




**MANUAL OF OPERATIONS**

**Version 2.0**  
**Date: 10-Aug-23**

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## Abbreviations

AE	Adverse Event
AHRC	Applied Health Research Centre
CAC	Central Adjudication Committee
DCC	Coordination Centre
CIHR	Canadian Institutes of Health Research
CTA	Clinical Trial Agreement (contract)
EC	Executive Committee
eCRF	Electronic Case Report Form
DSMC	Data and Safety Monitoring Committee
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
ISF	Investigator Site File
IRB	Institutional Review Board
ITT	Intention to Treat
PHAC	Public Health Agency of Canada
RCT	Randomized Controlled Trial
REB	Research Ethics Board
SAE	Serious Adverse Event
SC	Steering Committee
SDM	Substitute Decision Maker
TCPS2	Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (version 2)

## 1. Introduction

### 1.1 Overview

<b>Title</b>	<b>Canadian Adaptive Platform Trial of <u>Treatments</u> for <u>COVID</u> in Community Settings (CanTreatCOVID)</b>
<b>Study design</b>	Open-label, individually randomized, adaptive platform trial
<b>Study duration</b>	Perpetual
<b>Participant duration</b>	24 months
<b>Objectives</b>	<p>1) Establish an adaptive platform trial aimed at evaluating the effectiveness (including comparative clinical and cost-effectiveness), practical challenges, and outcomes of therapeutics for SARS-CoV-2 for non-hospitalized patients in Canada, engaging a variety of healthcare settings.</p> <p>2) Generate evidence on treatment effectiveness and outreach to communities made vulnerable by social and economic policies, particularly those historically excluded from research.</p> <p>3) Provide rapid evidence to inform clinical and health system management and public health leaders, decision-makers, and planners within Canada and internationally.</p>
<b>Expected number of participants</b>	This adaptive platform trial incorporates Bayesian adaptive design principles, where the ultimate number of arms can change and the ultimate number of participants in each arm is not established using a fixed, <i>a priori</i> calculated sample size.
<b>Inclusion and exclusion criteria</b>	<p><u>Inclusion</u>: Age 50 years and older or 18-49 with 1 or more chronic high-risk medical conditions or immunosuppression within 5 days of onset of SARS-CoV-2 symptoms.</p> <p><u>Exclusion</u>: Currently admitted to hospital or in an emergency department (ED) for more than 24 hours, previously randomized to CanTreatCOVID, currently participating in a clinical trial of a therapeutic agent for acute SARS-CoV-2 infection that is not/suspected not compatible with the study therapeutics, already taking a study therapeutic or contraindication to a</p>

	study therapeutic, or inability for participant or caregiver to provide informed consent.
<b>Study interventions</b>	Usual Care  <i>Therapeutics for SARS-CoV-2 in out-patient settings will be added, to be determined by the Canadian COVID-19 Out-Patient Therapeutics Committee</i>
<b>Methodology</b>	<b>Outcome (primary):</b> COVID-related emergency department visit or hospitalization or death at 28 days <b>Outcome (secondary)</b> Time to recovery; Symptom severity; incidence of post-acute sequelae of SARS-CoV-2; quality of life; costs and cost/QALY

## 1.2 Background & Rationale

As the world enters the third year of the COVID-19 pandemic, over 6.4 million people globally have died of SARS-CoV-2.<sup>1</sup> While vaccines have reduced the proportion of patients requiring hospitalization and critical care and thus prevented health systems from being overwhelmed, SARS-CoV-2 will likely become endemic.<sup>2</sup> New variants will emerge and reduced vaccine effectiveness against future strains remains a concern.<sup>3</sup> While monoclonal antibody treatments have been effective, several (e.g. bamlanivimab, casirivimab/imdevimab, and sotrovimab) have already proven vulnerable to antiviral resistance.<sup>4,5</sup> As with certain antivirals (e.g. remdesivir), they require IV infusion, are expensive, and are usually administered in specialized centres for outpatient treatment in those at highest risk.<sup>6</sup> **Effective, safe, convenient, affordable, and evidence-based therapeutics that can be used in communities with high vaccination rates to limit the severity of SARS-CoV-2 infection, reduce hospitalizations, and reduce short- and long-term symptoms remain urgently needed.**<sup>7</sup>

Studies to date have evaluated numerous potential agents in community settings for mild to moderate infections, but current Canadian<sup>8,9</sup>, American,<sup>10</sup> and international guidelines<sup>11,12</sup> identify only nirmatrelvir/ritonavir (Paxlovid™) as a recommended therapeutic.<sup>12</sup> Fluvoxamine has moderate evidence,<sup>13</sup> inhaled steroids have weak evidence but may be considered,<sup>12,14</sup> and molnupiravir is currently under Health Canada review.<sup>15</sup> Nirmatrelvir/ritonavir is a promising treatment, however the key RCT that evaluated this treatment, the Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (EPIC-HR) study, was in unvaccinated patients, and predated the most recent variants of SARS-CoV-2.<sup>16</sup> Subsequent data released from the EPIC-SR study was not able to demonstrate efficacy in the primary outcome of time to recovery, nor in the key secondary outcome of hospitalization or death at 28 days. The sub-group analysis for 721 vaccinated adults with at least one risk factor for progression to severe COVID-19 demonstrated a non-significant relative risk reduction (RR 0.43; 95%CI 0.11-1.64).<sup>17</sup> A recent systematic review and network meta-analysis of antivirals for non-severe SARS-CoV-2 infection concluded that it was essential to evaluate the effectiveness of nirmatrelvir/ritonavir and other new agents in the vaccinated population and against more recent variants.<sup>18</sup>

Three major problems are currently faced by clinicians, provincial decision makers, public health leaders, and patients:<sup>19</sup>



- i. Almost all published trials have included only unvaccinated patients. **It is unclear whether and to what extent existing therapeutics are effective in partially or fully vaccinated patients, or among those with prior infection.**
- ii. **Therapeutics have not been compared to one another**, and the comparative effectiveness, safety and cost-effectiveness/cost-utility has not been established.<sup>20</sup>
- iii. Currently, **no therapeutic has been evaluated specifically for its potential in reducing the likelihood of post-acute sequelae of SARS-CoV-2.**

### ***Why is an APT for COVID therapeutics in community settings needed now?***

First, vaccines against SARS-CoV-2 have reduced infection severity and significantly fewer patients are presenting to emergency rooms and hospitals.<sup>21</sup> Patients with mild to moderate symptoms – including those at high risk of deterioration – present to primary care and other community settings.<sup>22</sup> This APT's recruitment strategies reflect settings where patients present early in the course of infection and where decisions about prescriptions are likely to be made, enhancing generalizability. Clinicians and patients need to know which therapeutics are the most effective. As approximately 85% of Canadians have access to a regular family physician or source of primary care,<sup>23</sup> it is likely that the prescribing of COVID therapeutics for a significant proportion of our target population will occur in that context. Effective therapeutics could significantly reduce the burden on EDs, hospitals, and intensive care units (ICUs) if case numbers rise and/or vaccine efficacy against severe disease wanes. Second, Canadian decision makers currently have limited evidence to inform decisions on procurement<sup>24,25</sup> and comparative efficacy trials are needed. Third, a nimble and durable trial structure is needed, such that Canadians do not have to rely on trials carried out in other countries and can generate their own data in real time.

**APTs are an ideal design to compare multiple therapies and to allow for new therapeutics to be added to the trial as they emerge.** APTs study multiple interventions in a single disease/condition in a perpetual manner, with new research questions focused on new interventions allowed to enter or leave the platform over time based on a decision algorithm. APTs use a master protocol to establish standard operating procedures and create a common clinical trial evaluation for all interventions, including interim analyses to determine whether enrollment to interventions can be stopped early for statistical efficiencies (sequential designs). During the COVID-19 pandemic, APTs have been crucial in identifying what does and does not work to treat SARS-CoV-2 for hospitalized patients.<sup>26</sup> For example, the RECOVERY Trial helped identify that dexamethasone significantly reduced mortality among ventilated patients.<sup>27</sup> REMAP-CAP identified the important role of intravenous steroids in ICU patients.<sup>28</sup> Later in collaboration with other APTs, ATTACC, REMAP-CAP, and ACTIV-IV investigators demonstrated therapeutic-dose heparin reduced progression to ICU level organ support and death in non-critically ill hospitalized patients with COVID-19.<sup>29,30</sup> Among patients seen in the community, the PRINCIPLE trial in the UK demonstrated the efficacy of inhaled budesonide.<sup>31</sup>

### **1.3 Study Objectives**

- i. Establish an APT aimed at evaluating the effectiveness (including comparative clinical and cost-effectiveness), practical challenges, and outcomes of therapeutics for SARS-CoV-2 to non-hospitalized patients in Canada, engaging a variety of healthcare settings.
- ii. Generate evidence on treatment effectiveness and outreach to communities made vulnerable by social and economic policies, particularly those historically excluded from research.
- iii. Provide rapid evidence to inform clinical and health system management and public health leaders, decision-makers, and planners within Canada and internationally.

**Central research questions:** *What is the comparative effectiveness of SARS-CoV-2 therapeutics for non-hospitalized patients? What is the comparative effectiveness in reducing post-acute sequelae of SARS-CoV-2? Are the tested therapeutics cost-effective? How does clinical- and cost-effectiveness differ by underlying patient risk and across diverse populations?*

## 1.4 Study Timelines

CanTreatCOVID is designed as an APT, supporting ongoing research on out-patient therapeutics for SARS-CoV-2 infection. This platform allows for the study to be perpetual, with multiple treatments evaluated at any given time, and over time. Frequent adaptive analyses are performed to determine whether the interventions under evaluation are still eligible for further testing or if randomization should be stopped due to demonstrated inferiority, superiority, or equivalence. The only limit on the duration of a platform trial is the availability of ongoing funding, the availability of new interventions to evaluate, and that the disease continues to be of clinical and public health importance. Should the whole study be stopped, the end of the trial is the date of the last scheduled long-term follow-up for any participant.

## 2. Study Organization

### 2.1 Sponsor

The Sponsor Investigator of the trial is Dr Andrew Pinto and Unity Health Toronto. The sponsor is responsible for ensuring the trial is carried out according to the approved protocol, regulatory and ethical requirements.

- **Andrew Pinto, Principal Investigator**  
Email: [Andrew.pinto@utoronto.ca](mailto:Andrew.pinto@utoronto.ca)
- **Benita Hosseini, Research Scientist**  
Email: [Benita.hosseini@unityhealth.to](mailto:Benita.hosseini@unityhealth.to)

### 2.2 Executive Committee (EC)

The Executive Committee is responsible for providing direction and oversight in collaboration with the sponsor. The Committee will also provide overall direction to research staff, receive reports from each committee and hub, oversee study operations, act as a central point of contact for knowledge users and collaborators, and implement knowledge translation activities.

*Members of the Executive Committee:*

*Andrew Pinto, Amanda Condon, Bruno da Costa, Peter Daley, Michelle Greiver, Corinne Hohl, Benita Hosseini, Peter Juni, Todd Lee, Kerry McBrien, Emily McDonald, Srinivas Murthy, Peter Selby*

### 2.3 Methods and Statistical Analysis Committee

This Committee will liaise with the study statistician, and support changes and updates to the Statistical Analysis Plan.

## 2.4 Recruitment and Communications Committee

This Committee will support the use of primary care EMR data for outreach, as well as support local practice engagement, linkage to emergency departments for recruitment, and link to infectious disease clinics and colleagues to support recruitment. This Committee will be supported by 25 patient/citizen representatives from diverse (age, gender identity, racial identity) populations in different geographic and socioeconomic contexts, as well as representative from community organizations.

## 2.5 Canadian COVID-19 Out-Patient Therapeutics Committee

The Committee will review and propose decisions regarding including, exclusion, stopping, adding, etc. therapeutics to the trial based on interim findings, any newly published data from Canadian or international trials, and integration of results from international trials.

## 2.6 Data and Safety Monitoring Committee (DSMC)

The DSMC will include a chair and 4 additional members that are external to the study team. All DSMC members for CanTreatCOVID will be required to complete a detailed disclosure of conflicts of interest, and these will be posted on our open website. The DSMC will serve a crucial role, receiving results reported as Group A (arm 1), Group B (arm 2), etc. Should there be a significant difference in outcomes or adverse events, data will be unblinded to the DSMC chair and then shared with the Steering Committee to reach a unanimous decision with respect to next steps (i.e., continue or stop the trial). Stopping rules will be pre-determined and included in the Statistical Analysis Plan related to efficacy, futility, and safety.

## 2.7 Data Management and Coordination Center (DCC)

The **Data Management and Coordination Centre (DCC)** is the **Applied Health Research Center (AHRC)**, which is an academic research organization fully integrated with the Li Ka Shing Knowledge Institute of St. Michael's Hospital (Unity Health Toronto) and affiliated with the University of Toronto (UofT) in Canada. The AHRC is responsible for day-to-day study operations (e.g. document collection, site training, site activation, data management.).

- **Rekha Thomas, Project Lead**  
Email: Rekha.thomas@unityhealth.to
  
- **Marzena Boczulak, Data Manager;**  
Email: marzena.boczulak@unityhealth.to

The main study database will be housed on secure servers at St. Michael's Hospital in Toronto, Canada and accessed by participating sites through the internet.

## 2.8 Funding

The CanTreatCOVID study is primarily funded through a peer-reviewed grant from the Canadian Institutes of Health Research (CIHR) from 01 June 2022 to 31 May 2023.

### 3. Site Training and Activation

#### 3.1 Delegation Log

All study staff that will participating in any related study related tasks must be listed on the Site Delegation Log and Signature Sheet. This must also be reviewed and approved by the Qualified Investigator delegating the staff's involvement in the study.

#### 3.2 Site Initiation Visit

An in-person Investigator's meeting is not planned. Site Initiation Visit (SIV) training will be provided by the Sponsor and the AHRC project manager via web-conference, and will be scheduled with each provincial hub (or small group of sites) prior to the site activation and study launch. The web-conference training is expected to take about 1-2 hours, which includes training on the protocol, study operations and a live demonstration of REDCap™ database(s). Attendance by the Qualified Investigator(s) and lead Research Coordinator (if applicable) is mandatory at the SIV. All other study site staff listed on the Study Task Delegation Log must either attend the SIV, or perform self-led training by reviewing the protocol and recording this on the Training Attestation.

#### 3.3 Site Activation

Participating clinical sites will be **activated** by the AHRC after the following conditions are met:

- (1) The **site contract** has been fully executed;
- (2) The AHRC has received a copy of all **essential documentation** listed below; and
- (3) After **training activities** are completed for every study member listed on the delegation log

Documentation required to be received by the DCC before activation includes:

<b>IRB/REB/Ethics Committee Approval</b>	Approval/favourable opinion of the current version of the protocol and patient informed consent form, and any written information provided to patients.
<b>IRB/REB/Ethics Committee Membership List</b>	Current list from the time IRB/REB approval is received.
<b>Patient Informed Consent Form</b>	Copy of IRB/REB/ethics committee approved local patient informed consent form.
<b>Protocol Signature Page</b>	Signed by the Qualified Investigator.
<b>Study Task Delegation Log</b>	Includes all study site personnel to whom the lead site Investigator has delegated study-specific duties and functions.
<b>SIV Attendance Log</b>	Documentation of all site staff who attended the SIV Training.

<b>Study Training Attestation</b>	Documented training activities for all study site personnel listed on the Study Task Delegation Log who did not attend the SIV.
<b>Curriculum Vitae (CV)</b>	An up-to-date signed/dated copy for the lead site Investigator and all study site personnel listed on the Study Task Delegation Log.
<b>GCP Training Certificate</b>	Proof of GCP and/or equivalent Human Subjects Research training/coursework for the lead site Investigator and all study site personnel listed on the Study Task Delegation Log.
<b>Medical or Professional License</b>	A copy of the medical license/hospital appointment letter (or equivalent) for the lead site Investigator and for sub-Investigators listed on the Study Task Delegation Log.
<b>REDCap™ Account Activation Form</b>	For any study site personnel that require access to the eCRF.

**Sites will not begin screening or enrolling patients before site activation.**

Activation will be confirmed via an email from the AHRC project manager to the lead Qualified Investigator and site staff, and a copy of the activation email should be stored in the Investigator Site File. Only after activation will clinical sites receive access to REDCap™ for randomization.

### 3.3.1 Essential Documents

The comprehensive list of essential documents as mandated by ICH GCP E6R2 Section 8.0 is detailed in Appendix I of this manual. All documents should be maintained by the Sponsor and Provincial Hub respectively through the conduct of the clinical trial and for the retention period after the end of the study i.e. 15 years.

### 3.4 Investigator Site File

Prior to the SIV, the AHRC Project lead will provide provincial hubs with study templates and an Investigator Site File (ISF) “table of contents” to assist with organization of local documentation. It is the site’s responsibility to ensure all essential documents are available and filed appropriately and in line with local requirements throughout the duration of the study. The DCC may request to see a copy of the documents maintained in the local ISF at any time. Local audits are the responsibility of the provincial Qualified Investigator.

## **4. Ethical Considerations**

### **4.1 General Protocol Policy**

The investigator/institution should conduct the trial in compliance with the protocol and in compliance with Good Clinical Practice (GCP) and any other relevant local regulations or requirements.

Any significant and/or systematic deviations from the protocol may compromise the scientific integrity of the study. Amendments to the protocol, if necessary, will be reviewed and approved by the Executive Committee with input from the Steering Committee.

