Evaluation of the Feasibility and Reproducibility of 2 Point-of-Care Tests for SARS-Co-V-2 Antibodies (INSIGHT 017)

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1 Protocol Summary

DESIGN

EPOC is designed to examine the feasibility of conducting point-of-care (POC) tests for SARS-CoV-2 antibodies and compare the reproducibility of these tests to tests run at a central laboratory on specimens obtained from the same study participants at the same time. This will involve recruiting 375 individuals at 20-30 US and international sites who have tested positive for SARS-CoV-2 and consenting them to up to 4 fingersticks, the collection of 9 mL of venous blood and responding to a set of standardized questions. All these activities will take place during a single study visit. The whole blood from the fingersticks will be used to test for SARS-CoV-2 antibodies using 2 POC tests, both of which have a CE mark, emergency use authorization (EUA) from the US Food and Drug Administration (FDA) and are Clinical Laboratory Improvement Amendments of 1988 (CLIA) waived. Participants and their providers will be instructed that the results of these tests are not to be used for patient management and the results of the tests will not be shared with participants or their providers. The 9 mL of blood will be processed locally and shipped to a central repository in the US where it will be labeled with a specimen code that can only be matched to the participant's other data using a participant identifier at the Statistical and Data Coordinating Center at the University of Minnesota (UMN). UMN will only have the specimen code and the participant identifier: the matching of the participant identifier to a participant can only be done at the sites.

In addition to this cross-sectional study (also referred to as the field test below), a nested case-control study utilizing specimens already collected from participants in the Therapeutics for Inpatients with COVID-19 (TICO) trial will be conducted. Participants in the TICO trial have already consented to the use of their specimens for future research on COVID-19. The POC tests will be conducted on these specimens and compared to results that have already been generated using an assay at a central laboratory called the GenScript cPass assay (referred to here as the GenScript assay).

The 2 POC assays that will be investigated under this protocol are the LumiraDx SARS-CoV-2 Antibody Test and the RightSign COVID-19 IgG/IgM Rapid Test. Both platforms will be used on all specimens. It is not the goal of this study to impact the indications for either test.

The primary objective of the field test is to test for an association between the outcome of the locally obtained POC test and the centrally obtained result from the GenScript assay on a blood sample obtained at the same time as the sample for the POC tests.

The primary objective of the nested case-control study is to test for an association between the POC test result on stored baseline specimens and the primary efficacy outcome in TICO on a subset of specimens from TICO participants for whom the GenScript assay result has already been determined. Since conducting POC assays on large numbers of stored specimens is time consuming (since each assay takes 10-20 minutes and

each individual specimen must be analysed), a case-control design will be utilized. The case definition is death or time to sustained recovery that exceeds 28 days. To maximize the difference between cases and controls, controls are defined as those with a time to sustained recovery of no more than 16 days. With these definitions there are 68 cases and 77 controls for a total sample size of 145. Of these participants, 104 experienced a sustained recovery (the primary outcome in TICO) and 20 died.

DURATION

Participants in the cross-sectional study will be completed with the study within 24 hours of consent. Actual participation will just involve the consent process, 2 POC tests, and completion of a case report form (CRF) and a blood draw, thus we expect participation to last no more than a few hours.

SAMPLE SIZE

Sample size for the cross-sectional study is targeted at 375. With this sample size the study will have 83% power for detecting a difference in the probability of a positive test between 2 assays when the odds ratio for the 2 assays is 2.6 and the smaller of the 2 probabilities of test discordance is 3%.

The sample size for the nested case-control study is 145. Analysis of the case-control population using the GenScript assay detected a sub-hazard ratio of 1.91. With a sub-hazard ratio of 1.91, 104 events provide 90% power for rejecting the null hypothesis that the sub-hazard ratio is 1 and this number of events provides 80% power for a sub-hazard ratio of 1.75.

POPULATION

The population for the field test was selected to match that of those participating in the TICO trials from which the case-control specimens were selected. This population consisted of adults hospitalized for COVID-19 with symptoms being present no more than 12 days. Participants needed to have a positive test result within 3 days or a positive test more than 3 days prior to randomization and progressive disease suggestive of ongoing SARS-CoV-2 infection. Participants must not have received neutralizing monoclonal antibodies (nMabs), SARS-CoV-2 hyperimmune intravenous immunoglobulin (hIVIG), or convalescent plasma. For this protocol participants must not have received these compounds within 6 months prior to collection of the blood samples for this protocol. Participants with severe disease (as defined by a list of conditions and interventions) are also excluded to be consistent with the TICO trials from which specimens will be used.

2 Introduction

2.1 Study Rationale

A platform trial of therapeutics for patients hospitalized for COVID-19 entitled “A Multicenter, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients with COVID-19”, referred to as Therapeutics for Inpatients with COVID-19 (TICO), has undertaken the investigation of 6 treatments thus far. TICO trials of bamlanivimab, sotrovimab (also known as VIR-7831), and BRII-196/198, a meta-analysis that included these trials, a trial of hIVIG, and the RECOVERY trial have identified the potential for baseline antibody levels to impact safety and efficacy outcomes with administration of nMab therapy[1,2,3,4,5,6]. The TICO trial of bamlanivimab found a statistically significant interaction for the primary efficacy outcome, and the TICO trial of BRII-196/198 was consistent with such an interaction. These studies have found that while there may be a benefit for patients who have not yet mounted an antibody response, patients with endogenous antibody probably do not benefit from this treatment, and this may result in misuse of resources and expose patients to unnecessary toxicity, increased costs, and treatment delays. Moreover, in addition to affecting response to therapy, results from the TICO trials also demonstrate that baseline antibody levels were predictive of safety and efficacy outcomes in the placebo group: those with endogenous antibody had better outcomes.

