrolment in other studies or hospitalization prior to day 28.

Figure 2 illustrates how information from the observational cohort study could be used to identify participants for an INSIGHT clinical trial or for FLU 003 Plus.

Figure 2: Study plan for participants in this observational study who may co-enrol in other protocols. Note: participants in this observational study with SARS-CoV-2 infection will be followed for 28 days regardless of participation in other protocols.



3.7 Study Withdrawal

Participants may withdraw from this observational study at any time at their request.

4 Evaluation

4.1 Data Analysis

Simple descriptive statistics will be used to describe all participants enrolled, as well as those with and without a positive test for SARS-CoV-2. Participant characteristics at enrolment will be summarized by geographic region, and by calendar time within geographic region. Participant characteristics will be compared for those with and without a positive test for SARS-CoV-2.

Symptoms, including severity of dyspnoea, will be summarized, and determinates of a positive test will be identified using logistic regression models. Factors other than symptoms include, for example, age, sex, co-morbidities, and time since onset of symptoms.

For participants who tested positive for SARS-CoV-2, follow-up data will be collected at days 7, 14, and 28. Disease severity at each time point will be summarized in an ordinal outcome that considers death, hospitalization, and general health status.

Risk factors for the outcomes (e.g., hospitalization, worsening of general health status) at 7, 14, and 28 days after enrolment will be examined using logistic regression models. Reasons for hospitalization will also be considered and analyses for specific reasons for hospitalization will be pursued. Risk factors will include demographic factors (e.g., age, sex, geographical region), clinical factors (e.g., co-morbidities, smoking status), symptoms and severity of dyspnoea at enrolment, and calendar time (to assess the influence of season, or a change in disease severity in the study population over time).

In addition to describing disease status at fixed time points, Kaplan-Meier estimates will be used to describe time to the composite outcome of hospitalization or death, overall and within subgroups. Factors associated with time to hospitalization or death will be investigated using Cox proportional hazards models.

All statistical models will be stratified by geographic region, unless the event numbers are too low. We will consider other stratifying models that include stratification by geographic region and calendar time if event numbers are sufficient.

As new data on COVID-19 become available, from this and other studies, data collection and analysis may change to address emerging research questions. Further details on the proposed data analysis will be provided in a Statistical Analysis Plan.

4.2 Data Monitoring

This observational study will be conducted under the direction of the INSIGHT 011 Protocol Team, the INSIGHT Scientific Steering Committee, and INSIGHT leadership. Members of the protocol team are given in Appendix C.

Interim data summaries will be reviewed at regular intervals, and as previously noted, data collection may be modified based on these summaries and findings from other studies.

5 Protection of Human Subjects & Other Ethical Considerations

5.1 Risks of Participation

There are minimal risks associated with study procedures. There may be discomfort associated with obtaining the upper respiratory tract swabs, but these are routine tests for determining if someone has a respiratory virus. Risk of testing may include false positive or false negative test results.

For those consenting to collection and storage of specimens, the risks of having blood taken include transient pain, bleeding, bruising, lightheadedness, fainting and, rarely, infection or a blood clot where the needle enters the body. If any adverse events occur that result from the blood draw or the upper respiratory swabs, sites should follow local IRB/IEC procedures for reporting.

5.2 Local Review of Protocol and Informed Consent

This study will be conducted by major medical centers participating in INSIGHT. Prior to the initiation of the study at each clinical research site, the protocol, informed consent form, and the participant information materials will be submitted to and approved by each site's overseeing IRB/EC. Any future amendments to the study protocol, informed consent, or participant information materials will be submitted and approved by each site's overseeing IRB/EC. After IRB/EC approval, sites must register for the protocol before enroling potential participants and must register for any protocol amendments.

5.3 Ethical Conduct of the Study

The study will be conducted according to the Declaration of Helsinki; the requirements of Good Clinical Practice (GCP) as defined in Guidelines, EU Clinical Trials Directive, and EU GCP Directive; Human Subject Protection and Data Protection Acts; the US Office for Human Research Protections (OHRP); or with the local law and regulation, whichever affords greatest protection of human subjects.

5.4 Informed Consent of Study Participants

All study participants must sign the IRB/EC approved informed consent form prior to any study-related procedures. See sample informed consent, Appendix A.

5.5 Confidentiality of Study Participants

The confidentiality of all study participants will be protected in accordance with GCP Guidelines and national regulations.