### **4.2 Informed Consent**

The Sponsor will provide all participating provincial hubs with a “master informed consent form” (mICF) and sub-protocol consent(s) which may be modified according to local requirements and standards. If modified, the ICF should be provided to the Sponsor/DCC team for review prior to submission to the local IRB/REB and the Sponsor/DCC may have comments, queries or requests.

The DCC must receive a copy of the local REB/IRB-approved current version of the patient ICF prior to site activation and enrolment of study participants.

The Sponsor-Investigator also maintains overall responsibility for the scientific and clinical content of the Informed Consent Form(s). The Qualified Investigator is responsible for the overall approval of the wording in the Master ICF and Sub-Protocol ICF(s), and approval of the differences between the Master ICF(s) and Local ICF. The Qualified Investigator may delegate the duty of obtaining informed consent to appropriate clinical site research personnel. The Qualified Investigator is responsible for assuring that any such designated member of the team is knowledgeable about the specific research study and the process of informed consent.

#### **4.2.1 Informed Consent Process**

- i. Patients admitted to the participating centers who are COVID-19 positive (with a confirmed Rapid Antigen or PCR test) will be screened for eligibility. Consecutive patients fitting the study inclusion and exclusion criteria will be approached and offered a verbal explanation and written information in the form of the participant consent form.
- ii. Informed consent, including the possibility of remote informed consent will be obtained for each research participant or the substitute decision maker prior to enrolment in the study and altering a subject’s care for the purpose of research. The consent must be obtained according to Sponsor, REB, GCP and local regulatory requirements.
- iii. In the case that a potential participant is unable to provide written consent, the investigator may obtain non-written consent, provided that the following conditions are met:



- a. the qualified investigator or designee reads the contents of the informed consent to the person;
- b. the person provides their informed consent before a witness; and
- c. an attestation by the witness that the person has provided their informed consent is provided to the qualified investigator as soon as feasible,

as adapted from section 36 (2) of *Health Canada's Interim Order Respecting Clinical Trials for Medical Devices and Drugs Related to COVID-19 issued May 23, 2020*. [[https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/interim-order-respecting-clinical-trials-medical-devices-drugs.html# Remote written informed](https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/interim-order-respecting-clinical-trials-medical-devices-drugs.html# Remote%20written%20informed)]

- iv. The Investigator or the designee will fully inform the participant or the substitute decision maker of all pertinent aspects of the research including the written information as approved by the REB. The process includes:
  - a. Only the currently approved, most recent version of the Informed Consent Form should be used for obtaining informed consent.
  - b. Giving the participant adequate information concerning the research /clinical trial in language that is as non-technical as possible.
  - c. Providing ample time and opportunity for the participant or the substitute decision maker to inquire about the details of the study
  - d. Responding participant's questions – all questions about the research should be answered to the satisfaction of the participant or the substitute decision maker.
  - e. Ensuring that the participant has comprehended this information
  - f. Obtaining the participant's voluntary consent.
- v. Informed consent will be documented by using the e-consent, written consent or verbal consent as approved by REB. The e-consent will be signed and dated by the participant or SDM, and by the person who conducted the informed consent discussion [ICH GCP 4.8.8].
- vi. The Qualified Investigator or designee will retain the original signed e-consent form in keeping with the terms of the sponsor and REB study approval. A copy of the consent form will be provided to the person signing the form at the time of consent. Another copy will be filed in the participant's record or filed in the ISF or in the database as required by the sponsor, the REB or the institution (site).
- vii. The Qualified Investigator and all site personnel are responsible for continuing the informed consent process throughout the participant's enrolment in the study. The participant or the substitute decision maker will be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the research. The communication of this information will be documented [ICH GCP 4.8.2]

- viii. If the consent form is revised during the course of a participant’s enrolment in the trial, then the participant will be re-consented by the Qualified Investigator or the designee with the revised REB approved consent form. The Qualified Investigator or designee will file the newly obtained original signed consent form in keeping with the terms of the sponsor and REB study approval. A copy of the consent form will be provided to the person signing the form at the time of consent. Another copy will be filed in the participant’s record.
- ix. In accordance to the ICH GCP Section 4.8 the Informed Consent Process should be documented by the consenting staff to ensure and document that all elements of the informed consent process are met.
- x. Provincial Hubs are to complete and file the Informed Consent Process Checklist (Section 4.2.2.) along with the Informed Consent Form, unless local site or REB checklists are to be implemented, as per institutional or local regulatory requirements. If the checklist or similar language is part of the Informed Consent form, this may suffice to fulfill this requirement.

#### 4.2.2 Informed Consent Process Checklist

The Informed Consent Process Checklist should be completed:

If e-consenting directly on the database in the Research Coordinator Attestation section or if via email then a hardcopy or softcopy should be retained in the participant file in the ISF.

<b>STUDY:</b>	<b>CanTreatCOVID – Informed Consent (v xx/dd-mmm-yyyy )</b>
<b>QUALIFIED INVESTIGATOR:</b>	
<b>PROVINCIAL HUB/SITE</b>	

<b>Participant ID:</b>	
<b>Date of Obtaining Written Informed Consent:</b>	
<b>Time of Obtaining Written Informed Consent:</b>	

All sections of the Informed consent were discussed with subject for the CanTreatCOVID study

Subject and/or authorized subject representative was given adequate time to read the consent form and discuss the study with study investigators and/or family members.



All questions were answered. Subject and/or authorized subject representative was given time to discuss.

Subject and/or authorized subject representative signed and dated the informed consent. A copy of the consent form was provided to the subject and/or authorized subject representative upon conclusion of the consent process.

Consent has been signed prior to any study procedures being performed.

<b>Consent Process documented by:</b>		
<b>Staff Name:</b>	<b>Signature:</b>	<b>Time of completion:</b>

### 4.3 Participant Confidentiality

The Qualified investigator must assure that patient anonymity will be maintained and that their identities shall be protected from unauthorized parties. The Provincial Hub should maintain the Master Linking + Participant log linking codes to the names/health records number of patients. The Qualified Investigator’s team should maintain documents that are not for submission to the DCC (e.g. participants’ written ICFs), in strict confidence. Additional local or national requirements for health information privacy must be followed.

### 4.4 Participant Discontinuation

Participants have the right to discontinue from the study intervention for any reason, at any time. All participants who are randomized will be followed for the remainder of the trial, unless the participant withdraws consent to participate in the follow up activities.

## 5. Screening and Eligibility

### 5.1 Screening and Eligibility

All local regulations should be followed as they pertain to screening activities. Potential participants will generally be identified by the Site Team. Initial eligibility may be assessed through a review of the medical chart or discussion with the patient, and if the patient appears to meet the eligibility criteria, the consent process may be initiated. No study assessments (including a pregnancy test done for study eligibility purposes only) may be carried out prior to obtaining informed consent.

Co-enrolment into other observational (non-interventional) studies is generally acceptable as long as this is approved by the local IRB/REB.

Co-enrolment into other interventional research studies should be discussed with the Sponsor.

### 5.2 Inclusion Criteria

Age 50 years and older or 18-49 with 1 or more chronic high-risk medical conditions or immunosuppression within 5 days of onset of SARS-CoV-2 symptoms.

### 5.3 Exclusion Criteria

Currently admitted to hospital or in an emergency department (ED) for more than 24 hours, previously randomized to CanTreatCOVID, currently participating in a clinical trial of a therapeutic agent for acute SARS-CoV-2 infection that is not/suspected not compatible with the study therapeutics, already taking a study therapeutic or contraindication to a study therapeutic, or inability for participant or caregiver to provide informed consent.

### 6. Schedule of Events

The schedule of events for participants is described in Table 1.

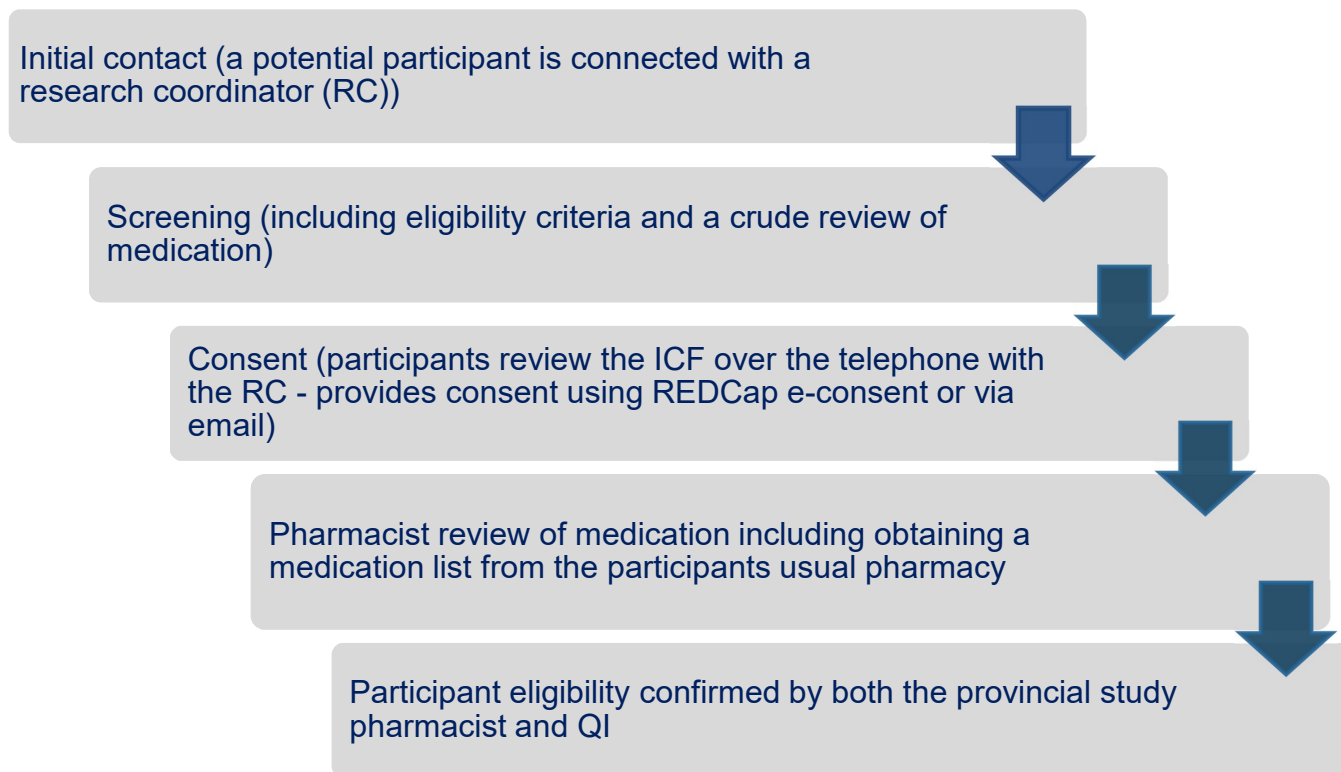
**Table 1: Participant schedule of events**

<b>Event</b>	<b>Description</b>
Initial Contact	A potential participant is connected with a Research Coordinator (RC) through one of the recruitment methods described [Section 8].
Screening	Participant is contacted by a Research Coordinator (RC) for initial screening, including eligibility criteria and a crude review of medications.
Consent	Participant reviews the ICF over the telephone with the Research Coordinator (RC) and is sent the ICF electronically via email, if possible. If willing to participate, the participant will verbally consent to be a part of the study and if possible, will electrically return a signed copy of the ICF via email.
Pharmacist's assessment of eligibility	A study pharmacist will perform a comprehensive review of the participant's medication list, which may involve obtaining additional data from the participant's regular pharmacy via phone. If additional information (medical history, lab data, etc.) is needed to assess eligibility, pharmacist may also use relevant digital health resources, like the Connecting Ontario portal for Ontario-based participants, to gather the necessary information. In cases where further details are required, the study team might reach out to the participant's primary care provider. The study pharmacist will then provide their recommendation to the PI regarding the participant's eligibility for the trial.
Participant eligibility confirmed	If both the provincial study pharmacist and PI agree regarding the medication review, the participant is enrolled in the trial.
Randomization	Participant is randomized to a trial arm.
Baseline data collection	Participant completes baseline data collection electronically or over the telephone with a Research Coordinator (RC) to

	provide information on sociodemographic characteristics, vaccination status, time to recovery, health service use, and quality of life.
Medication order placed	If participant randomized to a treatment arm, either the distribution pharmacy receives the order and ships the study drugs or they may be stored and shipped by the study team from a secure location.
Day 1 check-in	Research Coordinator (RC) connects with the participant to confirm that the medication was received and started within the 5 day timeline and that there were no serious adverse events upon taking the first dose.
Daily diary (14 days from onset of study medication use)	Participant completes an online daily diary for 14 days, assessing time to recovery, symptoms, symptom severity, and continuation of study medication, other medication use, and healthcare services use.
Follow up at 21 days	Participant completes the 21 day follow up electronically or over the telephone with a Research Coordinator (RC) to provide information on time to recover, health service use, early discontinuation, and quality of life.
Follow up at 28 days	Participant completes the 28 day follow up electronically or over the telephone with a Research Coordinator (RC) to provide information on time to recover, health service use, early discontinuation, long COVID, and quality of life.
Follow up at 90 days	Participant completes the 90 day follow up electronically or over the telephone with a Research Coordinator (RC) to provide information on time to recover, health service use, long COVID, and quality of life.
Follow up at 36 weeks	Participant completes the 36 week follow up electronically or over the telephone with a Research Coordinator (RC) to provide information on time to recover, health service use, long COVID, and quality of life.
Follow up at 12 months	Review of administrative data to determine health service use, if participant consented to allowing access to data. Pending additional funding after Year 1, quality of life data will be collected at 12 months and converted using standard approaches to QALYs. Cost-utility analysis will be calculated as the incremental cost per QALY gained.
Follow up at 24 months	Review of administrative data to determine health service use, if participant consented to allowing access to data. Pending

	<p>additional funding after Year 1, quality of life data will be collected at 24 months and converted using standard approaches to QALYs. Cost-utility analysis will be calculated as the incremental cost per QALY gained.</p>
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## 6.1 Screening to Randomization



- a. The Research Coordinator should ensure to complete the Provincial specific consent forms according to the location of the participant. For example, if a participant is from Ontario then the REB approved Ontario specific consent forms should be administered
- b. When the participant agrees to participate in the trial, a signed copy of the ICF should be returned back via email or via REDCap database portal.  
If it is not possible for the participant to return a signed ICF, verbal consent will be sought via telephone, in the presence of a witness. The Witness attestation form should be completed to confirm the participant has provided informed consent verbally.
- c. The Pharmacy Eligibility should be completed by the pharmacist. All concomitant medication reported by the participant (i.e. drug name, dose, frequency, start/end date) should be inputted by the pharmacist

- d. The QI eligibility form should be completed by the QI. All concomitant medication inputted by the pharmacist should be reviewed by the QI prior to qualifying the participant to the study.
- e. Eligibility can be assessed by eliciting medical history and relevant information, including a drug history, directly from the participant. In some cases (i.e., patients with chronic liver disease or chronic kidney disease) eligibility checking will be assessed additionally by reference to relevant medical information obtained from the participant’s primary care (where the person confirming eligibility deems this necessary).

## 6.2 Randomization

Randomization will occur after informed consent is obtained and all eligibility criteria have been confirmed by the Pharmacist and Qualified Investigator. Randomization is contingent upon prior completion of the eligibility criteria form which confirms the full eligibility of the patient.

### a. *Randomization to Study Intervention:*

- Once a participant is randomized to the study intervention arm, an email notification should be submitted to the Provincial pharmacy to dispense the study drug.
- A prepared notification with the participant’s ID number, name, address and phone number should be submitted to the study pharmacy by email.

## 6.3 Study Visits and Data collection forms

Event	Form(s)	Completed by	Focus of event
<b>Screening</b>	Screening form	Research Coordinator	Screen and review participant for eligibility to randomize into study
	e-Consent(s)	Research Coordinator	
	Pharmacy/QI Eligibility	Pharmacist, QI	
	Randomization	Research Coordinator	
<b>Baseline</b>	Demographic Data, Risk Factors, Social Needs, COVID Symptoms	Participant AND/OR Research Coordinator	Collect Baseline data
	Visit Date, EQ-5D, Height and Weight	Research Coordinator	
<b>Day 1 check-in</b>	Day 1 form	Research Coordinator	To confirm receipt of study drug (intervention arms only), confirm follow-up

			procedure (all arms) and answer queries
<b>Day 4 check-in</b> <i>(only if randomized to Intervention – Paxlovid)</i>	Day 4 form	Research Coordinator	To monitor side effects and concomitant medications usage
<b>Day 1-14</b>	Day 1-14 Daily Diary Flu Pro Plus (only if participant is assigned to complete)	Participant and Research Coordinator	
<b>Follow up at 21 days</b>	Day 21	Participant and Research Coordinator	Focus on time to recover, health service use, early discontinuation and quality of life
<b>Follow up at 28 days</b>	Day 28	Participant and Research Coordinator	Focus on time to recover, health service use and quality of life
<b>Follow up at 90 days</b>	Symptom Burden Questionnaire Visit Date, Follow-up on Day 90, EQ-5D, Height and Weight	Participant AND/OR Research Coordinator Research Coordinator	Focus on health service use, long COVID, and quality of life
<b>Follow up at 36 weeks</b>	Symptom Burden Questionnaire Visit Date, Follow-up Week 36, EQ-5D, Height and Weight	Participant AND/OR Research Coordinator Research Coordinator	Focus on health service use, long COVID, and quality of life
<b>Follow up at 12 months</b>	12 months	Research Coordinator	Review of administrative data to determine health service use, if participant consented to allowing access to data

<b>Follow up at 24 months</b>	24 months	Research Coordinator	Review of administrative data to determine health service use, if participant consented to allowing access to data
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## 6.4 Visit Window

The acceptable range for completion of each of the visit are as indicated below. Any visit that diverges from the allowed range should be filed as a protocol deviation.