In the TICO trials, antibody levels were assessed using a surrogate neutralizing antibody assay that detects the ability of antibodies to block the interaction of the receptor binding domain (RBD) of the spike protein with the host ACE-2 receptor (the GenScript cPass assay, referred to as the GenScript assay here). While these results point to promising approaches to the provision of care, these results are of limited clinical value as the use of this assay for patient management is extremely challenging due to time and laboratory requirements. This is due to the requirement that the assay be run in batches at a central laboratory, and this delays the determination of the presence of endogenous antibody. Given the urgency of treatment early in the course of disease, this delay could impact patient outcomes.

There are a large number of POC antibody tests with an EUA from the FDA available for detection of antibodies to SARS-CoV-2, thereby presenting an opportunity to rapidly determine if a patient has endogenous antibodies, which can then be used for patient management. Under the current EUAs, these tests only produce a qualitative interpretation of serostatus. This limits their ability to be used for participant management as the cut-offs are generally selected to optimize specificity. Optimization of specificity is sensible for an assay designed for large scale screening, where false positives are the primary concern. In contrast, if there is a safety concern associated with administration of nMabs to those who are seropositive, false negatives are the primary concern. Hence, there is interest in studying POC antibody tests that produce a rapid quantitative result so that the operating characteristics of different cut-offs can be investigated. This would inform using other cut-offs for timely patient management.

There are 2 aspects of a POC testing platform of interest when designing a trial that may use such a test for patient management: 1) performance of the POC test in a hospital setting where patients would be consented and screened for enrolment; and 2) the ability of the results from the POC test to reproduce the association of baseline antibody levels with clinical outcomes that has been found with the GenScript assay. While the former will be examined prospectively at clinical sites that enroll patients, the latter will use stored specimens from completed TICO trials for expeditious evaluation of the association of POC test results with major TICO outcomes in the context of treatment with nMabs (e.g., a 90-day composite safety outcome and time to sustained recovery, the primary endpoint of TICO trials). Ideally, one would want to determine if

there is an interaction between the result of a POC antibody test and outcomes of interest in TICO, as was found using the GenScript assay, but this would require analysing a larger number of stored specimens than is practical to have acceptable power. As a compromise, here we focus on detecting an association between baseline antibody status using the POC test results and safety and efficacy outcomes of interest in TICO among those in the placebo group from completed TICO trials. The hypothesis to be tested here is that those with endogenous antibody as determined by the POC assay will have better outcomes as was observed using the GenScript assay.

This protocol will examine 2 POC platforms: the LumiraDX and the RightSign platforms. Both platforms have a US FDA EUA and a CE mark for a CLIA-waiver when used on fingerstick whole blood. The LumiraDX platform provides a qualitative result in 10-20 minutes and can also provide a quantitative assessment, but this cannot be provided at the POC at this time. (A quantitative POC test is currently under development by the manufacturer). The RightSign platform is exclusively qualitative with a 10-20-minute turnaround time. Table 1 provides further information and links to more detailed information about each assay. Both assays are certified under the CLIA, 42 U.S.C. §263a, that meet requirements to perform medium complexity tests. Nothing is known at this time about the performance of either assay on emerging variants of concern.

Date EUA Issued or Last Updated	Entity	Diagnostic (Most Recent Letter of Authorization) and Date EUA Issued	Attributes[3]	Authorization Documents[2]	Antigen in the assay used to detect antibodies	Readout
08/02/2021	LumiraDx UK Ltd.	LumiraDx SARS-CoV-2 Ab Test 08/02/2021	Total Antibody (Ab), Fluorescence Immunoassay, Fingerstick Whole Blood	HCP, Recipients, IFU	RBD and S-protein mixture	A dedicated fluorescence detector reads total Ab (immunoglobulin G [IgG], immunoglobulin M [IgM] and immunoglobulin A [IgA]); qualitative
12/21/2020	Hangzhou Biotest Biotech Co., Ltd.	RightSign COVID-19 IgG/IgM Rapid Test Cassette 06/04/2020	IgM and IgG Lateral Flow, Fingerstick Whole Blood	HCP, Recipients, IFU	RBD	One IgG band and one IgM band

Table 1: Further information about the 2 POC assays to be investigated under this protocol.

2.2 Background

TICO is a platform trial designed to efficiently identify treatments for adults who have been hospitalized with COVID-19. A manuscript providing details on the protocol has been published[7] so here a brief description of the trial is provided. As a platform trial, multiple agents can be investigated simultaneously which allows for efficiencies due to a shared placebo group. Each investigational agent is studied in a randomized placebo-controlled trial with an early futility assessment based on two 7-category ordinal outcomes assessed at day 5 of follow-up to assess efficacy and a composite of grade 3 and 4 adverse events (AEs), serious adverse events (SAEs), clinical organ failure or serious infection or death through day 5 to assess safety. The primary efficacy outcome is time to sustained recovery, which is the first time after

randomization at which someone returns to their pre-hospitalization residence and stays there for 14 days prior to day 90. All-cause mortality through 90 days of follow-up is an important secondary outcome.

Thus far, 6 agents have entered the platform trial with the first 4 being nMabs or combinations of nMabs. These agents are as follows:

1. Bamlanivimab.
2. Sotrovimab (also referred to as VIR-7831).
3. BRII-196/198.
4. AZD7442.
5. MP0420.
6. PF-07304814.

The study has been completed and papers have been written describing the outcomes for the first 3 compounds, while the results for the remainder are still blinded. These 3 trials were stopped for futility at the time of the early futility assessment. Baseline antibody results are available for the first 3 compounds using the GenScript assay.

Analyses of the qualitative GenScript results from participants in the placebo arm of the first 3 trials (n=320) found that being seropositive was associated with superior efficacy and safety outcomes. Competing risk regression was used to test for an association between the baseline qualitative result from the GenScript assay and time to sustained recovery. The result was statistically significant with a sub-hazard ratio of 1.45 and a 95% confidence interval (CI) of (1.17, 1.81). The estimated hazard ratio for death (positive/negative) was 0.17 with a 95% CI of (0.05, 0.57), hence also statistically significant[6].