6 Other Important Documents and Policies

6.1 Reference Documents

Study procedures and case report forms are found on the INSIGHT study website.

6.2 Data Collection and Monitoring

Study data will be collected on standardized case report forms. Data will be collected during participant visits to health-care providers, via telephone, text, or other electronic communication, and possibly by chart abstraction. In some instances, it may be necessary to obtain and abstract records from another clinic, hospital or healthcare facility. Written permission for this is generally required and should be obtained at the time of enrolment when study consent is obtained. Study data and case report forms will be made available to site monitoring personnel.

6.3 Storage and Use of Specimens

Proposed research utilizing stored samples will be reviewed and approved by the Protocol team, the INSIGHT Scientific Steering Committee (SSC), and NIAID. Samples will not be sold to third parties or used directly to produce commercial products.

If a participant requests that his/her specimens collected to date be destroyed, this will be honored. Upon being informed that a participant has withdrawn consent for storage of specimens, the study database will be updated to indicate this, the specimen repository will be notified, and every effort will be made to have the specimens destroyed. Any data already generated from the use of specimens will be retained.

6.4 Record Retention

The investigator is responsible for retaining all essential documents listed in the ICH GCP Guideline. Records should be maintained in compliance with IRB/EC, local, and national medical records retention requirements, whichever is longest. All stored records are to be kept confidential to the extent required by national, state, and local law.

Should the investigator wish to assign the study records to another party and/or move them to another location, the investigator must provide written notification of such intent to the sponsor with the name of the person who will accept responsibility for the transferred records and/or their new location. The sponsor must be notified in writing and written permission must be received by the site prior to destruction or relocation of research records.

6.5 Publications and Presentations

Publications and presentations related to data obtained from this study will adhere to the INSIGHT Publications and Presentations Policy found on the INSIGHT website (www.insight-trials.org).

APPENDIX A: SAMPLE INFORMED CONSENT FORM

CONSENT FOR PARTICIPATING IN AN NIH-FUNDED RESEARCH STUDY
SITE INVESTIGATOR: _____ PHONE: _____

An International Observational Study of Outpatients with SARS-CoV-2 Infection

Short Title: INSIGHT 011: International SARS-CoV-2 Infection Observational Study (ICOS)
Sponsored by: The University of Minnesota
Funded by: National Institute for Allergy and Infectious Diseases, US National Institutes of Health

A Multicenter Study of the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT)

OHRP Requirements to be read by the sites: (*remove this text box from your site-specific consent)*

PLEASE NOTE THAT THIS SAMPLE LANGUAGE DOES NOT PREEMPT OR REPLACE LOCAL IRB/EC REVIEW AND APPROVAL. INVESTIGATORS ARE REQUIRED TO PROVIDE THE LOCAL IRB/EC WITH A COPY OF THIS SAMPLE LANGUAGE ALONG WITH THE LANGUAGE INTENDED FOR LOCAL USE. LOCAL IRBs/ECs ARE REQUIRED TO WEIGH THE UNIQUE RISKS, CONSTRAINTS, AND POPULATION CONSIDERATIONS AS A CONDITION OF ANY APPROVAL. ANY DELETION OR SUBSTANTIVE CHANGE OF INFORMATION CONCERNING RISKS OR ALTERNATIVE TREATMENT MUST BE JUSTIFIED BY THE INVESTIGATOR, APPROVED BY THE LOCAL IRB/EC, AND NOTED IN THE IRB/EC MINUTES. JUSTIFICATION AND IRB/EC APPROVAL OF SUCH CHANGES MUST BE FORWARDED TO THE INTERNATIONAL COORDINATING CENTER. SPONSOR-APPROVED CHANGES IN THE PROTOCOL MUST BE APPROVED BY THE LOCAL IRB/EC BEFORE USE UNLESS INTENDED FOR THE ELIMINATION OF APPARENT IMMEDIATE HAZARD. NEW INFORMATION SHALL BE SHARED WITH EXISTING SUBJECTS AT NEXT ENCOUNTER, WITH ALL NEW SUBJECTS PRIOR TO INVOLVEMENT, OR AS THE LOCAL IRB/EC MAY OTHERWISE ADDITIONALLY REQUIRE.