Follow up visit	Allowed range for visit
Day 1	0 day
Day 4	0 days
Day 21	+/- 1 day
Day 28	+/- 1 day
Day 90	+/- 3 days
Week 36	+/- 5 days

## 7. Investigational Product

### 7.1 Description of Study Intervention

- i. **Control**  
No study intervention – usual standard care
- ii. **Active study medication**  
Nirmatrelvir/Ritonavir (Paxlovid™)

As this trial progresses, therapeutics for SARS-CoV-2 in out-patient settings to be evaluated will be determined by the Canadian COVID-19 Out-Patient Therapeutics Committee, which will evaluate the latest evidence on new therapeutics and makes recommendations to the Steering Committee.

### 7.2 Administration of the Study Intervention

#### 7.2.1 Paxlovid

Dosing	Paxlovid™ is nirmatrelvir tablets co-packaged with ritonavir tablets. Nirmatrelvir must be co-administered with ritonavir. Failure to correctly co-
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	<p>administer nirmatrelvir with ritonavir will result in plasma levels of nirmatrelvir that will be insufficient to achieve the desired therapeutic effect.</p> <p>The dosage for Paxlovid™ is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all three tablets taken together orally twice daily for 5 days. Participants will be advised to complete the full 5-day treatment course.</p> <p>The 5-day treatment course of Paxlovid™ should be initiated as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset.</p>
Dosing Considerations	<p>If the participant misses a dose of Paxlovid™ within 8 hours of the time it is usually taken, the participant should take it as soon as possible and resume the normal dosing schedule. If the participant misses a dose by more than 8 hours, the participant should not take the missed dose and instead take the next dose at the regularly scheduled time. The participant should not double the dose to make up for a missed dose.</p> <p>If a participant overdoses with Paxlovid™, they will be advised to get in touch with their primary care provider or local emergency department, if required.</p> <p>If a patient requires hospitalization due to severe or critical COVID-19 after starting treatment with Paxlovid™, the patient should complete the full 5-day treatment course at the discretion of their healthcare provider.</p> <p>Paxlovid™ can be taken with or without food. The tablets should be swallowed whole and not chewed, broken, or crushed.</p>
Adherence	Adherence to trial medication will be assessed by self-report.
Side Effects	<ul style="list-style-type: none"> <li>● Allergic or hypersensitivity reactions: eg, hives, skin rash, swelling of the mouth, lips, or face, hoarseness, throat tightness, trouble swallowing or breathing</li> <li>● Altered or impaired sense of taste → 6%</li> <li>● Diarrhea → 3%</li> <li>● Nausea → 1%</li> <li>● Vomiting → 1%</li> <li>● Headache → 1%</li> <li>● Muscle pain → 1%</li> <li>● High blood pressure → 1%</li> </ul> <p><b>Important Notes regarding side effects:</b></p> <ul style="list-style-type: none"> <li>● When possible, other medicine will be given to you by your usual doctor to make side effects less serious and more tolerable.</li> </ul>



	<ul style="list-style-type: none"> <li>• Many side effects go away shortly after the study intervention is stopped, but in some cases, side effects can be serious, long-lasting, permanent, or may even cause death.</li> <li>• New drugs may have serious side effects not yet been discovered, or long-term effects that are unknown.</li> <li>• It is possible that other drugs (prescription and non-prescription drugs), vitamins, or herbals can interact with the study intervention. This can result in either the intervention not working as expected or result in severe side effects.</li> </ul>
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### 7.3 Ordering the Investigational Product procedures

1. Once eligibility is confirmed, the Participant is Randomized to the Study Treatment (on the RedCap Cloud database)
2. If the participant is Randomized to the Investigational Product (i.e. Paxlovid) the Research Coordinator populates the Study Drug Request Form with the following information:

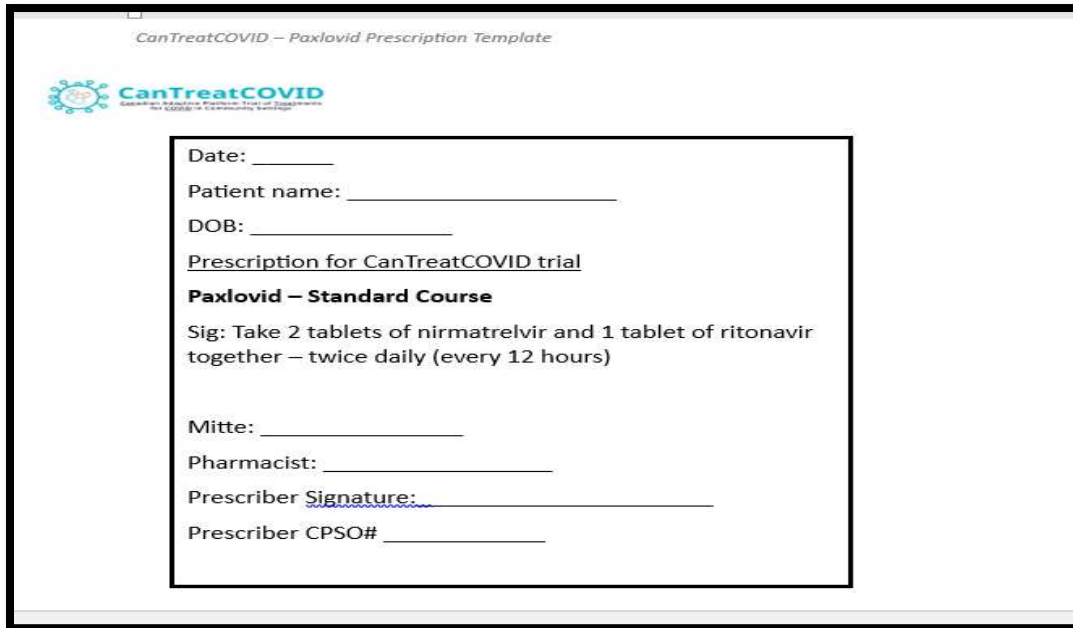


**CanTreatCOVID**  
Canadian Adaptive Platform Trial of Treatments  
for COVID in Community Settings

<b>Randomization Date</b>	DD-MM-YYYY
<b>Subject ID on REDCap Academic</b>	
<b>Subject ID on REDCap Cloud</b>	
<b>Participant Full Name: Last Name, First Name Middle Name/s</b>	
<b>Address for shipping</b>	
Street Number Street Name	
Entry Code/Buzzer Code	
City	
Postal Code for shipping	
<b>Participant's Email address (for tracking shipment)</b>	
<b>Telephone number for coordinating shipment</b>	
<b>Alternate contact for shipping</b>	
Name	
Phone number	

3. Research Assistant emails the Pharmacy form to the Study Pharmacist Research Pharmacist uses the Pharmacy Form to build the Prescription template for the specified

participant



*CanTreatCOVID – Paxlovid Prescription Template*

**CanTreatCOVID**  
Canadian Adaptive Platform Trial of  
Treatments for COVID in Community Settings

Date: \_\_\_\_\_  
 Patient name: \_\_\_\_\_  
 DOB: \_\_\_\_\_

Prescription for CanTreatCOVID trial

**Paxlovid – Standard Course**

Sig: Take 2 tablets of nirmatrelvir and 1 tablet of ritonavir together – twice daily (every 12 hours)

Mitte: \_\_\_\_\_  
 Pharmacist: \_\_\_\_\_  
 Prescriber Signature: \_\_\_\_\_  
 Prescriber CPSO# \_\_\_\_\_

4. Research Pharmacist arranges for the fax to be sent to the Research Pharmacy.

#### 7.4 Provincial Site Pharmacy

The Provincial Pharmacy assigned by the Site will document the procedures and documentation in the form of an SOP to support the CanTreatCOVID research project and submit it to the AHRC Project Lead

The objective of the SOP will document processes:

1. To ensure the proper receipt, handling, storage, dispensing, shipping of research medicines
2. To ensure all the research project documentation requirements are established and achieved for the duration of the project.
3. To ensure all required Health Canada documentation is completed and retained in a timely fashion.
4. To ensure accountability for all aspects of research medicines dispensing for CanTreatCOVID research project

**The essential Investigational Product documents (provided in the Pharmacy Logs template) that should be retained by the Site and submitted to the AHRC as requested. The Pharmacy Logs includes:**

- Receipt of Obtaining Investigational Product (including Shipping records, temperature logs)
- Storage and Handling the Investigational Product
- Dispensing and Accountability of the Investigational Product
- Destruction process and logs of the Investigational Product

## 7.5 Investigational Product Label

According to Division 5 of the Health Canada Food and Drug Regulations and Clinical Trials for Drugs relating to COVID19 Regulations, the Sponsor should ensure that the drug bears a label that sets out the following information in both official languages (C.05.011):

<input type="checkbox"/>	(a) A statement indicating that the drug is an investigational drug to be used only by a qualified investigator Example: <i>Investigational drug to be used only by Qualified Investigator / Drogue de recherche réservée uniquement à l'usage de chercheurs compétents</i>
<input type="checkbox"/>	(b) The name, number or identifying mark of the drug
<input type="checkbox"/>	(c) The expiration date of the drug
<input type="checkbox"/>	(d) The recommended storage conditions for the drug
<input type="checkbox"/>	(e) The lot number of the drug
<input type="checkbox"/>	(f) The name and address of the sponsor
<input type="checkbox"/>	(g) The protocol code or identification

## 8. Adverse Events and Serious Adverse Events

### 8.1 Definitions

**Adverse Event (AE):** Any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An **adverse drug reaction (ADR)**, as opposed to an adverse event, is characterized by the fact that a causal relationship between the treatment and the event is suspected (i.e. there is a reasonable possibility the AE is related to the study drug).

All adverse events/drug reactions that occur from the time of dosing to the time of discharge should be assessed, but only AEs which are unexpected and/or related to the study drug shall be recorded in the electronic case report form (eCRF). The

**Serious Adverse Event (SAE):** Any adverse event reaction that at any dose results in any of the following outcomes:

- Death
- Life-threatening (an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Inpatient hospitalization or prolonged hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect

**Unexpected Adverse Event:** An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. product monograph). Unexpected refers to an experience that has not been previously observed, and includes events that are more severe than expected or occur more frequently than expected.

## 8.2 Grading

The severity of an adverse event is assigned by the site. The term **severity** is used to describe the **intensity** of a specific event, such as mild, moderate, severe or life-threatening.

AE severity (intensity) may be classified as follows:

<b>Mild:</b>	Does not interfere with the patient’s usual daily activities; intervention not indicated.
<b>Moderate:</b>	Interferes to some extent with usual daily activities; minimal, local or noninvasive intervention indicated
<b>Severe:</b>	Interferes significantly with usual daily activities (severe or medically significant but not immediately life-threatening); intervention is required. (If hospitalization or prolongation of hospitalization is indicated for treatment, the AE becomes an SAE).
<b>Life Threatening:</b>	Life-threatening consequences; urgent intervention indicated.
<b>Death:</b>	Death related to AE.

**SEVERITY vs. SERIOUS:** Please note severity does not determine whether an AE meets the definition of seriousness, which is based on the patient/event *outcome or action* criteria usually associated with events that pose a threat to a subject’s life or functioning. In example, a severe headache may be of very minor clinical significance, whereas severe bleeding requiring a transfusion is.

## 8.3 Relationship to the study drug

The causal relationship between an adverse event and the study drug is determined by the site principle investigator or co-investigator. The relationship to the study drug is one of the main criteria for reportability of an AE/SAE to the Coordinating Centre.

<b>Unrelated:</b>	The AE is <i>clearly NOT</i> related to the study drug (Note: a definitive alternative etiology for the event must exist)
<b>Unlikely:</b>	The AE is <i>doubtfully</i> related to the study drug.
<b>Possibly:</b>	The AE <i>may be</i> related to the study drug.
<b>Probable</b>	The AE is <i>likely</i> related to the study drug.
<b>Definite:</b>	The AE is <i>clearly</i> related to the study drug.

## 8.4 Reporting AEs and SAEs

- Adverse events will be monitored from the time of randomization to week 36.

- AE can be collected through the daily diary, communicated on study surveys or to research staff directly, or communicated through the toll-free study hotline between 7 AM - 8 PM ET **+1 (888) 888-3308**.

#### 8.4.1 AE Reporting Process

1. Each clinical event or worsening or deterioration of a clinical condition after inclusion of the subject in a clinical study should be reported to the Site Investigator and documented in the case report form.
2. Participants should be informed of the importance of reporting all physical changes which occur during the clinical study to the research coordinators.
3. The research coordinator should accurately and regularly document all reported adverse events in the *Adverse Event eCRF*.
4. For all reported AEs/ADRs, the following information should be documented in the *Adverse Event eCRF*: dates of onset and of resolution of the event, description, intensity and outcome of the event, actions taken and relationship to study drug.
5. The severity (intensity) of each AE recorded in the eCRF should be assigned to one of the following categories:
  - **Mild:** An event that is easily tolerated by the subject, causing minimal discomfort, and not interfering with everyday activities
  - **Moderate:** An event that is sufficiently discomforting to interfere with normal everyday activities.
  - **Severe:** An event that prevents normal everyday activities.
6. At baseline, the research coordinator will inquire if the patient has any co-morbidities or other medical problems. If so, research coordinator will need to record them in the **Comorbidity eCRF** and specify that the conditions were pre-existing and occurred prior to randomization.
7. At each of the follow-up survey or phone calls, the research coordinator will inquire if the subject has had any new clinical experience, diagnosis, and/or deterioration of any existing clinical condition since the last study survey. If so, research coordinator will need to record them in the *Adverse Event eCRF*.
8. Whenever the research coordinator becomes aware of an AE/ADR, they must also report the event to the Qualified Investigator within the appropriate timeline.
9. With respect to any adverse event reported, the Site Investigator should clinically assess the event and ensure that appropriate medical treatment is provided to a subject during, and after, his/her participating in the study.
10. The Qualified Investigator assessment of AEs/ADRs includes:
  - i. **Intensity:** The intensity of an event can be classified as mild, moderate, or severe. However, the medical importance of the event itself, for example, a severe headache, may not require an immediate report to the Sponsor-PI/Project Lead and regulatory authorities. The terms, serious and severe, are not synonymous.
  - ii. **Relationship with study medication:** The research team should determine, according to clinical judgement, if there is a reasonable doubt as to causal relationship. Attribution may be certain, likely, possible, or unlikely. The adverse event could also be unrelated.

- iii. **Seriousness:** events are classified as serious if associated with effects threatening the life or physiological functions of a subject. It includes any untoward medical occurrence that is fatal, life-threatening or that requires inpatient hospitalization or prolongation of existing hospitalization or that results in a persistent or significant disability/incapacity, as well as birth defects or congenital abnormalities.
11. The Qualified Investigator is responsible for reviewing all completed Adverse Event eCRF to verify causality and for determination of serious events that require reports to the Sponsor-PI/Project Lead and REB.
  12. If the event is not serious, the information must be documented in the Adverse Event eCRF, managed medically as appropriate, and then followed until resolution.
  13. If the event is serious, both Adverse Event eCRF and Serious Adverse Health Event eCRFs, the Qualified Investigator must confirm how the adverse health event meets the definition of serious and assess its expectedness and its relationship to the study drug. Any serious, unexpected adverse event that is possibly related to the research study, must be reported to the Sponsor-PI and Project Lead (Coordinating Center) within 24 hours of its awareness and to the REB as per their reporting requirements.

#### 8.4.2 SAE reporting

All SAEs that occur from the Enrolment until Week 36 follow up must also be reported on a separate SAE Report Form of the eCRF within 24 hours, regardless of their relatedness to the study drug.

#### 8.4.3 SAE reporting time frame

		Reporting Timeframe	Means of Reporting
<b>“Non-serious” expected AEs</b>	<ul style="list-style-type: none"> <li>• Expected AEs neither fatal nor life threatening</li> </ul>	<b>DO NOT REPORT</b>	--
<b>“Unexpected” AEs</b>	<ul style="list-style-type: none"> <li>• Unexpected</li> <li>• Increased severity/frequency</li> <li>• Related to study drug/procedures</li> </ul>	<b>Within 5 days</b>	eCRF “Adverse Events” log form
<b>SAEs</b>	<ul style="list-style-type: none"> <li>• Death</li> <li>• Life threatening</li> <li>• Inpatient Hospitalization/prolonged hospitalization</li> <li>• Persistent or significant disability/incapacity</li> <li>• Congenital anomaly/birth defect</li> </ul>	<b>Within 24 hours</b>	eCRF: “Adverse Events Report” and “SAE Report” form  <b>Always email or Sponsor and Project manager, regardless of reporting method, to confirm receipt</b>

#### 8.4.4 SAE Reporting Process

1. Upon becoming aware of a possible SAE, the Qualified Investigator should assess the seriousness, the expectedness and relatedness of the adverse event to the research study. For all SAE that are unexpected and reasonably related to the research study, the Site must immediately complete the SAE eCRF and provide additional details in the Serious Adverse Event Reporting Form
2. The Site will report SAEs within 1 business day of the date and time that the event was judged as meeting SAE criteria.
3. The Qualified Investigator will be responsible for confirming receipt of the SAE notification, and must therefore email the Sponsor-PI and Project Lead the *Serious Adverse Event Reporting Form* (in addition to entering the information in the SAE eCRF).  
*If the eCRF is unavailable, SAE information will be communicated through a paper SAE Report Form and AE form and emailed to the PL. The Site will be required to enter this information as soon as the SAE eCRF becomes functional.*
4. The Project Lead will acknowledge receipt of the SAE notification to the Site and ensure that all required information for reporting is present, including *name and contact of person reporting the SAE, event name, date of onset, relatedness and reason for seriousness*. As required, the Project Lead will follow up with the Site until these items are obtained. The Site will be provided timelines for responding to the requested information in the correspondence sent by the Project Lead.
5. When sufficient information exists for assessment, the Project Lead will notify the Sponsor-PI (or designate) and the Medical Monitor by email correspondence to ensure there is adequate information to review and assess the SAE within 1 business day.
6. The Medical Monitor will acknowledge receipt of the initial report by emailing the PL within 1 business day.
7. The Medical Monitor may contact the Site to request any additional safety or clinical information as needed, and the requested information should be provided by entering it directly into the eCRF. Any information that does not lend itself to the reporting form will be emailed to the Medical Monitor.  
The Medical Monitor will acknowledge receipt of information by email. The Project Lead must be copied on all correspondence.