While the semi-quantitative GenScript results do not have any authorization for use in patient management, there is evidence that the use of different thresholds for dichotomizing this semi-quantitative result leads to different estimates of the magnitude of the association between the antibody test and time to sustained recovery. By using a lower threshold for antibody levels and thereby reducing the specificity and increasing the sensitivity for being seropositive, one detects a stronger association. The threshold used for the qualitative result finds that 46% of the 320 participants in the placebo arm are seropositive. If the threshold is lowered so that 58% of the participants are seropositive, we find that the sub-hazard ratio increases from 1.45 to over 1.6.

2.3 Point-of-Care Platforms

2.3.1 LumiraDX SARS-CoV-2 antibody test

Assay summary: The LumiraDx SARS-CoV-2 Antibody Test is a single use fluorescence immunoassay device designed to detect the presence of SARS-CoV-2 total antibody in human serum, plasma (dipotassium EDTA), venous whole blood (dipotassium EDTA), and fingerstick whole blood. The test is run on a microfluidic test strip which is inserted into a device that will display the qualitative results within 11 minutes of specimen application. Table 2 displays the sensitivity as a function of the number of days since a positive reverse transcription polymerase chain reaction (RT-PCR) test: averaging over the time since the first known positive test, the sensitivity is 97%. Using 240 specimens known to be negative, all specimens were found to be negative, giving an estimated specificity of 100% with a 95% CI of 99%-100%[8]. There are two targets: the Spike RBD and the Spike 1 (S1) and pan Ig antibodies directed against these targets are detected. A qualitative result is displayed on the device and a semi-quantitative measure of the fluorescence can be accessed as research use only. The device is portable and can be moved on a cart between uses.

Time from positive RT-PCR test to blood collection (days)	Number of samples	Number and percent positive	95% CI
0-7	17	15 (88.2)	64%-99%
8-14	6	6 (100)	54%-100%
15 or more	49	49 (100)	93%-100%
Total	72	70 (97.2)	90%-100%

Table 2: Sensitivity of the LumiraDX assay for various numbers of days from a positive test.

Figure 1: *A depiction of the operation of the LumiraDX testing platform. Note that for this protocol only the specimen identifier will be captured by the instrument, not personal identifiers.*

Principle of the assay: The test works using microfluidics. Serum, plasma, venous whole blood, or fingerstick whole blood are applied to the sample application area of the test strip and inserted in the instrument. Each test strip contains 4 channels: 2 channels for the RBD, 1 channel for S1, and 1 channel for controls. Fluid moves the specimen up into the cartridge where it is mixed with reagents including magnetic particles coated with the RBD, S1, or control depending on the channel. Antibodies in the serum, plasma, or whole blood specific for RBD or S1 bind to the magnetic beads. A secondary pan-human Ig antibody conjugated to fluorescence then binds to the antibodies. The magnetic particles are captured in a magnetic field, and any unbound antibodies are removed using air. The fluorescent signal is then measured.

The analysis is based on the amount of fluorescence the instrument detects within the measurement area of the test strip. The qualitative results are displayed on the Instrument touchscreen in approximately 11 minutes from the addition of sample as “Positive +” or “Negative -”. The semi-quantitative measure of the fluorescence can be accessed as research use only.

2.3.2 RightSign COVID-19 IgG/IgM rapid test

Assay summary: The RightSign COVID-19 IgG/IgM Rapid Test Cassette is a lateral flow immunochromatographic assay for the detection of SARS-CoV-2 antibodies in venous whole blood, serum, or plasma. The test is run on a disposable lateral flow device (test cassette). The test targets IgG or IgM antibodies specific for the Spike RBD. The readout of the assay is qualitative: positive for IgG and/or IgM or negative within 10-20 minutes of specimen application. Tables 3 and 4 summarize the sensitivity as a function of the number of days since the first positive polymerase chain reaction (PCR) test. Averaging over the number of days since first known positive test the sensitivity of the IgM assay is 93%, while the sensitivity of the IgG assay is 94%. Specificity was estimated using 210 specimens known to be negative and the result was negative for IgM 206 times and negative for IgG 209 times. This gives an estimated specificity of 98% with a 95% CI of (95%, 99%) for IgM, and an estimated specificity of 100% with a 95% CI of (97%, 100%) for IgG[9]. For analyses that simply treat the RightSign assay as positive or negative, the RightSign test will be considered positive if the test is positive for IgM or IgG.

Time from positive PCR test to blood collection (days)	Number of samples	Number and percent positive	95% CI
0-7	9	6 (67)	30%-93%
8-14	83	77 (93)	85%-97%
15 or more	158	150 (95)	90%-98%
Total	250	233 (93)	89%-96%

Table 3: Sensitivity of the RightSign IgM assay for various numbers of days from a positive test.

Time from positive PCR test to blood collection (days)	Number of samples	Number and percent positive	95% CI
0-7	9	6 (67)	30%-93%
8-14	83	76 (92)	83%-97%
15 or more	158	152 (96)	92%-99%
Total	250	234 (94)	90%-96%

Table 4: Sensitivity of the RightSign IgG assay for various numbers of days from a positive test.

Principle of the assay: This test uses anti-human IgM antibody (test line IgM), anti-human IgG (test line IgG) and goat anti-mouse IgG (control line C) immobilized on a nitrocellulose strip. The conjugate pad contains recombinant SARS-CoV-2 antigen (based on the Spike protein RBD domain) conjugated with colloid gold. During testing, the specimen binds with SARS-CoV-2 antigen-conjugated gold colloid coated particles in the test cassette. When a specimen followed by assay buffer is added to the sample well, IgM and/or IgG antibodies if present, will bind to COVID-19 conjugates making an antigen-antibody complex. This complex migrates through the nitrocellulose membrane by capillary action. When the complex meets the line of the corresponding immobilized antibody (anti-human IgM &/or anti-human IgG), the complex is trapped forming a colored line which confirms a reactive test result. Absence of a colored line in the test region indicates a non-reactive test result. To serve as a procedural control, a colored

line should always appear in the control line region, indicating that the proper volume of specimen has been added and membrane wicking has occurred.