This is a research study to find out what might predict whether people who test positive for COVID-19 get sick enough to be admitted to the hospital. You are being asked to participate because you have either very recently tested positive for COVID-19, or are being tested for the virus that causes COVID-19. It is your choice whether to be in this study or not. If you haven't yet had your test for COVID-19, you will still get that test in the usual way, whether or not you agree to be in this study.

This study does not provide any treatment for COVID-19. You do not have to be in this study if you do not want to be. If you agree to be in the study, you can stop at any time. Your decision about whether to be in this study or to stop the study will not affect

your usual medical care or any benefits to which you are otherwise entitled. There is no cost to you for being in this study, and you will not be paid for being in the study.

We are doing this study in many countries around the world. We hope to have thousands of people with COVID-19 be in this study.
[The following text box is required for sites in the US, in accordance with the 2018 Common Rule.]

KEY INFORMATION

- You can join the study if you have already tested COVID-19 positive within the last 3 days or if you are being tested on the day of joining the study.
- If you are positive for COVID-19, we will call you at 7, 14, and 28 days after you enroll to see how you are doing.
- If you are negative, you won't be followed after the enrolment visit, but you will be told your result.
- There are no risks or direct benefits to you from being in this study. You will help us learn more about how COVID-19 affects people like you. You may have the chance to join other studies about COVID-19.
- This study does not include any treatments apart from your usual care. You and your doctor will decide how to treat your COVID-19.
- You do not have to be in this study. You can stop being in the study at any time. This will not change your medical care or other benefits.

What do you have to do in the study?
If you agree to be in this study, we will ask you about what other medical conditions you have, what symptoms you are having, whether you smoke, and what medicines you are taking. We will ask you to give us contact information for one or two people who will know how to reach you if we cannot reach you to follow your medical progress.

[The next sentence should only be included for sites consenting participants for blood collection and storage. See specimen consent in Appendix F.]
We will ask if you are willing to have some blood taken and 1-2 extra swabs of your nose and/or throat done; this will be described in a separate consent form. For people having a nose or throat swab for COVID-19 at the same time as enrolling into this study, you will go home to wait for your test results. We will call you to let you know the results of your test for COVID-19. If your test is negative, you do not have to do anything else for the study. We will keep the information you have already given us.

If you already have a COVID-19 positive test when you join the study, or if you test for positive for COVID-19 at enrolment in the study, we will follow you for a total of 28 days. We will contact you three more times by phone, e-mail, text, or some other way that you have agreed to at about 7, 14 and 28 days after you joined the study. At each contact, we will ask about how you are feeling, your prescribed medication and treatments, and whether you have been admitted to the hospital or returned to your

normal activities. If you are hospitalized, study medical staff will ask you for your permission to obtain medical records from the hospital. If we are not able to reach you, we will try to contact the other people you named to find out how you are doing. After the third contact at 28 days, you are finished with this study.

If you join this study, we will also seek your permission to contact you again at a later date. If you gave your permission to be contacted again you could be invited to join either an extension to this study or a new study to collect long-term data on how people who joined this study are doing. You can still take part in this study even if you don't want to be contacted about a future study.

What are the risks and benefits of being in this study?
There are no risks to you to be in this research study. You will not get any direct benefit from being in this study, but it may help others in the future if we can get a better understanding of how COVID-19 affects different people. You may have the opportunity to participate in other studies about COVID-19.

How is your privacy protected?
We will take every reasonable step to keep your information private and to prevent misuse of it. You will not be identified by name, or in any other way, in anything published about this study. You will be identified only by a code. We will not release information from your records without your written permission.

[The following paragraph is for sites outside the US only]
We will do everything we can to keep your personal information private, but we cannot guarantee that nobody will get it. We may have to release your personal information if required by law.

[The following is for all sites]
These people may see your medical and research information:

- the *[insert the name of the site]* ethics committee (institutional review board, IRB);
- the research staff and monitors and people they designate as helping with the study;
- US and other participating countries' health and regulatory agencies.

All of these people are committed to protect your privacy.

As the research staff at *[insert the name of the site]*, we are required to make sure that people not involved with this study cannot see your research and medical information while collecting personal information about you. We will keep your information in a safe place and will handle your personal information very carefully.

Your study data are sent electronically to the University of Minnesota (UMN) in the US through a secure application. By signing this consent, you agree to having your data sent to UMN. No information that could directly identify you is sent to UMN. In this information, you are identified only by a code number, your year of birth, and a 3-letter code that you or the study staff choose. This is called "pseudonymized data". Access

to the data at UMN is limited through security measures, and no data breach or unauthorized access has ever occurred in this system. After the study is over, the data will be stored securely for the period required by law.