Updates to the SAE and AE in the eCRF will be documented and tracked by the eCRF system.

8. Within 1 business day of the Medical Monitor acknowledging the SAE notification, the Medical Monitor will determine and communicate the following to the Project Lead and the Site through email correspondence:
  - i. Causality and expectedness in accordance with the investigational product monograph/Investigator's Brochure

- ii. Assess whether Health Canada reporting is required, and if so, whether it is a 7 or 15 day report (7 days for fatal or life-threatening SUADRs / 15 days for other SUADRs)

The Project Lead will then confirm the submission due date and time.

*Timelines for expedited reporting are based on the date and time in which the Site first became aware of the SAE.*

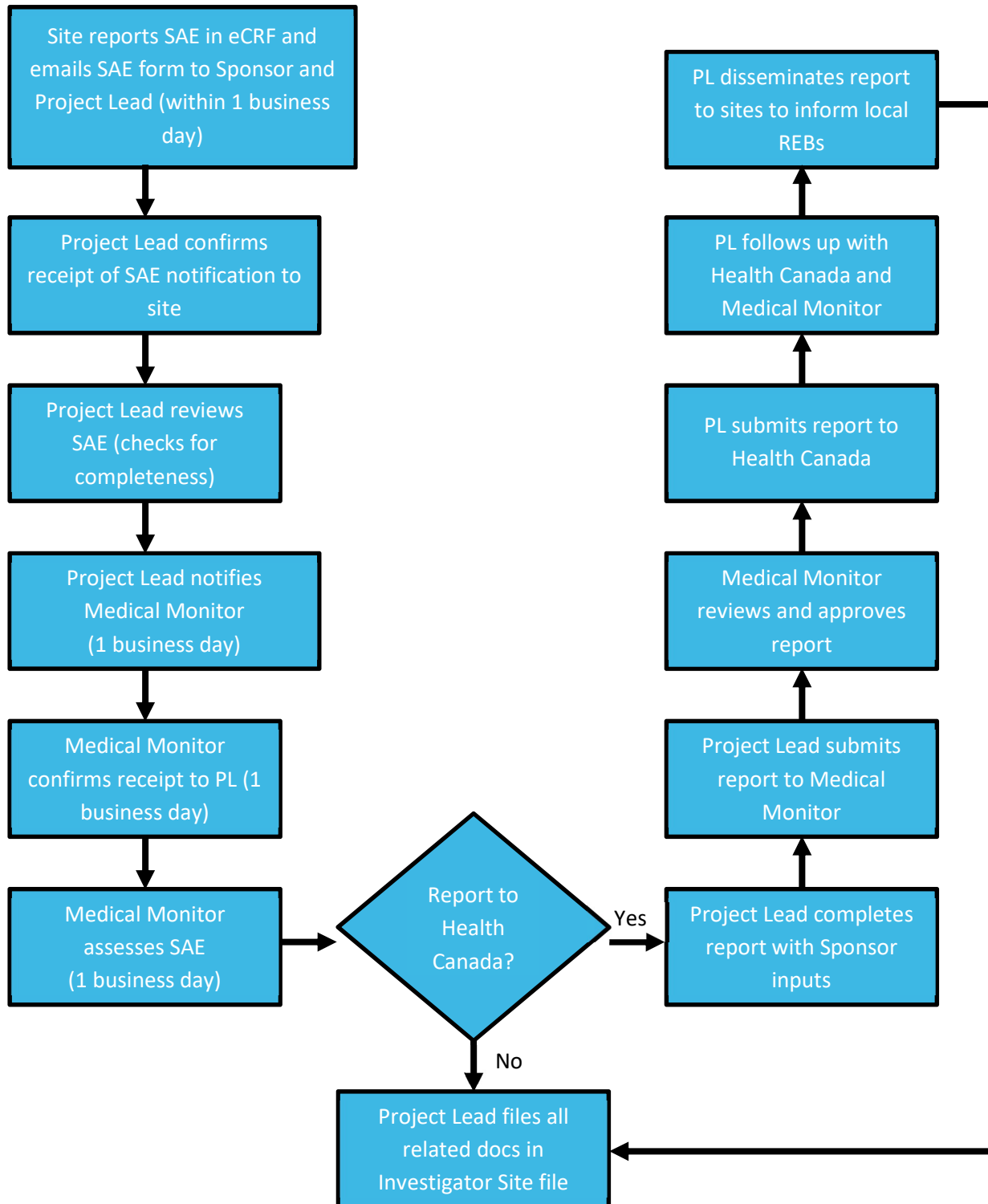
Where a second assessment takes place and there is a difference in opinion on the relatedness of the event, the 'worst case' assessment will be used for reporting purposes.

Additionally, in the event where the safety of the patient is dependent on knowing the patient's treatment arm, unblinding may be permitted.

9. If the Medical Monitor determines that the event requires expedited reporting to Health Canada, the below steps will occur. Otherwise, these steps should be skipped.
  - i. The Project Lead will complete the ADR expedited reporting form (Appendix 2) and send it to the MM
  - ii. The Medical Monitor will review the reporting form and approve, or provide any required edits to the Project Lead.
  - iii. The Project Lead will submit the approved reporting form and cover page to *Health Canada Therapeutic Products Directorate according to reporting guidelines i.e. Email or Fax*
  - iv. The Project Lead is responsible for tracking the reported SAE and following up with Health Canada, the Site, and the Medical Monitor as necessary until the SAE report is considered closed.
10. The Project Lead will circulate the SUADR report to all Sites and direct each Site to notify their local REB per local requirements.
11. All correspondence regarding the SAE including all versions of the SAE report and any SAE print-outs from the eCRF will be filed in the Investigator Site File (ISF) by the Project Lead. In addition, the Site must file all correspondence relating to SAEs originating at their site in their site binder.



### 8.4.5 SAE Reporting Process Flow



## 8.4.6 Reporting to REBs

### **Reporting Site-level Serious Adverse Events**

All local SAEs that are deemed to be an unanticipated problem (unexpected, definitively, probably or possibly related to the research study) should be reported to the REB **within fifteen (15) calendar days** of the study team becoming aware of the event. All fatal or life-threatening SAEs must be reported **within seven (7) calendar days**. Follow-up reports of the SAE should be submitted to the REB whenever new relevant information regarding the SAE becomes available until the resolution of the SAE.

*Note:* Only serious adverse events that occur while the local research participant is actively participating in the research study should be reported to the REB. Serious adverse events/unanticipated problems should be reported to the REB for the duration of the study (i.e. until the study is closed at the REB).

The following adverse events ordinarily should only be reported to REB annually during the Continuing Review:

- o Serious adverse events that are considered expected (such as COVID-19 related hospitalization)
- o Serious adverse events that are considered not related to the study drug, whether the event is expected or not;
- o Non-serious adverse events, whether expected or not.

### **Reporting External (Non-Site) Serious Adverse Events to Site Institutional REB**

An external serious adverse event is an SAE experienced by a research participant enrolled in a multi-centre trial at others participating sites. The Site shall report external SAEs to their REB only if a determination has been made that the external SAE meets **all** the criteria of an unanticipated problem (i.e., unexpected and related or possibly related to the research) and requires a change to the protocol and/or consent form and/or requires immediate notification to research participants for safety reasons as recommended by the DMSC.

In the case that there are unexpected external SAEs that are unexpected and related or possibly related to the research study and requires a change to the protocol and/or consent form and/or requires immediate notification to research participants for safety reasons, Sponsor-PI or designee shall inform all participating sites.

Site will then be required to submit these SAEs to their REB no later than **fifteen (15) days** after receipt. The SAEs reporting should also include at a minimum a Sponsor-PI analysis of the significance of the event or an analysis from the DSMB, with (where appropriate) a discussion of previous similar events, and a position statement as to whether any changes are required to the approved documents.

## 9. Withdrawing Participants from the Study

If a participant withdraws from the study, record this in the eCRF by completing the “End of Study Treatment and/or End of Study/Termination” form and indicating the reason for premature discontinuation from the study.

Participant withdrawal should also be noted in the participant’s research chart in the form of a Note to File. Reasons for withdrawal include participant death, loss to follow-up, treatment failure, intolerance to study drug, or unwillingness to participate.

## 10. Participant Death

All participant deaths must be reported in the eCRF, including the cause of death are considered reportable SAEs and must be reported to the Sponsor and AHRC within 24 hours of learning of the event. Please refer to the SAE reporting section above for details. Upon death, in the eCRF the SAE, Death and End of Study forms will be completed and the reason for premature discontinuation from the study will be reported as “death”.

Due diligence should be made to obtain a death certificate and/or autopsy report of the deceased individual (if possible). Copies of the de-identifying and redacted death certificates and autopsy reports should be forwarded to the DCC for review by the Medical Monitor (as required), and the originals maintained in the participant’s research chart.

## 11. Participants Lost to Follow-up

The research coordinator should perform due diligence to contact participants who miss scheduled follow-up visits. In the event that a participant is lost to follow-up the research coordinator will record this information in the participant research chart. Additionally, this should be captured in the eCRF by completing the “End of Study Treatment” and/or “End of Study/Termination” form and indicating the reason for premature termination from the study as “lost to follow-up”.

## 12. Study Completion

When the participant completes the final study visit or withdraws from the study, the research coordinator should document this in the eCRF. The “End of Study/Termination” form will be completed indicating that the participant has completed the study.

## 13. Protocol Deviations

Adherence to the CanTreatCOVID procedures as stipulated in the protocol will be tracked in the Protocol Deviation Log in the eCRF.

## 14. Source Documents

The signed ICF (if completed via email) must be maintained on site or the signed e-consent should be retained on the database. Source data must be made available for perusal by representative(s) of the Sponsor upon request/during a monitoring visit.

A list of source documents that should be retained in the participant’s file includes but not limited to are:

- Copy of Participant ICF (signed) and Informed Consent Process Checklist, if consent is obtained via email

- A copy of the positive COVID-19 test (Rapid Antigen Test or Polymerase Chain Reaction Test)
- A copy of the medication log received from participant's local pharmacy
- Receipt of Study treatment dispensed to Participant
- CanTreatCOVID Logs
- Pharmacist email confirmation if participant is taking or added any new contraindicating concomitant medication during the course of the trial.
- Any occurring SAE documentation and notes

## 15. Records Retention

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. The investigator's study file will contain the protocol/amendments, Ethics Review Board and governmental approval (if required) with correspondence, sample informed consent, staff curriculum vitae and authorization forms and other appropriate documents/correspondence.

Should the investigator wish to assign the study records to another party or move them to another location, the DCC must be notified in advance.

Where source documents are required for the continued care of the patient, appropriate copies should be made.

Trial records should be stored as per local requirements or for *15 years* after the completion of the trial, whichever is longer.

The DCC will transfer the Investigator Site File and study documents to the Sponsor at the end of the trial and additionally house all trial records for *15 years* after the study completion.

## 16. Monitoring

The AHRC will be responsible for the remote monitoring of participating study sites. The AHRC is committed to ensuring that this study is appropriately monitored to ensure adherence to the protocol, Good Clinical Practice, relevant SOPs, operational manuals, local requirements, and Health Canada requirements. Additional details of the Monitoring aspects is detailed in the Monitoring Plan.

### 16.1 Overview of Monitoring plan

Type of Monitoring Visit	Occurrence	What will be reviewed?
Source Data Verification	10% of randomized patients at each Hub	<ul style="list-style-type: none"> <li>▪ accuracy and completeness of eCRF</li> <li>▪ source verification of critical data variables</li> </ul>

Interim Monitoring Visit	Scheduled after 5 participants are randomized	<ul style="list-style-type: none"> <li>Review of Investigator Site File and IP accountability</li> <li>Participant records of Informed consent, eligibility, safety and critical data variables</li> </ul>
Close Out Visit	Scheduled after all participants have completed study assessments and all data entered into the eCRF	<ul style="list-style-type: none"> <li>Source data verification before database lock</li> </ul>
For-Cause Monitoring	Scheduled at anytime mainly due to data quality issues	<ul style="list-style-type: none"> <li>Will check for data quality issues</li> <li>100% Source data verification</li> </ul>

## 17. Data Entry Guidelines

### 17.1 Electronic Case Report Forms (eCRFs)

Electronic data capture will be used for this trial, meaning that all study data will be entered in electronic case report forms (eCRFs) at the investigational site. Data collection will be completed by authorized study site personnel designated by the Investigator. Appropriate training and security measures will be completed with the Investigator and all authorized study site personnel prior to the study being initiated and any data being entered into the system for any study subjects.

The study data will be housed on a secure in-house server at St. Michael's Hospital in Toronto, Canada throughout the duration of the study, and up to 10 years after the study is complete. An encrypted CD of the tabulated study data will be stored by the Sponsor for 15 years after completion of the study.

The CRFs must be kept in order and up-to-date so that they always reflect the latest observations on the participants enrolled in the study. Data will be entered into the eCRF within 5 days of data collection.

### 17.2 REDCap Academic Data Entry Guidelines

These guidelines have been compiled to assist with the data entry process for the [CanTreatCOVID] study. They provide an overview of what to expect as navigating through the forms that have been created for this study.

In order to access the REDCap™ database, it is required to have an account. An account activation form, has to be submitted to the Project Manager at the Applied Health Research Centre (AHRC). Once granted access to the study, a username and a generic password will be assigned, which will be prompted to change upon logging in for the first time.



**REDCap™**

**Log In**

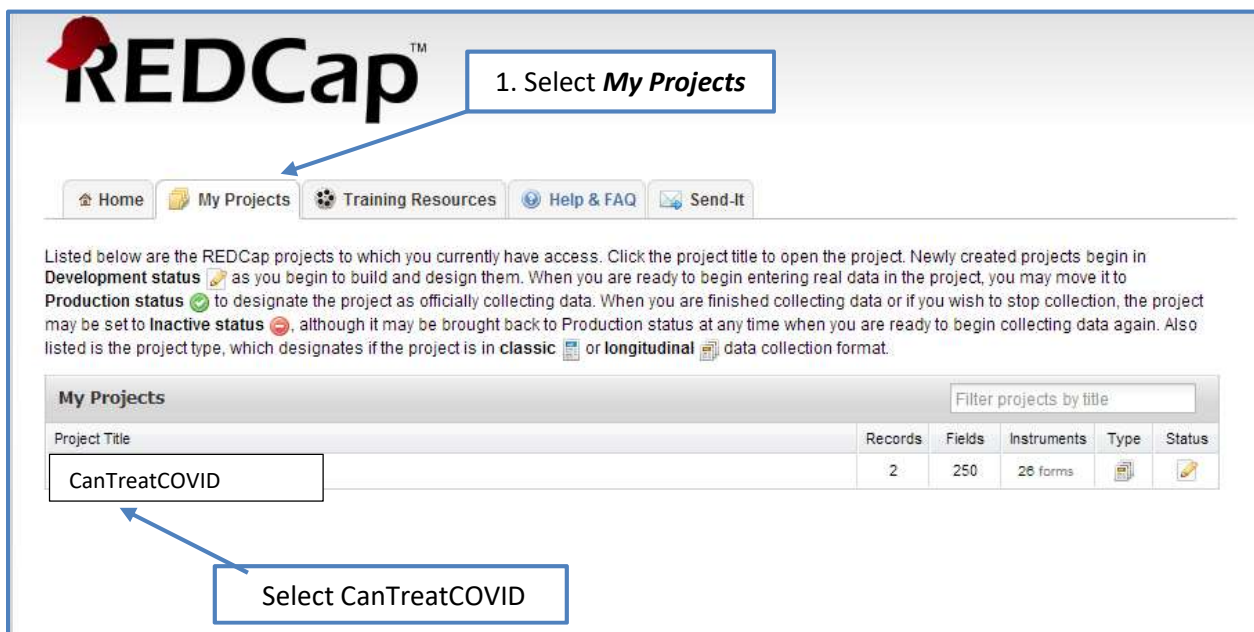
Please log in with your user name and password. If you are having trouble logging in, please contact [Chris Ducharme](#).

1. Enter username → Username:

Password:  ← 2. Enter password

[Forgot your password?](#)

Once logged on to REDCap™, 2 Factor authentication will be required to enter the database. Navigate to the **My Projects** tab and select **[CanTreatCOVID]**.