Figure 2: A depiction of the operation of the RIghtSign testing platform.

3 Methodology

3.1 Study Design

There are several related questions that this protocol is designed to answer, and these are reflected in 2 different components of the design. There will be a cross-sectional study designed to evaluate how the POC test works in practice and how the results are related to the GenScript assay measured on a plasma sample collected at the same time as the fingerstick blood samples for the two POC tests to be evaluated. This will involve recruiting and consenting individuals presenting to the clinical sites with a positive test for SARS-CoV-2. Consenting participants will have a fingerstick for each POC test conducted. If a test fails, 1 additional fingerstick may be conducted for each POC test (so, up to 4 fingersticks may occur). In addition, a 9mL blood specimen will be collected. Participants and care providers will not be informed of test outcomes. After the fingersticks, blood collection, and responses to a set of standardized questions from a CRF, the participant will have completed involvement with the study. The blood specimen will allow for both a comparison with the GenScript assay and the assessment of the impact of processing, freezing, and shipping on the POC test results. There will also be a nested case-control study to understand how POC tests carried out on stored plasma specimens from completed TICO trials are related to outcomes measured in the TICO protocol. Consent from TICO participants has already been obtained for the use of their stored specimens, so the case-control study will not involve additional consent or the recruitment and follow-up of patients.

For the field test, POC platforms will be distributed to 20-30 sites in the US and internationally for completion of the two POC tests on 15 participants at each site. In addition to conducting the POC test on site as per the instruments' instructions (using blood from a fingerstick), a blood specimen will be obtained for processing, freezing, and shipping to a central lab for central testing using the GenScript assay and repeat POC testing using plasma. If a POC test is indeterminate the test will be repeated 1 time and the outcome of the indeterminate test and the second test will be recorded. If the second test is also indeterminate that will be recorded but the test will not be conducted again on that participant. This procedure applies to POC testing at the sites and at the central laboratory.

A nested case-control study will also be conducted to allow for testing of the association between antibody levels at baseline, as assessed by the POC tests and safety and efficacy outcomes among participants randomized to the placebo group in the bamlanivimab, sotrovimab, and BRII-196/198 trials of TICO. The case definition is death or time to sustained recovery that exceeds 28 days. To maximize the difference between cases and controls, controls are defined as those with a time to sustained recovery of no more than 16 days. With these definitions there are 68 cases and 77 controls for a total sample size of 145. Among these participants, 104 experienced a sustained recovery and 20 died.

Conduct of this nested case-control study will require use of the POC assay on stored specimens. One cannot conduct such tests in a batched fashion which makes this analysis time consuming. This testing will be facilitated by procuring multiple POC platforms at a central location. The use of multiple platforms will allow for multiple tests to be conducted in parallel which is more efficient since each specimen must be run one at a time, and each takes 10-20 minutes.

3.2 Study Objectives

3.2.1 Field test

The overall objective of the field test is to determine if a POC test can be used to identify individuals who lack endogenous antibodies. The **primary objective** is to test for an association between the outcome of the locally obtained POC test and the centrally obtained result from the GenScript assay on a blood sample obtained at the same time as the sample for the POC test. There are also a number of secondary objectives that will investigate the feasibility of this approach, and others that will help interpret the outcome of the primary objective. These are as follows:

1. Determine the frequency with which the POC test fails to give an unambiguous result.
2. Determine the time required to obtain a POC result.
3. Determine the magnitude of the association between the locally obtained POC test result by the 20-30 sites and the same POC assay on the same specimens determined centrally after processing, freezing, storing, and shipping.
4. Determine the magnitude of the association between the POC test result and the GenScript assay on the same specimens both determined centrally.

Secondary objective 3 will provide information on the impact of processing (centrifugation for plasma), freezing, storing, and shipping on the test results using the same assay while secondary objective 4 will provide a head-to-head comparison of the assays using the same specimen subjected to the same handling procedures. Specimen handling and the specific assay used both likely contribute to differences we may observe between the local POC test and the results from the GenScript assay.

3.2.2 Central laboratory

The overall objective of central testing of stored specimens is to understand the impact of baseline serology, as assessed by the POC tests, on outcomes of relevance for the TICO trial. The **primary objective** is to test for an association between the POC test result on stored baseline specimens and the primary efficacy outcome in TICO on a subset of specimens from TICO participants for whom the GenScript assay has result has already been determined. Secondary objectives are as follows:

1. Test for an association between each POC test result on stored baseline specimens and efficacy/safety outcomes in TICO in a case-control design.
2. Compare the POC test results to the GenScript results and other antibody test results such as those from Bio-Rad and Quanterix that have already been obtained for these stored specimens.
3. Select a threshold for the quantitative LumiraDX result to optimize the association between the dichotomized assay result and safety and efficacy outcomes using the stored specimens.
4. Compare the 2 POC platforms to each other and the GenScript result using locally (at each site) and centrally determined POC results.
5. Examine associations between these antibody assays and antigen assays which have already been obtained for the stored specimens.
6. Determine the effect of vaccination and other participant characteristics on the antibody test results.

3.3 Sample Size and Statistical Considerations

3.3.1 Local versus central POC test result

The power for comparisons of results from paired qualitative tests on specimens was assessed using Schlesselman's formula for the power of McNemar's chi-square test[10]. This requires specification of the odds ratio and the probability of 1 test being positive when the other is negative (denoted p_{01} in the table). Table 1 shows the power as it depends on these 2 parameters with a sample size of 375. By taking the odds ratio to be greater than 1 we are assuming that p_{01} is the smaller of the 2 probabilities of 1 test being positive while the other is negative. For example, p_{01}=0.01 and an odds ratio of 2.2 implies that the 2 probabilities that one test is positive while the other is negative are 0.01 and 0.022, and the probability that the 2 tests agree is 96.8%. As can be seen in Table 5, with a sample size of 375 the power of the test is low in this scenario (0.24), but this is fairly strong agreement across the assays. As can be seen from the same table, the test will have over 80% power if p_{01}=0.03 and the odds ratio is at least 2.6. This corresponds to the discordance probabilities of 0.03 and 0.078 and the corresponding probability that the 2 tests agree is 89.2%. With this configuration of probabilities for test agreement the standard error for the difference in the probability that the 2 tests are positive is 0.023. There is currently no data available for this comparison.