UMN may share your data with other people who study COVID-19. UMN will remove the code number, year of birth, and 3-letter code from your data before sharing. This is called "anonymizing the data" and makes it impossible for anyone to link the data back to you. We will not ask you for additional consent for this sharing. UMN will only share data for research projects that are approved by INSIGHT.

This study has a Certificate of Confidentiality from the US Federal government. This means that UMN cannot share any data it has about you with national, state, or local civil, criminal, administrative, legislative, or other authorities unless you specifically allow us to share it.

[Note for US sites: Because each institution typically has requirements for specific HIPAA language in the consent or in a separate document, none is provided in this template. Follow your institutions' requirements for informing potential participants of their rights under HIPAA.]

[The following section (up to "What if you are hurt as part of this research?") is for countries subject to the GDPR or similar legislation requiring this information. It should only be included in consents for sites subject to such legislation. It will vary from place to place whether it must be in this consent document, a separate consent document, or an information sheet that does not require signature. The amount of information provided may be reduced as long as it still meets requirements of the particular country (e.g., not all countries/ECs require an enumeration of all of a data subject's rights).]

What are your rights regarding your data?
UMN is a public research university, and this study is funded primarily by the US Federal government. The State of Minnesota and the US Federal government require UMN to follow regulations and policies that are meant to protect your privacy. UMN is also required to comply with the General Data Protection Regulation (GDPR), because it processes data obtained from European residents.

There is no specific independent supervisory authority overseeing the processing of data in the US. Any complaint you might have about the use of your data would be made to your national data protection authority.

The GDPR gives you additional rights which we would like to inform you about below.

Right to Information
You have the right to know what data about you is being processed. You can also get a free copy of this data.

Right to Correction
You have the right to correct any information about you which is incorrect or had become incorrect.

Right to Erasure/Anonymization
The sponsor is required under both EU and US law to retain data from research studies such as this one for many years. However, you have the right to request that your personal data be completely anonymized. This is done by destroying the information at your study center that links your identity to the pseudonymized data held by UMN. This means that no one would ever be able to link the data held by UMN to you personally.

Right to Restriction of processing
Under certain conditions, you have the right to demand processing restrictions, i.e. the data may then only be stored, not processed. You must apply for this. Please contact your study doctor or the data protection officer of the study center if you want to do so. This right may be limited if the restriction would affect the reliability of the study results.

Right to Data portability
You have the right to receive the personal data that you have provided to the study center. This will allow you to request that this information be transmitted either to you or, where technically possible, to another agency designated by you.

Right to Contradiction
You have the right to object at any time to any specific decision or action taken to process your personal data. This right is limited for data that have already been processed and may be limited if your objection would affect the reliability of the study results.

Right to Withdrawal of this consent
You may withdraw your consent at any time with effect for future data collection. This withdrawal may be in an informal or verbal communication to your study doctor. If you withdraw your consent this will not affect the lawfulness of the data processing that has been or will be done with data collected until you withdraw consent. Data already collected will be anonymized.

If you would like to use one of these rights, please first contact the person responsible for the data collection at your study center:
Person responsible for data collection at the study center:
Name:
Address:
Phone:
Email

For concerns about data processing and compliance with data protection requirements you can also contact the data protection officer responsible for the study center:

Data protection officer responsible for the study center:
Name:
Address:
Phone:
Email

In addition, you have the right to lodge a complaint with the competent authority if you believe that the processing of personal data concerning you is contrary to the GDPR:
Data protection authority responsible for the study center:
Name:
Address:
Phone:
Email

What if you are hurt as part of this research?
We will provide treatment right away if you are hurt because of the research. The costs may be charged to you or your insurance company. We will give you information about where you can get additional treatment. You do not give up any of your legal rights by signing this form.

Site Instruction:
If the information above is not correct for your country/site, please revise the information to inform the subject of the following: 1. what treatment will be provided to the subject; 2. who will pay for the treatment; 3. if there is any plan for compensation for research-related injury issues, such as lost wages, etc.