**REDCap™**

1. Select **My Projects**

Home My Projects Training Resources Help & FAQ Send-It

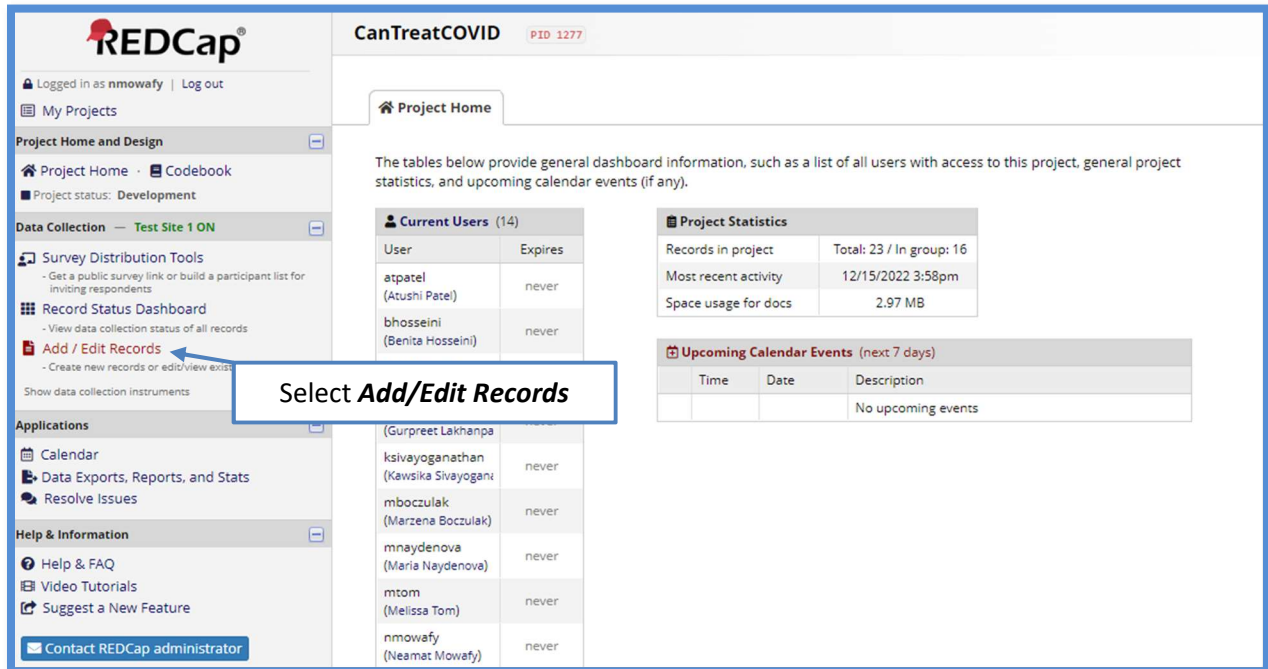
Listed below are the REDCap projects to which you currently have access. Click the project title to open the project. Newly created projects begin in **Development status** as you begin to build and design them. When you are ready to begin entering real data in the project, you may move it to **Production status** to designate the project as officially collecting data. When you are finished collecting data or if you wish to stop collection, the project may be set to **Inactive status**, although it may be brought back to Production status at any time when you are ready to begin collecting data again. Also listed is the project type, which designates if the project is in **classic** or **longitudinal** data collection format.

**My Projects**

Project Title	Records	Fields	Instruments	Type	Status
CanTreatCOVID	2	250	26 forms		

Select CanTreatCOVID

To add new subjects or to see a list of subjects that have already been entered into the database, click on **Add/Edit Records** from the **Data Collection** panel on the left hand side of the screen.



**REDCap** CanTreatCOVID PID 1277

Logged in as nmowafy | Log out

My Projects

**Project Home and Design**

- Project Home
- Codebook
- Project status: Development

**Data Collection — Test Site 1 ON**

- Survey Distribution Tools
- Record Status Dashboard
- Add / Edit Records**

**Current Users (14)**

User	Expires
atpatel (Atushi Patel)	never
bhosseini (Benita Hosseini)	never
(Gurpreet Lakhana)	
ksivayoganathan (Kawsika Sivayogani)	never
mboczulak (Marzena Boczulak)	never
mnaydenova (Maria Naydenova)	never
mtom (Melissa Tom)	never
nmowafy (Neamat Mowafy)	never

**Project Statistics**

Records in project	Total: 23 / In group: 16
Most recent activity	12/15/2022 3:58pm
Space usage for docs	2.97 MB

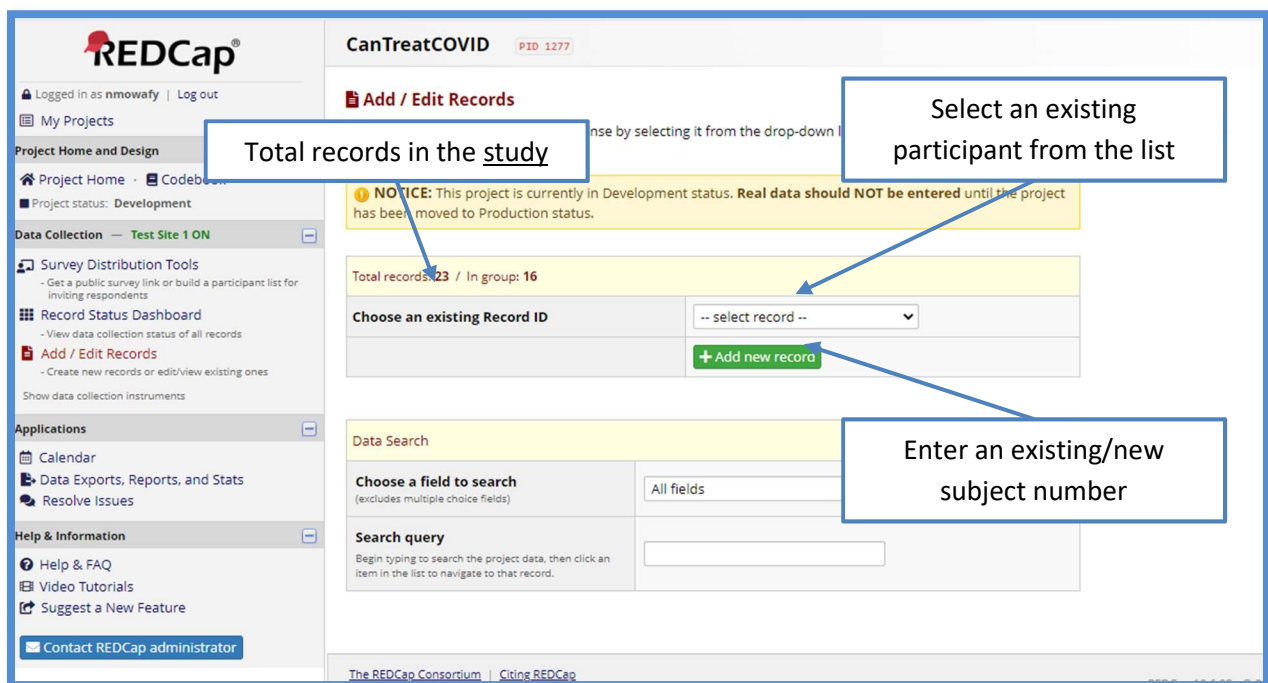
**Upcoming Calendar Events (next 7 days)**

Time	Date	Description
		No upcoming events

**Select Add/Edit Records**

Note that the **Total records** on the **Add/Edit Records** screen indicates the total number of subjects that have been entered in the database for the study, not the total number of subjects for the site. However, data is only viewable for the site(s) that access is granted.

Add a new subject to the database by entering a new subject number. Subject numbers are assigned in consecutive order. Modify existing records by selecting the subject number from the drop-down list or manually entering their subject number.



**REDCap** CanTreatCOVID PID 1277

Logged in as nmowafy | Log out

My Projects

**Project Home and Design**

- Project Home
- Codebook
- Project status: Development

**Data Collection — Test Site 1 ON**

- Survey Distribution Tools
- Record Status Dashboard
- Add / Edit Records**

**Add / Edit Records**

Choose an existing Record ID: -- select record --

**Total records in the study**: 23 / In group: 16

**Select an existing participant from the list**

**Enter an existing/new subject number**

**NOTICE**: This project is currently in Development status. Real data should NOT be entered until the project has been moved to Production status.

**Data Search**

Choose a field to search: All fields

Search query: [ ]

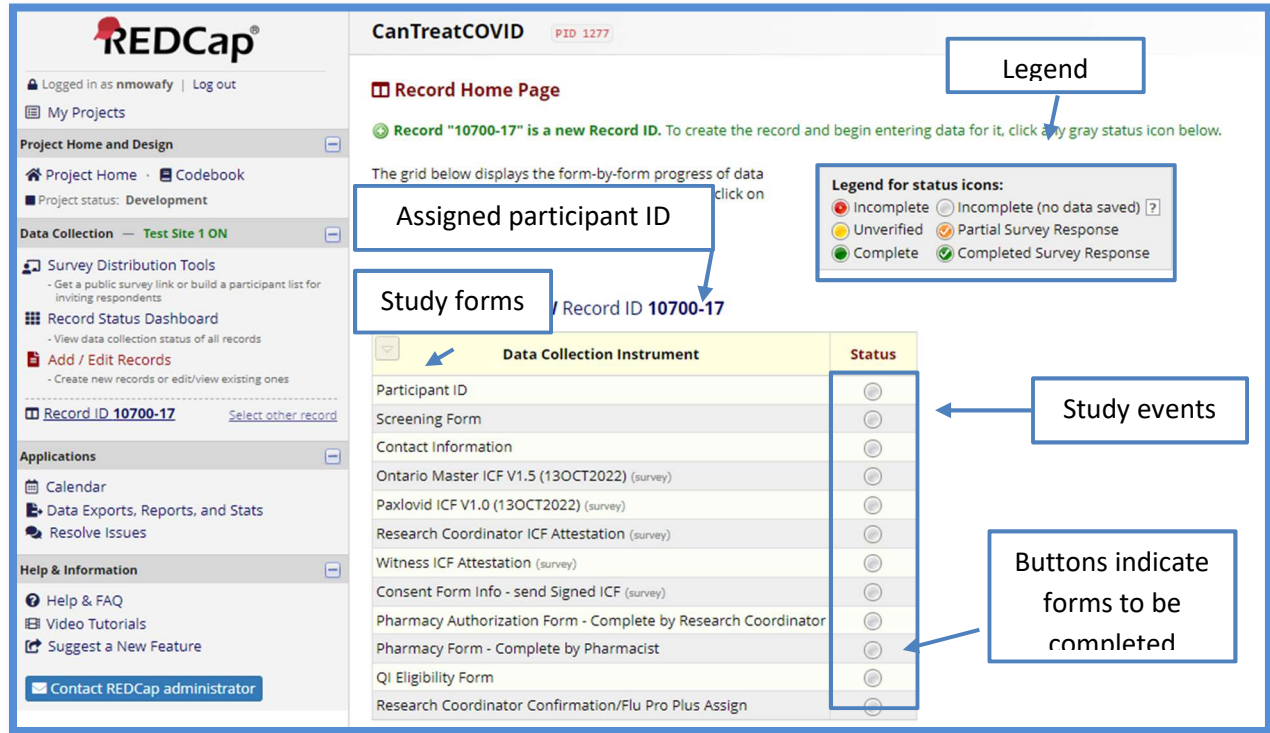
**Total records in the study**

**Select an existing participant from the list**

**Enter an existing/new subject number**

Upon entering or selecting a subject number, the page will be redirected to the subject's **Event Grid**, which displays all of the forms to be completed for each of the study events.

Each of the study events are listed horizontally across the top of the grid, while forms to be completed are listed vertically along the left hand side. Coloured buttons indicate the completion status for each form. Accessing any of the forms can be done by clicking on the corresponding button.



**REDCap**  
CanTreatCOVID P1D 1277

Record Home Page  
Record "10700-17" is a new Record ID. To create the record and begin entering data for it, click on any gray status icon below.

The grid below displays the form-by-form progress of data

**Legend**

**Legend for status icons:**

- Incomplete
- Incomplete (no data saved)
- Unverified
- Partial Survey Response
- Complete
- Completed Survey Response

**Assigned participant ID** / Record ID 10700-17

**Study forms**

Data Collection Instrument	Status
Participant ID	<input type="radio"/>
Screening Form	<input type="radio"/>
Contact Information	<input type="radio"/>
Ontario Master ICF V1.5 (13OCT2022) (survey)	<input type="radio"/>
Paxlovid ICF V1.0 (13OCT2022) (survey)	<input type="radio"/>
Research Coordinator ICF Attestation (survey)	<input type="radio"/>
Witness ICF Attestation (survey)	<input type="radio"/>
Consent Form Info - send Signed ICF (survey)	<input type="radio"/>
Pharmacy Authorization Form - Complete by Research Coordinator	<input type="radio"/>
Pharmacy Form - Complete by Pharmacist	<input type="radio"/>
QI Eligibility Form	<input type="radio"/>
Research Coordinator Confirmation/Flu Pro Plus Assign	<input type="radio"/>

**Study events**

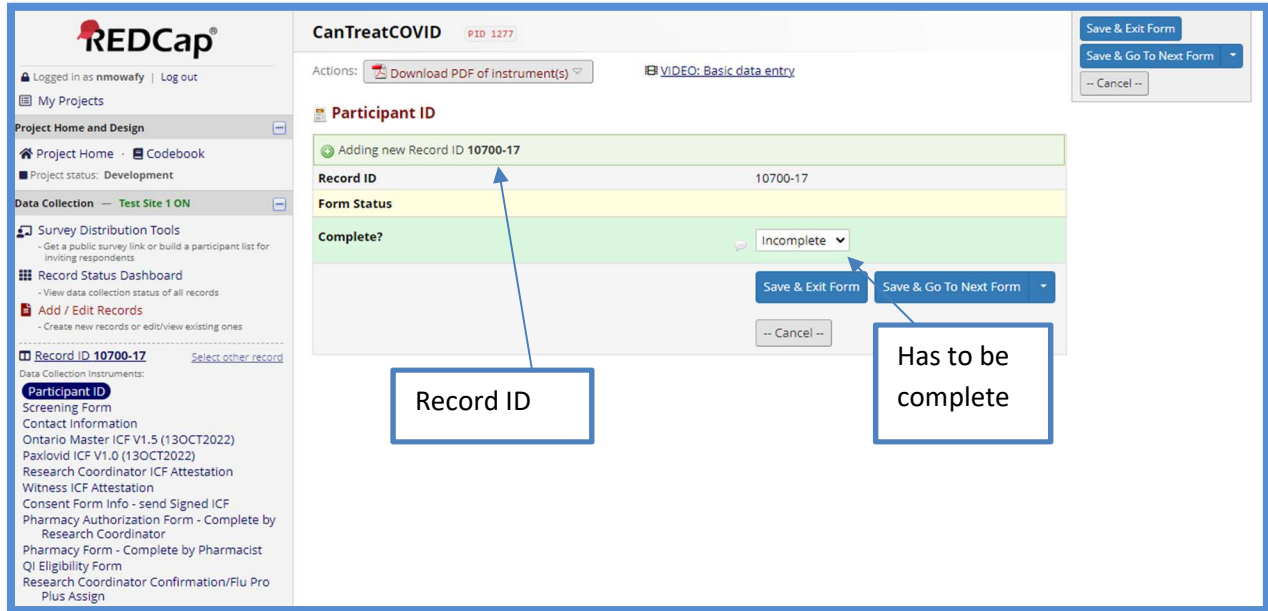
**Buttons indicate forms to be completed**

To begin data entry for a subject, click on the button corresponding to the **[Form Name]** form underneath the **[Event Name]** heading. This will bring you to the first form to be completed.



## 1. [Participant ID Form]

The Participant ID form, displays the Record ID [new record].  
Select Complete and then Save To Go to the Next Form.

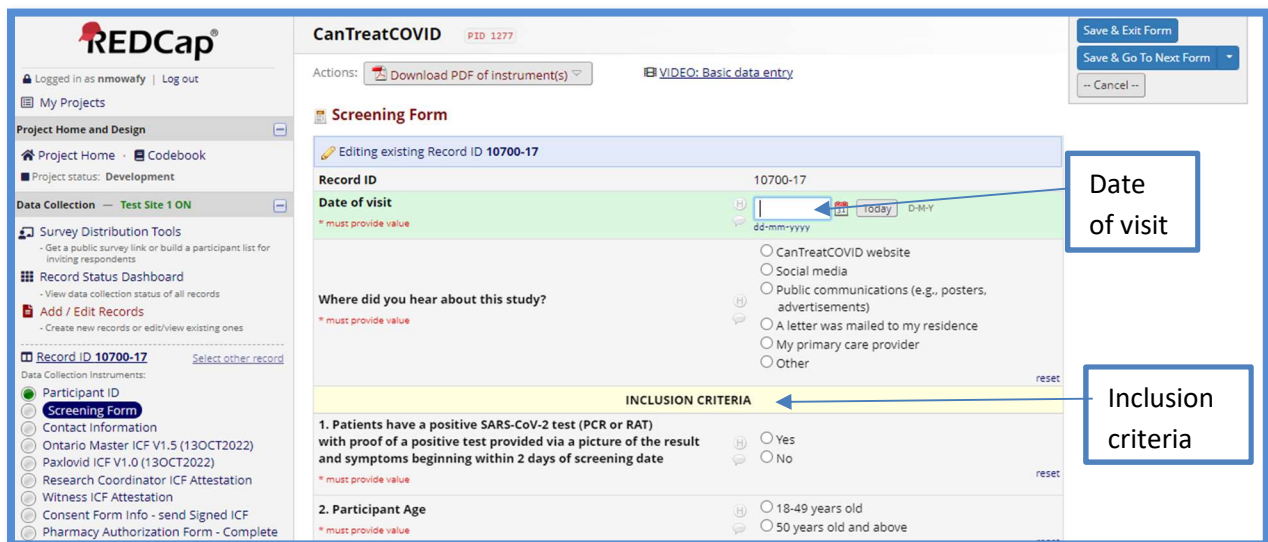


The screenshot shows the REDCap interface for the 'Participant ID' form. The record ID is 10700-17. The 'Form Status' is 'Incomplete'. A dropdown menu is open, showing 'Incomplete' selected. Below the dropdown are buttons for 'Save & Exit Form', 'Save & Go To Next Form', and '-- Cancel --'. A callout box labeled 'Record ID' points to the record ID field. Another callout box labeled 'Has to be complete' points to the 'Save & Go To Next Form' button.