Odds ratio	p_{01}=0.01	p_{01}=0.03	p_{01}=0.05
2.0	0.19	0.49	0.72
2.1	0.21	0.56	0.79
2.2	0.24	0.62	0.85
2.3	0.27	0.68	0.89
2.4	0.30	0.74	0.93
2.5	0.33	0.79	0.95
2.6	0.36	0.83	0.97

Table 5: The power of McNemar's chi-square test for testing the agreement of 2 assays as it depends on the odds ratio and the smaller of the 2 probabilities for test discordance. This assumes the sample size is 375.

3.3.2 Local and central POC test result versus GenScript cPass assay result

Sample size considerations for these comparisons are similar to those from the previous section, but we do have data from 302 participants on the relationship between the central POC test using the RightSign platform and the GenScript assay using stored specimens for both assays. The association depends on which isotype is measured with the RightSign assay: there is evidence that the odds ratio is different from 1 for IgM (odds ratio 7.5, $p<0.001$) but not for IgG (odds ratio 1.1, $p=0.82$). These preliminary data indicate that 375 samples obtained as part of the field test will provide more than adequate power for detecting a difference for the GenScript assay and RightSign IgM assay and very low power for detecting a difference between the GenScript assay and the RightSign IgG assay due to the high degree of association between the latter pair of assays.

3.3.3 Case-control comparison

An analysis of the qualitative GenScript result with the 145 patients that will be used for the nested case-control study found a significant difference ($p=0.002$) in the time to sustained recovery, with a sub-hazard ratio of 1.91 (95% CI: 1.35, 2.7) for baseline serostatus, indicating that seropositive patients had a quicker time to sustained recovery. (This used the Fine-Gray approach to modelling competing risks). The quantitative result from this assay also demonstrated a statistically significant association with time to sustained recovery and adjustment for study level effects did not impact the associations meaningfully. An analysis of case control status also detected an odds ratio that was significantly different from 1 ($p=0.015$) with an odds ratio of 2.34 (95% CI: 1.18, 4.65).

With a sub-hazard ratio of 1.91, 104 events provide 90% power for rejecting the null hypothesis that the sub-hazard ratio is 1, and this number of events provides 80% power for a sub-hazard ratio of 1.75. An analysis of case control status has lower power and would require an odds ratio of 2.72 to have 80% power for detecting an association between baseline antibody levels and case control status with this sample size (larger than what was observed for the GenScript assay).

3.4 Participant Selection for the Field Test

Interested sites will be selected based on their ability to recruit patients that meet the eligibility criteria for TICO. Planned enrollment into TICO is not necessary for participation in the field test. All participants will need to consent to participate in the field test component of the protocol, including those co-enrolled in TICO. The inclusion and exclusion criteria for the field test are as follows:

3.4.1 Inclusion criteria

1. Age ≥ 18 years.
2. Informed consent by the patient or the patient's legally authorized representative (LAR) for up to 4 fingersticks for POC testing and a blood draw for stored blood samples.
3. SARS-CoV-2 infection, documented by a nucleic acid test (NAT) or equivalent testing within 3 days prior to consent OR documented by NAT or equivalent testing more than 3 days prior to consent AND progressive disease suggestive of ongoing SARS-CoV-2 infection per the responsible investigator. (For non-NAT tests, only

those deemed with equivalent specificity to NAT by the protocol team will be allowed. A central list of allowed non-NAT tests is maintained for TICO and that list will also be used for this protocol.)

4. Duration of symptoms attributable to COVID-19 ≤ 12 days per the responsible investigator.
5. Requiring admission for inpatient hospital acute medical care for clinical manifestations of COVID-19, per the responsible investigator, and NOT for purely public health or quarantine purposes.

3.4.2 Exclusion criteria

1. Prior receipt of SARS-CoV-2 hIVIG, convalescent plasma from a person who recovered from COVID-19, or SARS-CoV-2 nMAb within 6 months of the blood draws for testing as part of this protocol.
2. Disease severity beyond that of stratum 1 in the TICO trial.
   This includes the following conditions:
   a. stroke
   b. meningitis
   c. encephalitis
   d. myelitis
   e. myocardial infarction
   f. myocarditis
   g. pericarditis
   h. symptomatic congestive heart failure (CHF; New York Heart Association [NYHA] class III-IV)
   i. arterial or deep venous thrombosis or pulmonary embolism

   Or current requirement for any of the following:
   a. high-flow supplemental oxygen
   b. non-invasive ventilation
   c. invasive mechanical ventilation
   d. extracorporeal membrane oxygenation
   e. mechanical circulatory support
   f. vasopressor therapy
   g. commencement of renal replacement therapy at this admission (i.e., not patients on chronic renal replacement therapy).
3. In the opinion of the responsible investigator, any condition for which, participation would not be in the best interest of the participant or that could limit protocol specified assessments.

A blood specimen for storage is required for participation in the study.

These eligibility requirements are nearly identical to those used in the TICO trial from which specimens will be used for the case-control study. One major difference is that TICO participants must agree to not participate in other COVID-19 treatment trials until after Day 5 (this is clearly not relevant for this protocol). The exclusion criteria here are more restrictive than those in the TICO trial. This is so participants in this protocol are comparable to those who enrolled in the TICO trials from whom specimens will be used for the case-control study. Those trials had more restrictive exclusion criteria than listed in the TICO protocol at the request of the FDA and match the exclusion criteria listed here. This will facilitate interpretation of analyses that use specimens from the field test and from the previously conducted trials. Eligibility criteria were also selected to be similar to those in the TICO trial to ensure these results are relevant for

future trials in hospitalized patients conducted by INSIGHT and aligned networks for which eligibility criteria are likely to be similar to TICO.