What if you have questions?
If you have questions about this study, or about the storage or use of your data, or if you are hurt by being in the study, you can contact *(site PI and contact information*). If you have questions about your rights as a research participant, you can contact *(name and contact information).*

SIGNATURE PAGE FOR CONSENT TO PARTICIPATE IN THE INSIGHT 011 STUDY (ICOS)

I have read the consent or have had it explained to me. I am satisfied that I understand the information. By signing this consent, I am stating that I want to join this study. I understand that I do not waive any of my legal rights as a study participant by signing this consent. I understand that I will receive a copy of the signed and dated consent.

OPTIONAL
I agree to being re-contacted by the study staff if this study is extended or if there is another INSIGHT COVID-19 study gathering information about long-term follow-up.

☐ Check here to indicate willingness to be informed about a future study of long-term follow-up.

_____	_____	_____
Participant's name	Participant's signature	Date

_____
Name of staff member conducting consent process (typed or printed)

_____ _____
Staff member's signature Date

_____
*Witness's name (typed or printed)

_____ _____
Witness's signature Date

***A witness to the participant's signature is strongly encouraged.**

NOTE: This consent form, with the original signatures, MUST be retained on file by the Investigator of Record. A copy of the signed and dated consent must be

given to the participant. A copy should be placed in the participant's medical record, if applicable.

APPENDIX B: TIME AND EVENTS SCHEDULE

Study Requirement	Enrolment	Follow-up Visits: Day 7, 14 and 28 [a)]
Informed consent	X	
Documentation of results of SARS-CoV-2 test	X	
Demographics	X	
Targeted medications	X	
Co-morbidities	X	
Upper respiratory tract swabs [b)]	X	
Serum specimen [b)]	X	
Health status assessment	X	X
Targeted symptoms	X	X
Dyspnoea severity	X	X
Targetted COVID-19 treatments and medications	X	X
Vital and hospitalization status		X

[a)] only participants with a positive test for SARS-CoV-2 at enrolment
[b)] only for participants of the specimen collection sub-study

APPENDIX C: INSIGHT 011 PROTOCOL TEAM

To oversee the implementation of this observational study, membership on the protocol team will include:

- Protocol co-chair(s)
- NIAID, Division of Clinical Research representatives
- INSIGHT University of Minnesota representatives
- INSIGHT International Coordinating Center representatives
- Collaborating laboratory representatives
- Site investigators
- Study biostatisticians
- Community representative

A core team consisting of the co-chair(s), ICC leaders, NIAID representatives, study statisticians and other representatives and the INSIGHT PI will also regularly convene to review study progress and address study conduct and administrative issues that arise.

APPENDIX D: REFERENCES ON THE INSIGHT WEBSITE

The INSIGHT website (**www.insight-trials.org**) will maintain updated links to the following documents referenced in the INSIGHT 011 protocol and to other information pertinent to the study:

- INSIGHT Publications and Presentations Policy
- CDC guidance on how to handle COVID-19 cases

APPENDIX E: LIST OF ACRONYMS

ACE2	Angiotensin Converting Enzyme 2
ARDS	Acute Respiratory Distress Syndrome
CDC	Centers for Disease Control and Prevention (U.S.)
COVID-19	Corona-Virus-Induced Disease 2019
EC	Ethics Committee
EU	European Union
DNA	Deoxyribonucleic Acid
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
ICC	International Coordinating Center
ICH	The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Institutional Ethics Committee
INSIGHT	International Network for Strategic Initiatives in Global HIV Trials
IRB	Institutional Review Board
mL	Milliliter
mm	Millimeter
NIAID	National Institute of Allergy and Infectious Diseases, NIH (U.S.)
NIH	National Institutes of Health (U.S.)
OHRP	Office for Human Research Protections (U.S.)
RNA	Ribonucleic Acid
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SSC	Scientific Steering Committee (INSIGHT)
UMN	University of Minnesota
U.S.	United States of America

APPENDIX F: SPECIMEN COLLECTION SUBSTUDY

Objective
The objective of the sub-study is to:

1. Establish a repository of upper respiratory tract and blood samples for future research.

These specimens will be used for future research aimed at molecularly characterizing the virus, including genetic analysis, and the measurement of biomarkers that predict progression of disease. For those who sign an additional consent for the INSIGHT Genomics Study (INSIGHT 004), DNA will be extracted for studies of host genetics to investigate the pathophysiology of COVID-19.