## 2. [Screening Form]

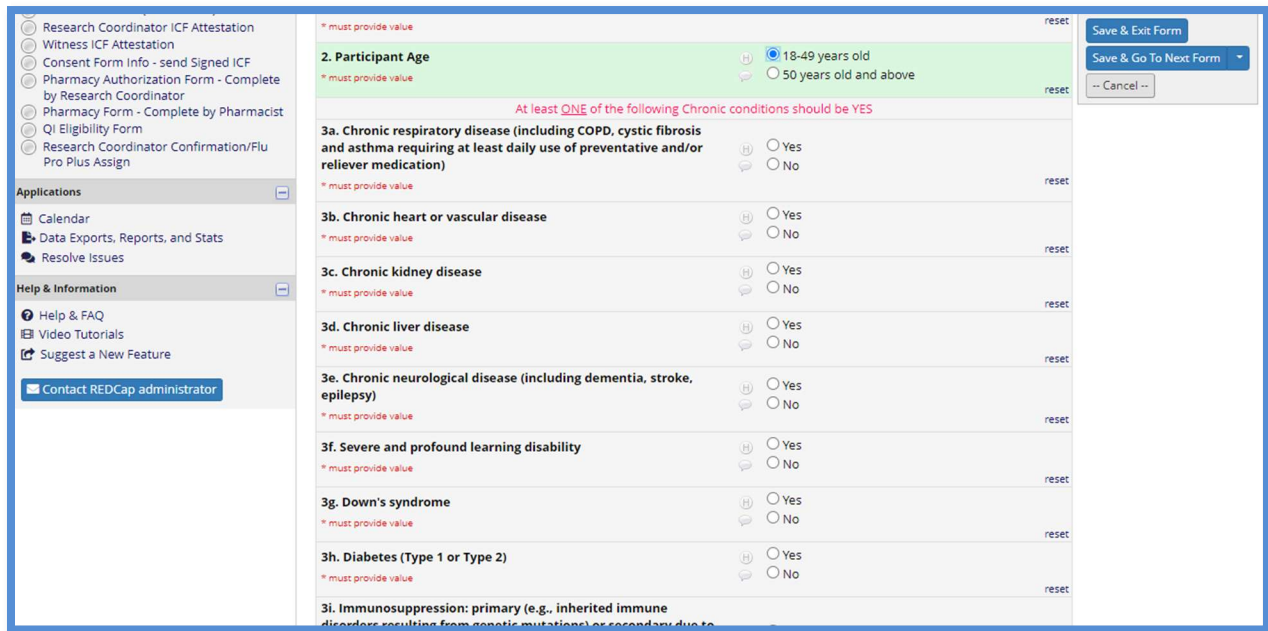
Enter the date of visit, and how the participant hear about the study.

Inclusion Criteria questions should be asked of the participant



The screenshot shows the REDCap interface for the 'Screening Form'. The record ID is 10700-17. The 'Date of visit' field is highlighted with a callout box labeled 'Date of visit'. Below it is a radio button question: 'Where did you hear about this study?'. Below that is the 'INCLUSION CRITERIA' section, which is highlighted with a callout box labeled 'Inclusion criteria'. The first criterion is: '1. Patients have a positive SARS-CoV-2 test (PCR or RAT) with proof of a positive test provided via a picture of the result and symptoms beginning within 2 days of screening date'. The second criterion is: '2. Participant Age'. The form includes buttons for 'Save & Exit Form', 'Save & Go To Next Form', and '-- Cancel --'.

If the participant age is 18-49 at least one of the chronic conditions should to be met

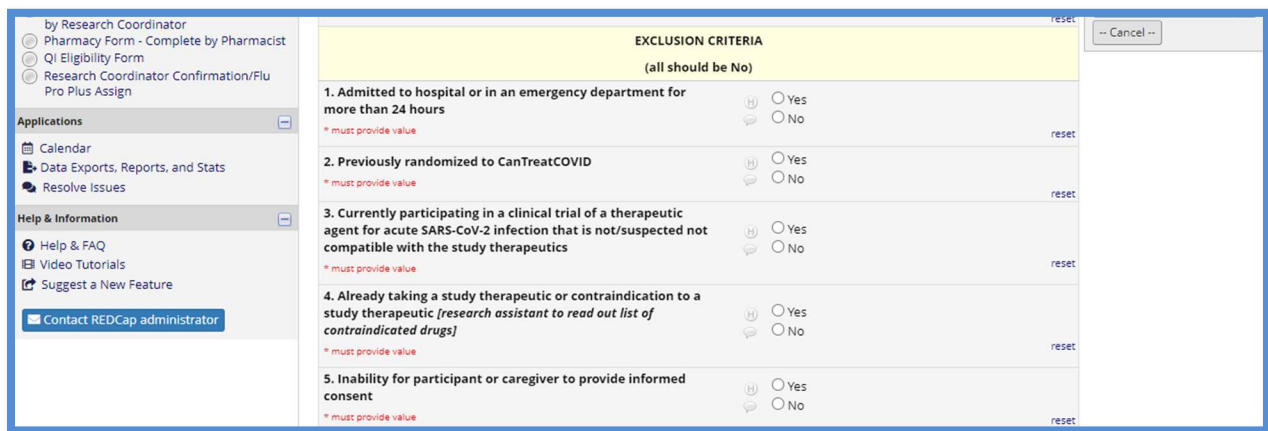


The screenshot shows a web-based form with a left-hand navigation menu and a main content area. The navigation menu includes sections for 'Applications' (Calendar, Data Exports, Reports, and Stats, Resolve Issues) and 'Help & Information' (Help & FAQ, Video Tutorials, Suggest a New Feature, Contact REDCap administrator). The main content area contains several questions:

- 2. Participant Age**: Radio buttons for '18-49 years old' (selected) and '50 years old and above'. A note below states: "At least ONE of the following Chronic conditions should be YES".
- 3a. Chronic respiratory disease (including COPD, cystic fibrosis and asthma requiring at least daily use of preventative and/or reliever medication)**: Radio buttons for 'Yes' and 'No'.
- 3b. Chronic heart or vascular disease**: Radio buttons for 'Yes' and 'No'.
- 3c. Chronic kidney disease**: Radio buttons for 'Yes' and 'No'.
- 3d. Chronic liver disease**: Radio buttons for 'Yes' and 'No'.
- 3e. Chronic neurological disease (including dementia, stroke, epilepsy)**: Radio buttons for 'Yes' and 'No'.
- 3f. Severe and profound learning disability**: Radio buttons for 'Yes' and 'No'.
- 3g. Down's syndrome**: Radio buttons for 'Yes' and 'No'.
- 3h. Diabetes (Type 1 or Type 2)**: Radio buttons for 'Yes' and 'No'.
- 3i. Immunosuppression: primary (e.g., inherited immune disorders resulting from genetic mutations) or secondary due to**: Radio buttons for 'Yes' and 'No'.

Each question has a 'reset' button on the right. The form also includes 'Save & Exit Form', 'Save & Go To Next Form', and 'Cancel' buttons.

For the Master Protocol Exclusion Criteria – all questions should be NO for the participant to be eligible for the trial



The screenshot shows a web-based form titled 'EXCLUSION CRITERIA (all should be No)'. The left-hand navigation menu is similar to the previous screenshot. The main content area contains five exclusion criteria questions:

- 1. Admitted to hospital or in an emergency department for more than 24 hours**: Radio buttons for 'Yes' and 'No'.
- 2. Previously randomized to CanTreatCOVID**: Radio buttons for 'Yes' and 'No'.
- 3. Currently participating in a clinical trial of a therapeutic agent for acute SARS-CoV-2 infection that is not/suspected not compatible with the study therapeutics**: Radio buttons for 'Yes' and 'No'.
- 4. Already taking a study therapeutic or contraindication to a study therapeutic [research assistant to read out list of contraindicated drugs]**: Radio buttons for 'Yes' and 'No'.
- 5. Inability for participant or caregiver to provide informed consent**: Radio buttons for 'Yes' and 'No'.

Each question has a 'reset' button on the right. The form also includes a 'Cancel' button.

Additionally, for the Paxlovid specific Exclusion Criteria – all questions should be NO to include patient into trial

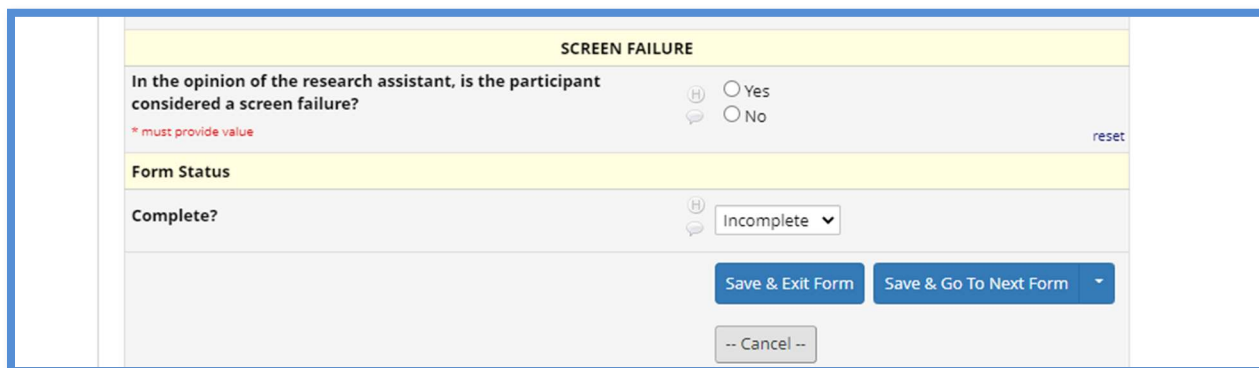
PAXLOVID		EXCLUSION CRITERIA	(all should be No)
6. History of clinically significant hypersensitivity to the active substances in Paxlovid™ (nirmatrelvir/ritonavir) or to any of its excipients	<input type="radio"/> Yes <input type="radio"/> No	reset	
7. Known rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption	<input type="radio"/> Yes <input type="radio"/> No	reset	
8. Current severe liver impairment (characterized by severe ascites, encephalopathy, jaundice, or prolonged INR). People with liver disease without any of these features are eligible	<input type="radio"/> Yes <input type="radio"/> No	reset	
9. Moderate or severe renal disease (defined as CKD stage 3, 4 or 5 or current acute kidney injury or most recent eGFR in the past 6 months <60 ml/min)	<input type="radio"/> Yes <input type="radio"/> No	reset	
10. Currently taking Paxlovid™	<input type="radio"/> Yes <input type="radio"/> No	reset	
11. Has a known or suspected pregnancy	<input type="radio"/> Yes <input type="radio"/> No	reset	
12. Breastfeeding	<input type="radio"/> Yes <input type="radio"/> No	reset	
13. Is of childbearing potential and is not willing to use a highly effective contraceptive	<input type="radio"/> Yes <input type="radio"/> No	reset	

[REDCap Academic – Version #1] Screening Form - Paxlovid Exclusion 8 + 9 (for chronic kidney or liver dysfunction)

Note added "if needed obtain copy of lab results or written documentation from family care provider confirming participant's eligibility "

7. Known rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption	<input type="radio"/> Yes <input type="radio"/> No	reset	
8. Current severe liver impairment (characterized by severe ascites, encephalopathy, jaundice, or prolonged INR). People with liver disease without any of these features are eligible	<input type="radio"/> Yes <input type="radio"/> No	reset	
<i>NOTE: (if needed obtain copy of lab results or written documentation from family care provider confirming participant's eligibility)</i>			
9. Moderate or severe renal disease (defined as CKD stage 3, 4 or 5 or current acute kidney injury or most recent eGFR in the past 6 months < 60 ml/min)	<input type="radio"/> Yes <input type="radio"/> No	reset	
<i>NOTE: (if needed obtain copy of lab results or written documentation from family care provider confirming participant's eligibility)</i>			
10. Currently taking Paxlovid™	<input type="radio"/> Yes <input type="radio"/> No	reset	
11. Has a known or suspected pregnancy	<input type="radio"/> Yes <input type="radio"/> No	reset	

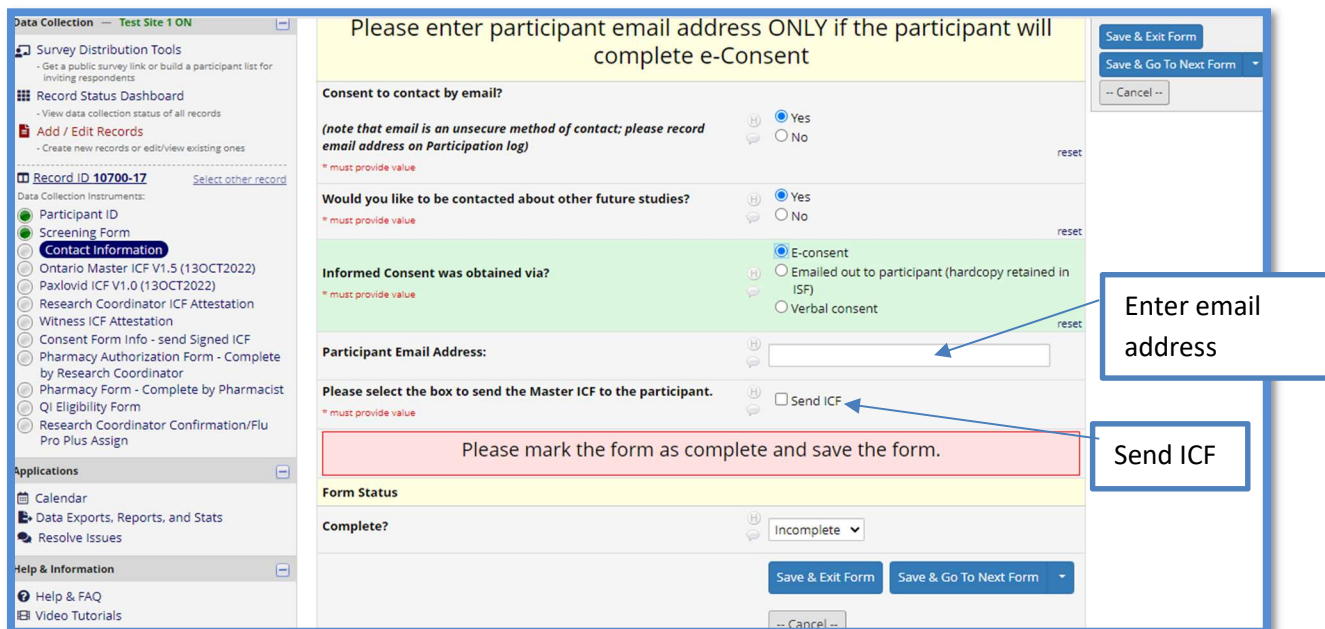
If any of Inclusion Criteria is not met, OR any of Master protocol OR Paxlovid Exclusion criteria is met the participant is deemed ineligible and considered a Screen failure. The participant should not be randomized into the trial



### 3.[Contact information]

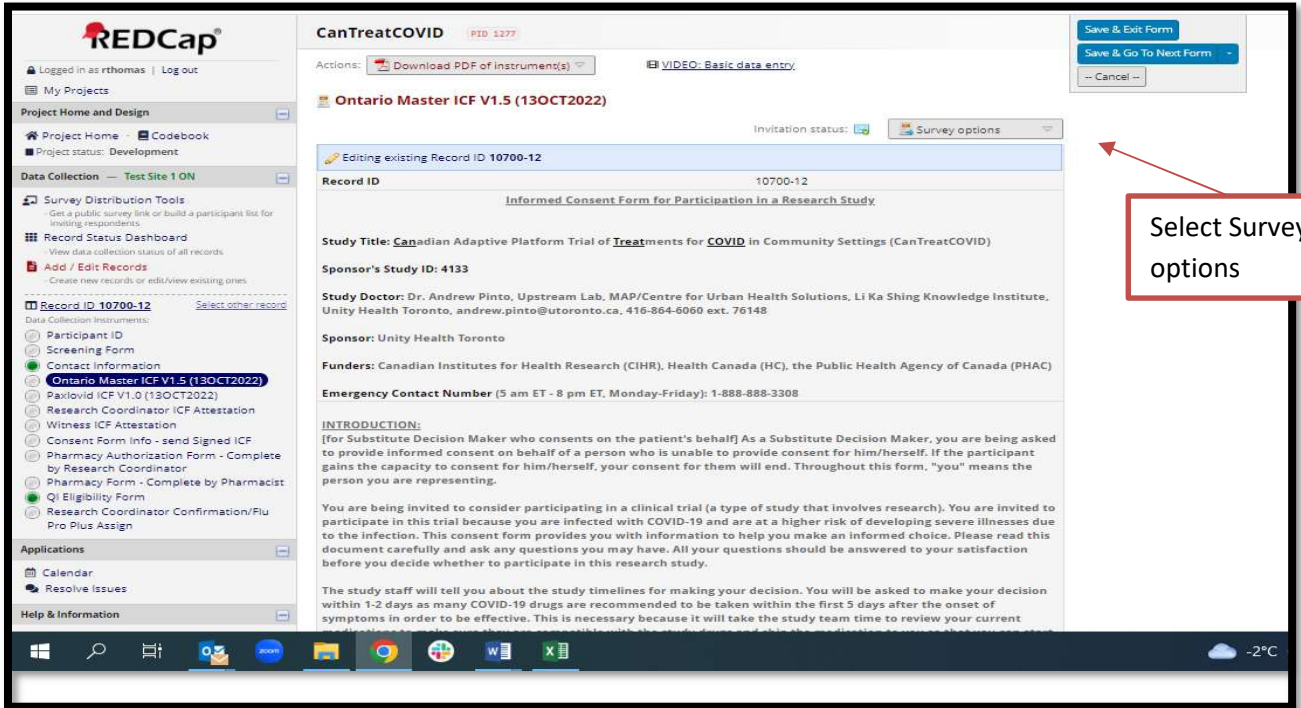
- i. Enter the participant email address if the participant will complete E-consent module on REDCap