Participant characteristics will be monitored during data collection and adjustments to the characteristics of those recruited for participation may be made.

3.5 Data and Blood Collection Plan

After providing written informed consent, a CRF will be completed for each participant and blood will be collected by up to 4 fingersticks and by a venous blood draw of 9 mL (in an EDTA collection tube for aliquoting plasma after centrifugation into 4 2 mL cryovials, each with about 1 mL of plasma). The blood from the fingersticks will be used to conduct the POC tests and the plasma cryovials will be stored locally in a -70°/-80° freezer until they can be shipped to the central biorepository. The CRF will capture the outcome of the POC tests, the length of time from the start of the assay to recording the test outcome, and selected data collected on the TICO Screening and Baseline and Randomization forms. This will include

1. Participation in other INSIGHT studies.
2. Demographics.
3. Date of onset of COVID-19 symptoms.
4. Severity of COVID-19.
5. Oxygen requirements.
6. History of chronic comorbidities.
7. SARS-CoV-2 vaccination information.
8. Targeted concomitant medications.
9. Height and weight.

Two fingerstick samples of blood will be obtained, one for each POC test. The plasma samples collected will be used for determination of antibody and antigen levels, and central laboratory determination of the two POC tests.

All study procedures will be performed by study personnel. Training materials and the consent document will clearly state that the results of the POC tests are not to be used for patient management and so should not be shared with the patient or care giver. All study procedures must be performed within 24 hours of completing the written informed consent.

Information will be collected from site staff about ease of use of each platform.

4 Data Analysis

4.1 Field Evaluation of Platforms: Ease of Use, Time for Test Result

The number and proportion of failed tests and tests not obtained within 20 minutes will be determined overall and for each site. The median and interquartile range of the time from the start of the assay to recording of the test outcome on the CRF will be determined overall and for each site.

4.2 Local versus Central POC Test Result Comparison

The primary analysis will test if the odds ratio for the association is 1 using McNemar's chi-square test with a significance level of 0.05. Samples for which either test result is missing will be excluded from this analysis. This test will be supplemented by a 95% CI for the difference in the probability of testing positive. Site level effects will be estimated by using generalized estimating equations for Bernoulli outcomes using a logistic link with pairs of results modelled as

being correlated (the test outcome is the binary outcome). This model will include fixed effects for the test type (i.e., local or central) and site. Sites may be grouped based on geography or ICC membership to improve the precision of site level estimates and the interaction between site and test type will be investigated. Subgroups based on age, existence of an immunocompromising condition and vaccination status will be investigated (provided enough individuals with an immunocompromising condition enroll). These subgroup analyses will test for an interaction between group membership and test type. This analysis will be used for both POC tests, and there will not be an adjustment for the conduct of the 2 sets of analyses.

In addition to the primary analysis, associations between test results and participant characteristics will be investigated. These characteristics include age, sex, existence of an immunocompromising condition and vaccination status.

4.3 Local and Central POC Test Result versus GenScript cPass Assay

The GenScript assay will also be conducted on the specimens at the central laboratory. The locally and centrally determined POC results will be compared to the GenScript result using McNemar's chi-square test and will be supplemented by 95% CIs for the difference in the probability of testing positive. Investigation of site effects and test performance in subgroups will be pursued as described in Section 4.2.

4.4 Association of POC Test Results with TICO Outcomes: A Nested Case-Control Study of Completed TICO Trials

TICO specimens selected for the case-control study will be shipped from the repository at Advanced Biomedical Labs LLC to the central laboratory for analysis. The Fine-Grey approach to competing risk regression will be used to test for an association between the POC test result and time to sustained recovery while controlling for the parent sub-study effect. A significance level of 0.05 will be used to test the null hypothesis that the regression coefficient associated with the presence of antibodies at baseline is zero. The association between baseline POC test results and time to death will be investigated using Cox models stratified by parent sub-study. The association between baseline POC test results and the primary safety composite at days 5, 28 and 90 will be investigated using logistic regression models that control for parent sub-study.

Finally, data will be pooled from the field test and the stored specimens for all qualitative assays conducted to test for differences. This would include the local POC, central POC, and GenScript results from the field test, the GenScript result for the stored specimens and the POC results for the stored specimens. This analysis will use generalized estimating equations for binary outcomes with effects for the type of assay (3 values), if the assay was conducted locally or centrally, and in which protocol/sub-study the participant enrolled. The association due to the specimen coming from the same person will be accounted for by including this information as a clustering effect in the model. Tests for differences in the assays will be based on the Wald test for the regression coefficients for the assays. No multiplicity adjustment will be made for these tests.

Associations between qualitative antibody and continuous antigen assays will be examined using 2 by 2 tables by dichotomizing the antigen assay results at the median level for a given trial, and Fisher's exact test will be used to test for an association. Logistic regression models will be used to compute adjusted odds ratios where adjustment will be made for parent study and site (where sites may be grouped as described above).

4.5 Analysis of the Quantitative Results from the LumiraDX Assay

All comparisons that were conducted using the qualitative result from the LumiraDX assay will be repeated using the quantitative result using the appropriate modification of the analysis to accommodate a continuous variable. Comparisons to the RightSign and qualitative GenScript results will use the Wilcoxon rank sum test with the 2 groups being determined by the outcomes of the RightSign or GenScript test (i.e., the ranks of the LumiraDX results for positive and negative results for the other assays will be compared). Adjusted analyses will be pursued using linear regression after transformation (e.g., logarithmic), if appropriate. Comparisons of the locally and centrally conducted LumiraDX assay will be conducted using linear regression with adjustments made by the inclusion of relevant covariates. The quantitative result will also be used in the competing risk regression models as a continuous covariate and as a set of indicator variables that represent the quartiles of the distribution of this assay (to avoid the linearity assumption).