Rationale
This sub-study will run alongside the main study but will additionally include the collection of baseline upper respiratory tract swabs and blood samples. To avoid the collection of a large number of stored samples from SARS-CoV-2 negative participants, selected sites participating in this sub-study will be activated when a relatively large number of those enroled are positive or enrolment strategies permit enrolment of large numbers of individuals who are positive.

Methodology
At the time of enrolment, alongside consent for the main study sites participating in the sub-study will be asked to obtain separate consents for:

1) Upper respiratory tract swabs and serum to be shipped to a central repository for future research on COVID; and

2) at those sites registered for the INSIGHT Genomics Study (INSIGHT 004), a whole blood sample.

These specimens will be sent to a central repository in the United States for storage.

SAMPLE INFORMED CONSENT FORM FOR SPECIMENS

CONSENT FOR PARTICIPATING IN AN NIH-FUNDED RESEARCH STUDY
SITE INVESTIGATOR: _____ PHONE: _____

Specimen Collection and Storage for An International Observational Study of Outpatients with SARS-CoV-2 Infection

Sponsored by: The University of Minnesota
Funded by: National Institute for Allergy and Infectious Diseases, US National Institutes of Health

A Multicenter Study of the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT)

OHRP Requirements to be read by the sites: (*remove this text box from your site-specific consent)*

PLEASE NOTE THAT THIS SAMPLE LANGUAGE DOES NOT PREEMPT OR REPLACE LOCAL IRB/EC REVIEW AND APPROVAL. INVESTIGATORS ARE REQUIRED TO PROVIDE THE LOCAL IRB/EC WITH A COPY OF THIS SAMPLE LANGUAGE ALONG WITH THE LANGUAGE INTENDED FOR LOCAL USE. LOCAL IRBs/ECs ARE REQUIRED TO WEIGH THE UNIQUE RISKS, CONSTRAINTS, AND POPULATION CONSIDERATIONS AS A CONDITION OF ANY APPROVAL. ANY DELETION OR SUBSTANTIVE CHANGE OF INFORMATION CONCERNING RISKS OR ALTERNATIVE TREATMENT MUST BE JUSTIFIED BY THE INVESTIGATOR, APPROVED BY THE LOCAL IRB/EC, AND NOTED IN THE IRB/EC MINUTES. JUSTIFICATION AND IRB/EC APPROVAL OF SUCH CHANGES MUST BE FORWARDED TO THE INTERNATIONAL COORDINATING CENTER. SPONSOR-APPROVED CHANGES IN THE PROTOCOL MUST BE APPROVED BY THE LOCAL IRB/EC BEFORE USE UNLESS INTENDED FOR THE ELIMINATION OF APPARENT IMMEDIATE HAZARD. NEW INFORMATION SHALL BE SHARED WITH EXISTING SUBJECTS AT NEXT ENCOUNTER, WITH ALL NEW SUBJECTS PRIOR TO INVOLVEMENT, OR AS THE LOCAL IRB/EC MAY OTHERWISE ADDITIONALLY REQUIRE.

We are asking you to allow us to collect and store samples to use for future studies about the virus that causes COVID-19. You are being asked to give samples because you are being tested or have been tested for the virus that causes COVID-19 and have agreed to be in the COVID-19 Observation study. It is your choice whether to give these extra samples. You can still be in the COVID-19 Observation study, whether or not you agree to give these extra samples.

You do not have to give these extra samples if you do not want to. You can ask later to have your samples destroyed if you decide you do not want them to be stored or used. Your decision about samples will not affect your usual medical care or any benefits to which you are otherwise entitled. There is no cost to you for giving your samples, and you will not be paid for it.

We are collecting samples from people in many countries around the world. We hope to have thousands of people with COVID-19 give their samples for future study about COVID-19.

[The following text box is required for sites in the US, in accordance with the 2018 Common Rule.]

KEY INFORMATION

- If you have agreed to be in the COVID-19 Observation study and agree to have 1-2 additional swab samples, and a blood sample taken, you can be in this study.
- Once you have given your samples, you are done with this study. You will still be followed in the COVID-19 Observation study.
- Your samples will be sent to a laboratory in the United States for storage. They will be used in the future to learn more about COVID-19 and the virus that causes it.
- There is no direct benefit to you from being in this study. You will help us learn more about how COVID-19 affects people like you.
- The extra swab samples can be taken from the nose and/or throat. Both types of swab can be a little uncomfortable but only for a short time. Also, the throat swab may make you gag. The nose swab may make you sneeze. The blood sample will be taken from your arm using a needle. This will hurt a little bit and may leave a bruise where the needle goes in.
- You do not have to be in this study. If you agree to be in this study, you can decide at any time to ask that your samples be destroyed. This will not change your medical care or other benefits.