**Select the box to Send ICF (as the system automatically emails the ICFs) to the participant**

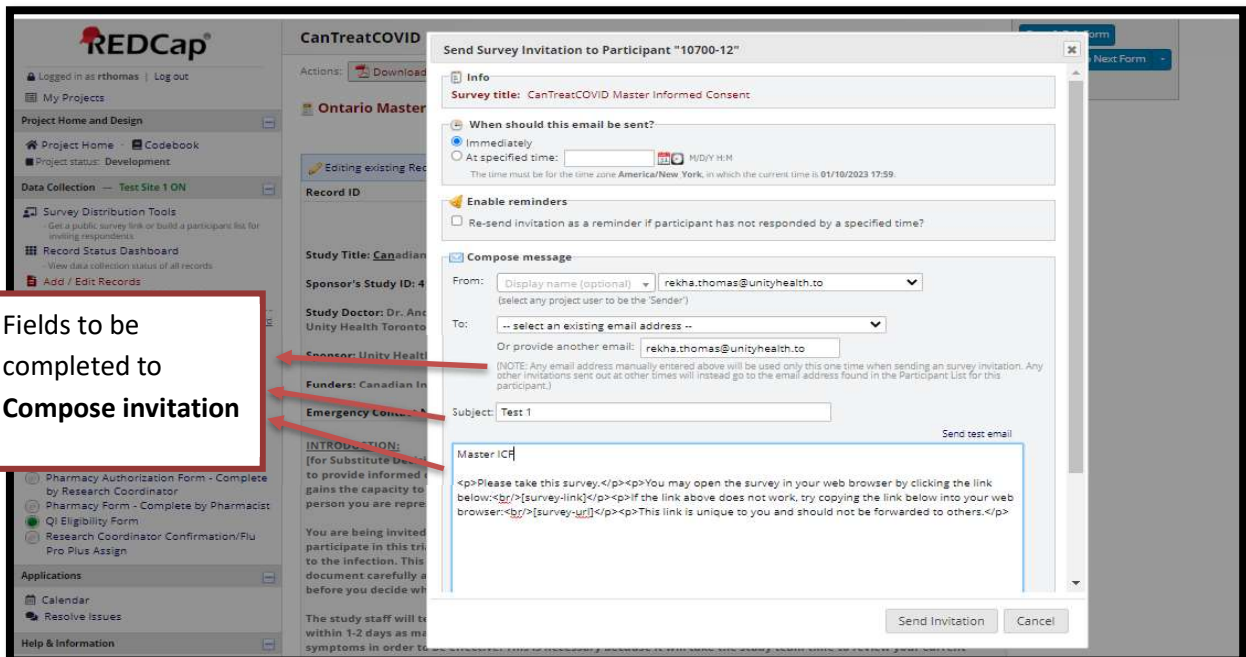


**Note:** If an incorrect email was initially entered then each ICF has to be sent to the participant as a Survey Invitation.

- Go to *Survey Options* and select '*Compose survey invitation*'

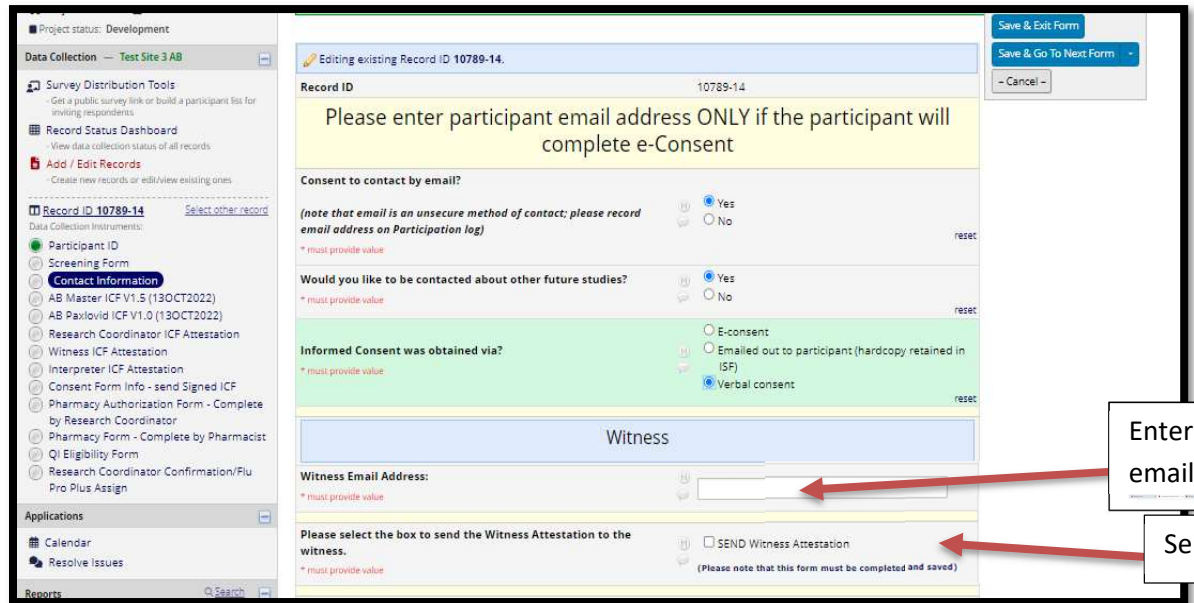


Compose the invitation by inputting the fields:  
*To (provide another email), Subject, Email description* and Send Invitation



Now repeat the same steps to send the **Paxlovid Informed Consent Form** to the Participant

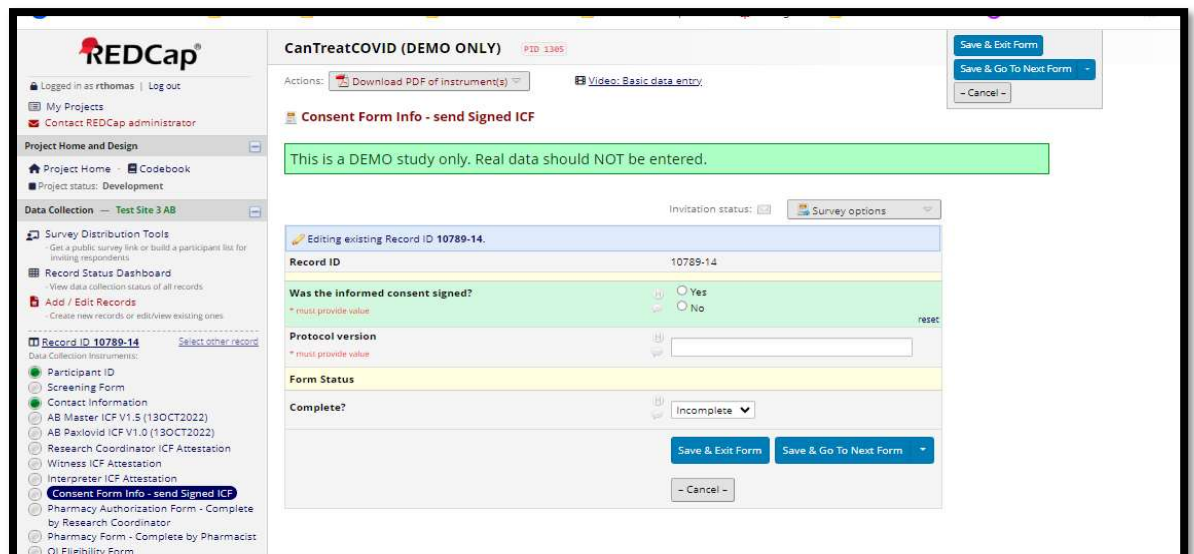
- ii. If informed consent will be obtained via **“Emailing Out”** to the participant’ the email address does not need to be entered in the database. Instead, a softcopy of the ICFs should be emailed out to the participant and a signed copy (including participant and coordinator signature) and Informed Consent Checklist should be retained in the Investigator Site file.
- iii. If informed consent is obtained via **‘Verbal Consent’**, the Witness Attestation form needs to be completed  
Note: Remember to Save the Contact Information page in order for the Witness Attestation form to be visible



**Enter witness email address**

**Select ‘Send’**

- iv. **Consent Form Info – send Signed ICF**  
If Emailed out or Verbal Consent option is selected for Informed Consent was obtained via? (eCRF Consent Information) then the PDFs will not upload in the Consent Form Info eCRF as there participant signed ICFs are not completed via the database



- v. Interpreter  
If Yes, for Interpreter translation then enter Interpreter email address and select Send the Interpreter attestation

#### 4. [Ontario Master ICF] [Paxlovid ICF]

When the Participants opens the email link to the ICFs, they are to select if the participant or substitute decision maker will sign the Informed consent form. The 'Add Signature' should be selected to provide a signature to the form.

## 5. [Research Coordinator ICF Attestation]

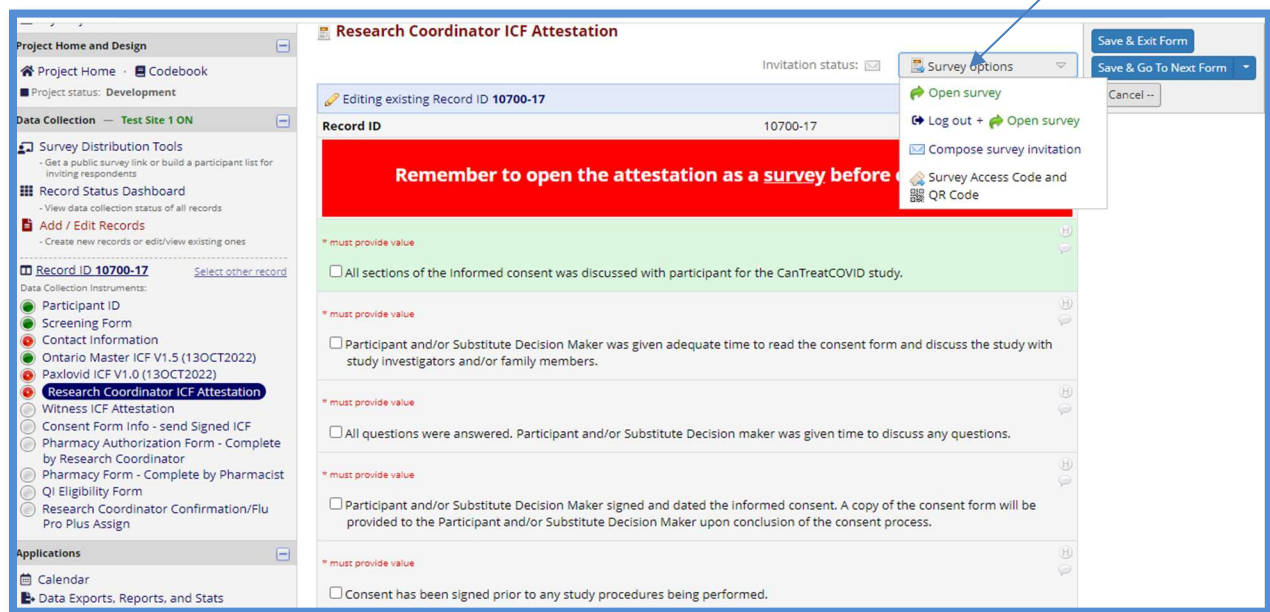
The Research Coordinator ICF Attestation is completed directly on the database.

Click 'Survey options' from the drop down list on the right upper corner and open the attestation as a survey

The Research Coordination Attestation should only be completed for e-consent and verbal consent modules.

If the ICF is emailed out to the participant, the signed ICFs and completed Informed Consent Checklist should be retained in the Investigator site file

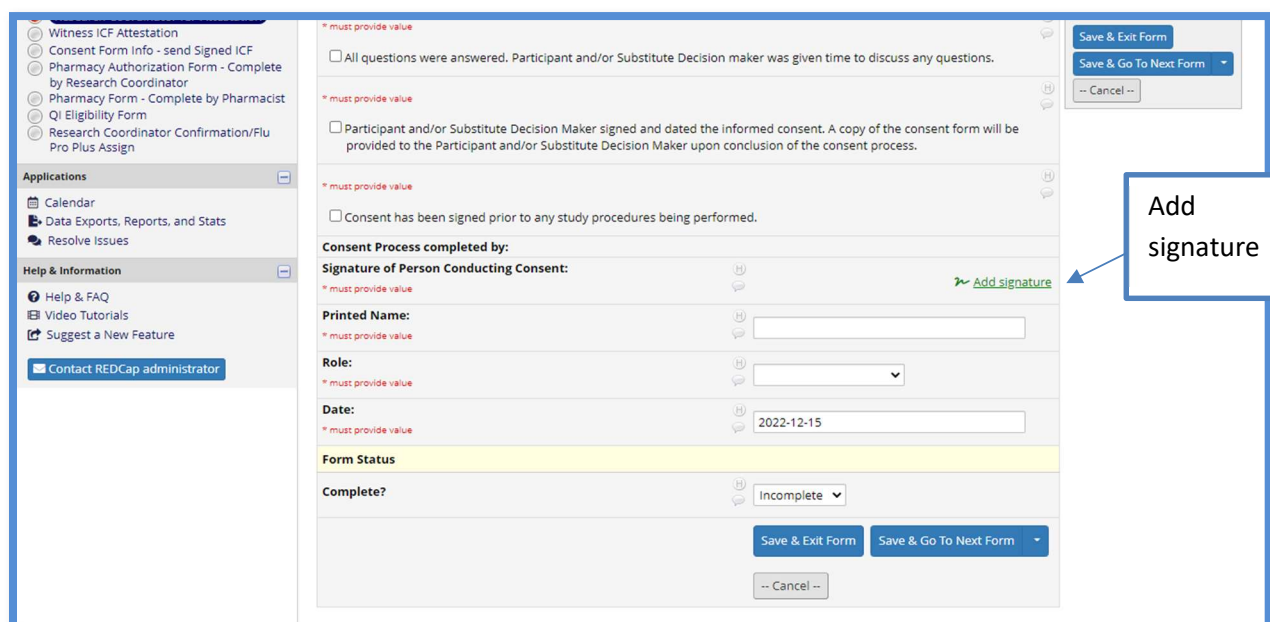
Open attestation survey from here



The screenshot shows the 'Research Coordinator ICF Attestation' form in a web application. On the left is a navigation sidebar with sections like 'Project Home and Design', 'Data Collection', and 'Record ID 10700-17'. The main content area shows the form title and a red banner that reads 'Remember to open the attestation as a survey before'. A dropdown menu is open in the top right corner, showing options: 'Survey options', 'Open survey', 'Log out + Open survey', 'Compose survey invitation', and 'Survey Access Code and QR Code'. The form itself contains several checklist items, each with a red asterisk indicating a required field. The items are:
 

- All sections of the Informed consent was discussed with participant for the CanTreatCOVID study.
- Participant and/or Substitute Decision Maker was given adequate time to read the consent form and discuss the study with study investigators and/or family members.
- All questions were answered. Participant and/or Substitute Decision maker was given time to discuss any questions.
- Participant and/or Substitute Decision Maker signed and dated the Informed consent. A copy of the consent form will be provided to the Participant and/or Substitute Decision Maker upon conclusion of the consent process.
- Consent has been signed prior to any study procedures being performed.

 At the top right of the form, there are buttons for 'Save & Exit Form', 'Save & Go To Next Form', and 'Cancel --'.



This screenshot shows the lower portion of the 'Research Coordinator ICF Attestation' form. The navigation sidebar on the left is partially visible. The main content area shows the signature section, which includes:
 

- A checklist item: 'All questions were answered. Participant and/or Substitute Decision maker was given time to discuss any questions.'
- Another checklist item: 'Participant and/or Substitute Decision Maker signed and dated the informed consent. A copy of the consent form will be provided to the Participant and/or Substitute Decision Maker upon conclusion of the consent process.'
- A third checklist item: 'Consent has been signed prior to any study procedures being performed.'
- A section titled 'Consent Process completed by:' containing:
  - 'Signature of Person Conducting Consent:' with a text input field and a green 'Add signature' link.
  - 'Printed Name:' with a text input field.
  - 'Role:' with a dropdown menu.
  - 'Date:' with a text input field containing '2022-12-15'.
- A section titled 'Form Status' with a 'Complete?' dropdown menu set to 'Incomplete'.