Other approaches to dichotomizing the quantitative LumiraDX results will be investigated and assessed. Potential values to use for dichotomizing the results will be based on deciles of the distribution and for each potential threshold the sub-hazard ratio for the impact of baseline serostatus on time to sustained recovery will be computed. An alternative cut-off may be selected if there are substantial differences in the hazard ratios.

5 Protection of Human Subjects and Other Ethical Considerations

5.1 Anticipated Risks and Benefits

There is no direct benefit to participants in this study. Risks are no more than minimal, consisting of a single small-volume venous blood draw and potential loss of confidentiality. Normal hospital procedures are considered an adequate safeguard for any potential risk of drawing blood. Safeguards to protect participants' identity are described in Section 5.5 below.

5.2 Participating Clinical Sites and Local Review of Protocol and Informed Consent

This study will be conducted by major medical centers participating in INSIGHT and partnering networks, including especially NHLBI networks. It is anticipated that potential participants will be recruited by the site investigators (and/or their delegates, as appropriate) and/or that positive SARS-CoV-2 laboratory testing will be used to enquire about potential enrollment. Information about this study will be disseminated to health care workers at enrolling sites.

Prior to the initiation of the study at each clinical research site, the protocol, informed consent form and any participant information materials will be submitted to and approved by a central/national institutional review board (IRB)/ethics committee (EC) and/or the site's local IRB/EC as required. Likewise, any future amendments to the study protocol will be submitted and approved by the same IRB(s) or EC(s). After IRB/EC approval, sites must register for this study before screening potential participants and must register for any protocol amendments. Protocol registration procedures are described in the protocol instruction manual (PIM).

5.3 Ethical Conduct of the Study

The study will be conducted according to the Declaration of Helsinki in its current version; the requirements of Good Clinical Practice (GCP) as defined in Guidelines, European Union

(EU) Clinical Trials Directive (2001/20/EC), and EU GCP Directive (2005/28/EC); International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guidelines; Human Subject Protection and Data Protection Acts; the US Office for Human Research Protections (OHRP); or with the local law and regulation, whichever affords greater protection of human subjects.

5.4 Informed Consent of Study Participants

Informed consent must be obtained (see sample in Appendix A) prior to conducting any study-related procedures. For patients who are incapacitated, informed consent may be obtained from a LAR. Capacity will be assessed according to local standards and policies. Local standards and policies will also determine who is legally authorized to consent for an individual who is incapacitated. Should the individual regain capacity during the study, their direct consent should be obtained at the earliest opportunity.

Electronic consent may be used when a validated and secure electronic system is in place to do so, if in compliance with national legislation and approved by the local IRB/EC. Other methods of obtaining documentation of consent may be used when site staff are unable to be in direct contact with a potential participant or a LAR due to infection-control restrictions. No matter how the participant's consent is obtained and documented, it is expected that consent will be preceded by research staff providing an explanation of the research and an opportunity for the participant (or their LAR) to have questions answered. Sites should follow all available local or national guidance on suitable methods for obtaining documentation of participant (or their LAR) consent.

5.5 Confidentiality of Study Participants

The confidentiality of all study participants will be protected in accordance with GCP guidelines and national regulations, including the US Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the EU General Data Protection Regulation (GDPR, EU 2016/679).

5.6 Regulatory Oversight

As previously stated, all sites will conduct the trial in accordance with the requirements of GCP as codified in their local law and regulation, under the oversight of their institution and competent regulatory authority.

As part of fulfilling GCP requirements for adequate trial monitoring, multiple modalities will be employed.

6 Storage and Use of Specimens

The plasma obtained from participants will be sent to a central biorepository in the US. In addition to the antibody and antigen tests described in this protocol, these specimens will be available for further study of SARS-CoV-2 and COVID-19. Any future use of these specimens will be reviewed and approved by a scientific steering committee overseeing research conducted by this collaboration. Results of these tests will not be shared with participants or their clinicians. Aggregated results of such tests will be presented. No individual results will be linked to a study participant.

7 Supporting Documentation

Detailed study procedures are described in the PIM which is available on the INSIGHT website. The laboratory manual provides detailed descriptions of procedures for specimen collection, storage, and shipping to the central biorepository.

APPENDIX A: Sample Informed Consent Form

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

Evaluation of the Feasibility and Reproducibility of 2 Point-of-Care Tests for SARS-Co-V-2 Antibodies (INSIGHT 017)

Short Title: INSIGHT 017: Evaluation of Point-of-Care (EPOC)
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 if new rapid tests for COVID-19 are easy to use for people with COVID-19 who are in the hospital. We are asking you to participate because you are in the hospital with symptoms of COVID-19 and have tested positive on a standard test. It is your choice whether to be in this study or not.

We are doing this study in many countries around the world. We hope to have about 300-400 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 are in the hospital with COVID-19 and have already tested COVID-19 positive on a standard test within the last 3 days, or if the test was more than 3 days ago and you have gotten sicker from COVID-19.
- If you agree to be in the study, you will have two finger sticks to draw blood. This will be tested on two different point-of-care (rapid) tests.
- You will also have a small amount of blood drawn from your arm to be tested in a central laboratory.
- Once you have done this, you are done with the study.
- There are minor risks to having blood drawn from your arm, but this risk is not different from blood draws that are already being done for your regular care.
- There are no direct benefits to you from being in this study. You will help us learn more about how these rapid tests work in people in the hospital with 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 is being studied?

The COVID-19 tests that are being used in the hospital are tests that have to be done in special laboratories by trained technicians. It can be hours or days before you get the result. Recent studies suggest that some COVID-19 treatments may work differently depending on whether you already have antibodies to COVID-19 in your blood. It would be helpful to have a COVID-19 antibody test that could give results quickly so your doctor has more information on what treatments might be most effective for you.