What do you have to do in the study?

If you agree, we will swab your nose and/or throat. If you are also being tested for COVID-19 when you join the study, this would mean you have up to 3 nose and/or throat swabs. We will also take blood from a vein in your arm using a needle. We will take about 2-4 teaspoons of blood. We will store the blood with the swab samples. We will not do any tests on these samples right now.

What are the risks or discomforts of having samples taken?

We will insert a new, clean needle into a vein in your arm to take blood. You may feel a pinch when the needle goes through your skin. You may get a bruise where the needle was put in. You may also have swelling, and the area may be sore. These things are common and should go away in a couple of days. There is a very small chance of an infection where blood is drawn. An infection could be treated with antibiotics.

Having your nose and/or throat swab samples taken will be uncomfortable. It may cause you to gag or sneeze.

What are the benefits of having samples taken?
There is no benefit to you of having samples taken. These samples may help us learn more about COVID-19 and SARS-CoV-2 and how it affects people, which may help other people in the future.

What will happen to your samples?
Your stored samples will be marked with your study code and not with your name. Only research investigators at the site where you are receiving care can link the code to your name.

Your samples will be kept at your site for now and periodically shipped to a specimen repository in the United States. They will be kept there for an indefinite amount of time to be used for research in the future.

No human genetic testing will be done on your samples. Your samples will not be sold. You will not be paid for any products that might result from this research.

The only risk of allowing us to store your samples would be an accidental release of your identity.

Some of the samples will be used along with your information collected in the COVID-19 Observation study (identified only by your study code) for future research. You will not be told about the future research. Future research with your samples may help us understand how the SARS-CoV-2 virus works in your body, study other infections or diseases, or develop treatments. The types of research may include development of new laboratory tests to better understand how people respond to infection or for studies to better understand virus infections, including the SARS-CoV-2 infection.

We plan to keep the samples indefinitely.

You can change your mind about the use of your samples for future research and withdraw consent for the storage and use of your samples at any time. You will need to contact the study doctor using the contact information listed on page 1 of this form. We will do our best to follow your wishes but cannot promise that we will always be able to destroy your samples. For example, if your samples were already used, we would not be able to destroy them, and we would keep any information that had already been taken from the samples.

How will your privacy be protected?
In the consent form you signed for the COVID-19 Observation study, we told you about your rights regarding your information. We told you how your information is kept private and identified with a code number instead of your name. Your samples will be stored with only that code number on them. The laboratory in the US where they will be stored will not have any information about you and will only see that code number on your

samples. Any laboratories that do tests on your samples will also not have any information about you.

INSIGHT, the group that is doing this study, may share your information and samples with other people who study COVID-19 and SARS-CoV-2. Your study code will be removed before sharing your data. This is called “anonymizing the data”. We will not ask you for additional consent for this sharing. Information and samples will only be shared for research projects that are approved by INSIGHT.

What if you are hurt as part of this research?
We do not expect any harm from giving samples.

What if you have questions?
If you have questions about this study, or about the storage or use of your samples, you can contact *(site PI and contact information*). If you have questions about your rights as a research participant, you can contact *(name and contact information).*

SIGNATURE PAGE FOR CONSENT TO GIVE EXTRA SAMPLES IN THE INSIGHT 011 STUDY (ICOS)

I have read this consent or have had it explained to me. I am satisfied that I understand the information. By signing this consent, I am stating that I am willing to give an extra 1-2 swab samples and a blood sample for future research, and to have these samples stored at a laboratory in the United States. I understand that I do not waive any of my legal rights as a study participant by signing this consent. I understand that I will receive a copy of the signed and dated consent.

_____	_____	_____
Participant's name	Participant's signature	Date

_____
Name of staff member conducting consent process (typed or printed)

_____ _____
Staff member's signature Date

_____
*Witness's name (typed or printed)

_____ _____
Witness's signature Date

***A witness to the participant's signature is strongly encouraged.**

NOTE: This consent form, with the original signatures, MUST be retained on file by the Investigator of Record. A copy of the signed and dated consent must be given to the participant. A copy should be placed in the participant's medical record, if applicable.

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