There are new tests available that can tell us about your antibodies in a few minutes. They do not have to be done in a lab. So far they have only been studied in people who are not in the hospital. We are doing this study to see if it is easy for these tests to be used right at your bedside in the hospital. This is called a “point-of-care” (POC) test.

We are looking at 2 different POC tests. One is called LumiraDX and the other is called RightSign.

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, and what medicines you have gotten to treat your

COVID-19. We will ask if you have been vaccinated against COVID-19. Your study team may be able to get this information from your medical record.

We will stick your finger with a small sharp tool called a lancet to get a little bit of blood to use for the rapid tests. We will do this twice, once each for the 2 different tests. If a test fails then we will stick your finger 1 more time, so you could have up to 4 finger sticks. We will not tell you the results of these tests. This is because we do not know how to use these test results to choose treatments for you. That would be investigated in future studies. The results of these tests will not be used to guide your care.

We will take about 9 milliliters (a little less than 2 teaspoons) of blood from a vein in your arm using a needle. We will send these samples to a central laboratory in the United States. More information is below.

Once you have done these things, you are done with 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 change your usual medical care or any benefits to which you are otherwise entitled.

The study will pay for the tests that are part of this study.

[The next paragraph is for US sites only. Sites in other countries should delete the next paragraph and replace it with the language appropriate for your location.]
You, your insurance company, or some other third-party payer must pay for any medicines or other tests for your COVID-19 and for your hospital costs.

What are the risks and benefits of being in this study?
The only risks to you to be in this research study are the risk of having blood taken and the possibility that someone could find out you are in the study. These risks are small and are the same as risks you already have from your hospital care. Having blood taken may be a little painful. You may have a bruise where the needle goes in. In rare cases, people have fainted or gotten an infection after having blood taken.

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 new tests for COVID-19 work.

What do we do with the samples at the central laboratory?
The study will test the blood samples to compare the results of the 2 POC tests to each other and to a standard antibody test. You and your doctor will **not** get the results of these tests.

Any blood samples that are left over after these tests will be stored at the central laboratory for as long as we are able to keep them. We hope to use these in the future to answer other questions about COVID-19, the virus that causes it, and how people respond to the virus. You and your doctor will **not** get any results from these tests.

You can withdraw your consent for us to keep these samples at any time. Let your study team know if you do not want the study to keep your samples anymore. We will make every effort to destroy all of your samples that are still at the central laboratory.

We will **not** test your genes (DNA). We will **not** sell your samples and they will **not** be used for research aimed at making money (commercial research). The laboratory where the samples are stored will not have any information that could identify you.

How do we protect your privacy?
We will take every reasonable step to keep your health information private and to keep anyone from misusing it. Your information (data) and samples 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 sponsor, the University of Minnesota (UMN), the group paying for the research (United States [US] National Institutes of Health [NIH]), other study staff, 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 must make sure that people not involved with this study cannot see your research and medical information. 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 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”. The UMN limits access to the data 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 as long as the law requires.

We will share your study data with the US NIH (which is paying for this study), and with regulators that oversee the study. We are required by law to do this. UMN may share your data and blood sample 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.

For one of the new tests we are studying, the LumiraDX test, the test results will be sent through the internet to LumiraDX’s computers. They are sent in a secure way and the information is encrypted (coded so no one can read it unless they have a special key). LumiraDX will then send this data to the UMN in a secure way. LumiraDX uses this test in many countries around the world and must follow the privacy laws of those countries, including the countries where this study is being done.

The test results sent to LumiraDX include the time, date, and hospital where the test was done. The only information that LumiraDX will have that could be linked to you personally is a number on the kit used to take your blood. This is a different code number than what is on the data that your site sends to UMN. These two numbers can be linked together at UMN and at your site, but only the site knows who you are. These numbers will not be part of any data that is shared as described above.

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?
If you are hurt because of being in this study, *[insert the name of the hospital/clinic]* will treat your injury right away. You or your insurance will have to pay for this treatment. The study cannot pay you or pay for any care for study-related injuries or for your illness.

[If the above is not true for your site, i.e., if trial insurance covers such cost, please replace the above with appropriate language.]

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 017 STUDY (EPOC)

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.

_____	_____	_____
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: List of Acronyms

Ab	antibody
ACE-2	angiotensin converting enzyme-2
AE	adverse event
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments of 1988
CRF	case report form
EC	ethics committee
EDTA	ethylenediamine tetraacetic acid
EU	European Union
EUA	emergency use authorization
FDA	US Food and Drug Administration
GCP	good clinical practice
GDPR	General Data Protection Regulation
hIVIG	hyperimmune intravenous immunoglobulin
ICC	International Coordinating Center
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IRB	institutional review board
LAR	legally authorized representative
NAT	nucleic acid test
nMab	neutralizing monoclonal antibody
OHRP	US Office for Human Research Protections
PCR	polymerase chain reaction
PIM	protocol instruction manual
POC	point-of-care
RBD	receptor binding domain
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event

TICO	Therapeutics for Inpatients with COVID-19
UMN	University of Minnesota
US	United States of America

APPENDIX C: INSIGHT 017 Protocol Team

A protocol team will be established to oversee implementation of this protocol. This team will include:

- Protocol co-chairs.
- NIAID, Division of Clinical Research representatives.
- INSIGHT University of Minnesota representatives.
- INSIGHT International Coordinating Center representatives.
- PETAL representatives.
- CTSN representatives.
- US Department of Veterans Affairs representatives.
- Collaborating laboratory representatives.
- Site investigators.
- Study biostatisticians.
- Community representative.

A core team consisting of representatives from these groups and the INSIGHT Principal Investigator will meet regularly to review study progress and address issues that may arise.

APPENDIX D: References

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[6] Babiker A. SARS-Cov-2 Serostatus and Antigen Levels: Prognostic Value and Impact on Clinical Effect of Passive Immunotherapy. ACTIV Passive immunit Biomarker Workshop, September 2021.

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