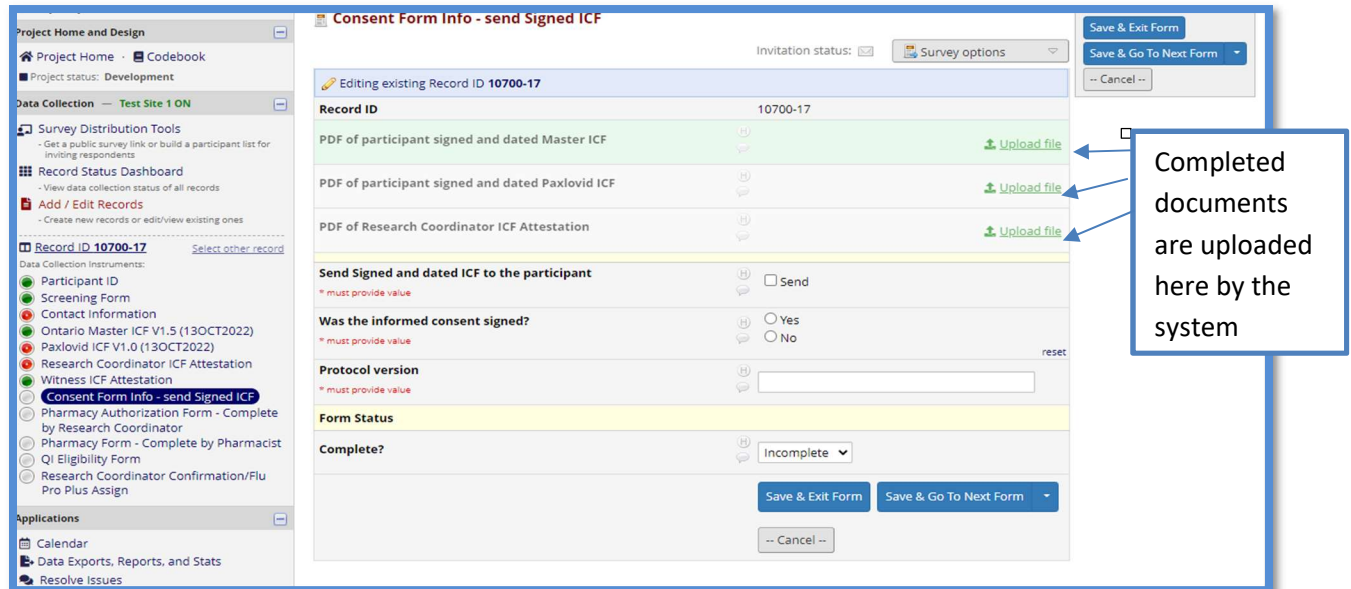
 At the bottom right, there are buttons for 'Save & Exit Form', 'Save & Go To Next Form', and 'Cancel --'.

Add signature



## 6. [Consent Form Info]

Once the ICFs are signed by the Participant and Research Coordinator Attestation is completed the system will upload the respective PDFs of the Master and Paxlovid ICF, and RC ICF attestation.



**Consent Form Info - send Signed ICF**

Invitation status: [icon] Survey options [dropdown]

Editing existing Record ID 10700-17

Record ID	10700-17
PDF of participant signed and dated Master ICF	[icon] Upload file
PDF of participant signed and dated Paxlovid ICF	[icon] Upload file
PDF of Research Coordinator ICF Attestation	[icon] Upload file

**Send Signed and dated ICF to the participant**  
\* must provide value [input] Send

**Was the informed consent signed?**  
\* must provide value [radio] Yes [radio] No

**Protocol version**  
\* must provide value [input]

**Form Status**

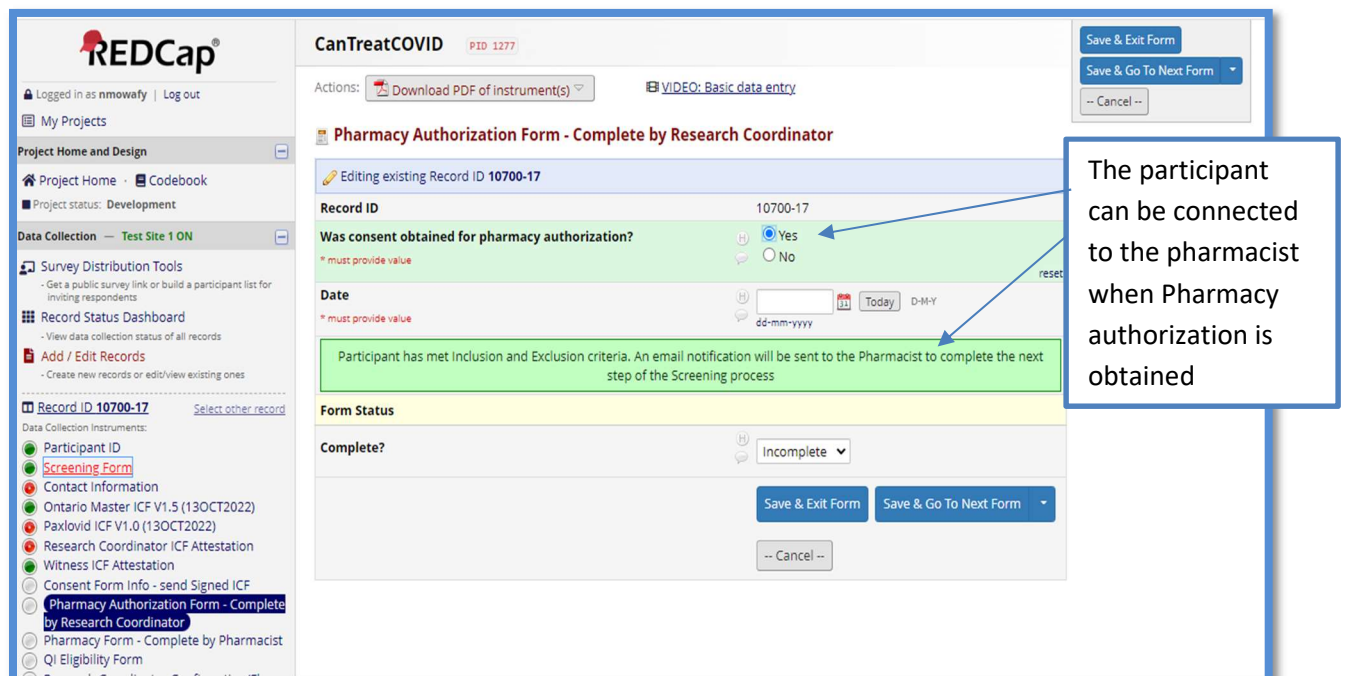
**Complete?** [input] Incomplete

Buttons: Save & Exit Form, Save & Go To Next Form, -- Cancel --

Callout: Completed documents are uploaded here by the system

## 7. [Pharmacy Authorization form]

This form has to be completed by Research coordinator or the Research assistant



**Pharmacy Authorization Form - Complete by Research Coordinator**

Actions: [icon] Download PDF of instrument(s) VIDEO: Basic data entry

Editing existing Record ID 10700-17

Record ID	10700-17
Was consent obtained for pharmacy authorization?	[radio] Yes [radio] No
Date	[input] Today D-M-Y

Participant has met Inclusion and Exclusion criteria. An email notification will be sent to the Pharmacist to complete the next step of the Screening process

**Form Status**

**Complete?** [input] Incomplete

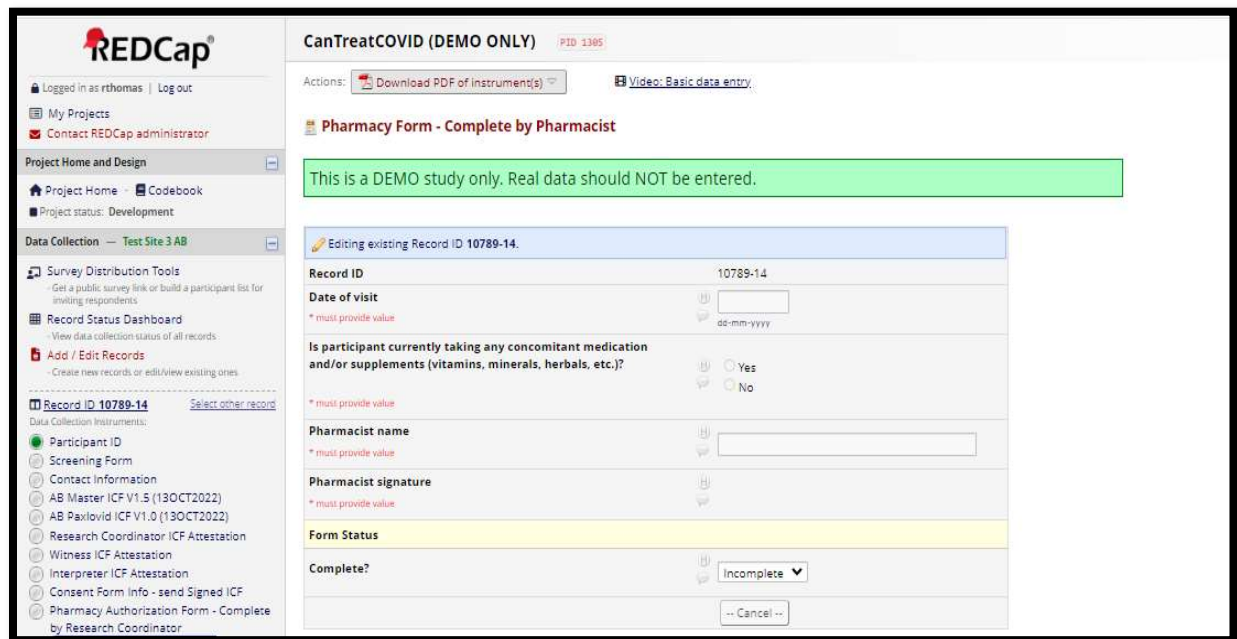
Buttons: Save & Exit Form, Save & Go To Next Form, -- Cancel --

Callout: The participant can be connected to the pharmacist when Pharmacy authorization is obtained

## 8. [Pharmacy form]

This form is completed by the Study Pharmacist to review for any Concomitant medications reported by the Participant (and also confirm with the Participant’s Pharmacy, if required). Any reported medications and/or supplements should be inputted by the Pharmacist in the text box.

If the participant is eligible and randomized, the Research Coordinator should later transfer all reported medications in the Concomitant Medications log in REDCap Cloud



The screenshot shows the REDCap interface for the 'Pharmacy Form - Complete by Pharmacist'. The form is for Record ID 10789-14. A green banner at the top states: 'This is a DEMO study only. Real data should NOT be entered.' The form fields include: Record ID (10789-14), Date of visit (dd-mm-yyyy), a question 'Is participant currently taking any concomitant medication and/or supplements (vitamins, minerals, herbs, etc.)?' with Yes/No radio buttons, Pharmacist name, Pharmacist signature, Form Status, and Complete? (Incomplete). A 'Cancel' button is at the bottom right.

## 9. [QI Eligibility form]

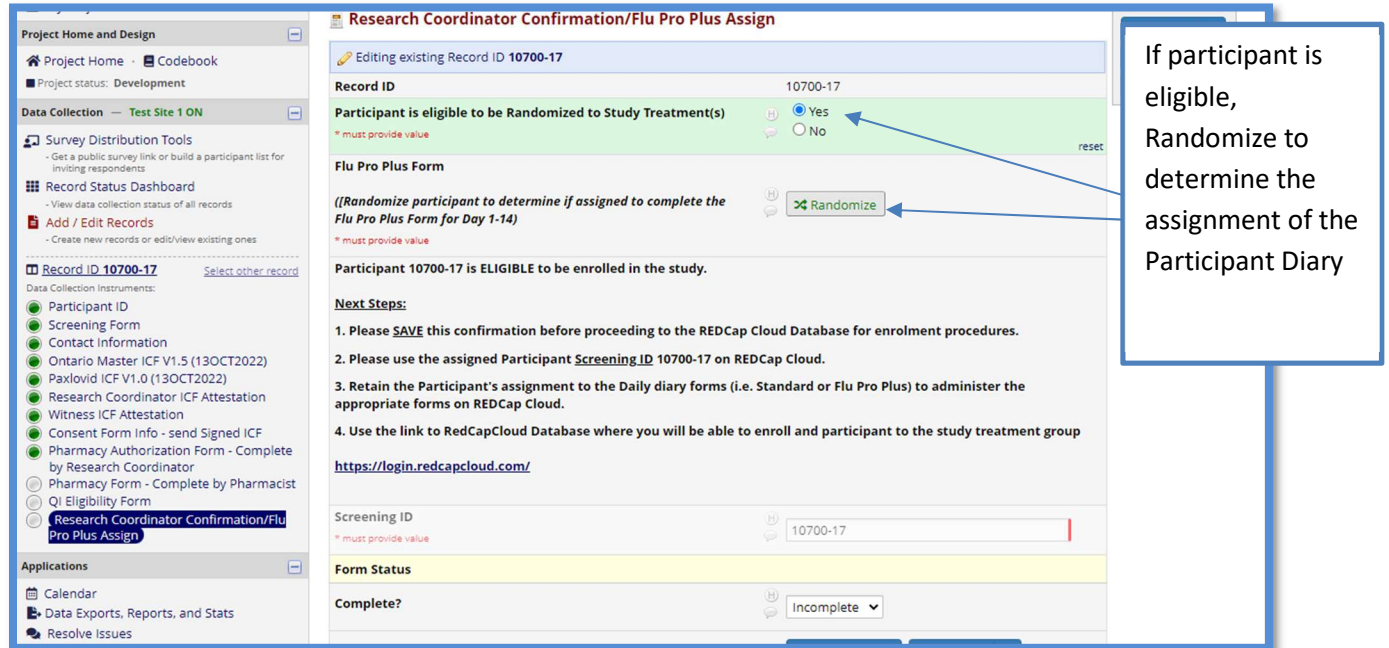
This form has to be completed by the QI to confirm participant eligibility



The screenshot shows the REDCap interface for the 'QI Eligibility Form'. The form is for Record ID 10700-17. The form fields include: Record ID (10700-17), a question 'In the opinion of the investigator/designee, is the participant eligible?' with Yes/No radio buttons, QI name, QI signature, Date (dd-mm-yyyy), Form Status, and Complete? (Incomplete). A 'Cancel' button is at the bottom right.

## 10. [Research Coordinator Confirmation form]

This form is completed by the Research Coordinator or the Research Assistant to proceed with enrolment.



**Research Coordinator Confirmation/Flu Pro Plus Assign**

Editing existing Record ID 10700-17

Record ID 10700-17

Participant is eligible to be Randomized to Study Treatment(s)  Yes  No reset

*\* must provide value*

**Flu Pro Plus Form**

((Randomize participant to determine if assigned to complete the Flu Pro Plus Form for Day 1-14))

*\* must provide value*

Participant 10700-17 is ELIGIBLE to be enrolled in the study.

**Next Steps:**

1. Please **SAVE** this confirmation before proceeding to the REDCap Cloud Database for enrolment procedures.
2. Please use the assigned Participant Screening ID 10700-17 on REDCap Cloud.
3. Retain the Participant's assignment to the Daily diary forms (i.e. Standard or Flu Pro Plus) to administer the appropriate forms on REDCap Cloud.
4. Use the link to RedCapCloud Database where you will be able to enroll and participant to the study treatment group

<https://login.redcapcloud.com/>

Screening ID  *\* must provide value*

**Form Status**

Complete?

If participant is eligible, Randomize to determine the assignment of the Participant Diary

Please **SAVE** this confirmation before proceeding to the REDCap Cloud Database for enrolment procedures.

Please use the assigned Participant Screening ID (i.e., here we have 10700-17) on REDCap Cloud.

Retain the Participant's assignment to the Daily diary forms (i.e. Standard or Flu Pro Plus) to administer the appropriate forms on REDCap Cloud.

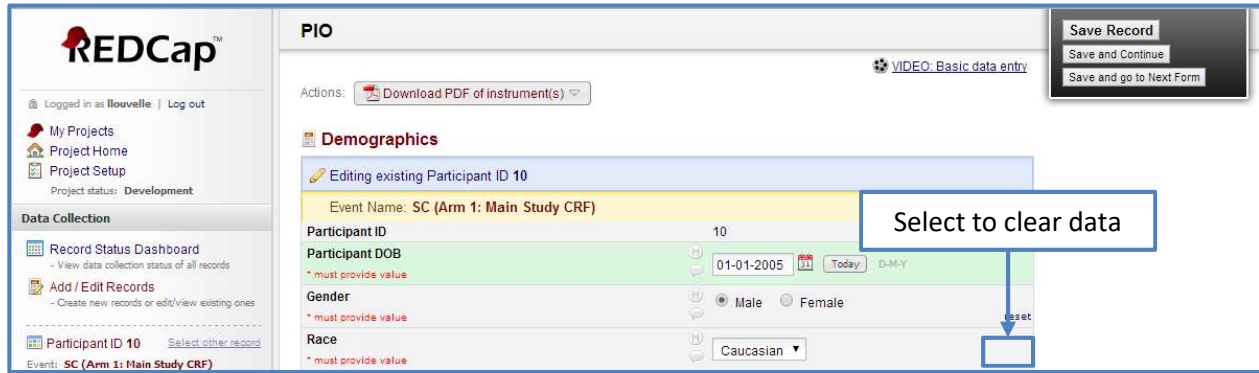
Use the link to RedCapCloud Database where you will be able to enroll and participant to the study treatment group

<https://login.redcapcloud.com/>

## 11. Tips for REDCap Academic Database

### i. Editing Data

To minimize errors when correcting previously entered data (e.g. correcting the **Gender** in the **Demographics** form), click “reset” (if available) to clear data fields and then enter the correct information.



## ii. Specifying Form Status

The last field of each form indicates to choose one of three form statuses from a drop down menu: incomplete, unverified, or complete. Once the form status is selected, a coloured button will appear next to the form name on the left panel of the screen, indicating the status.

### Incomplete

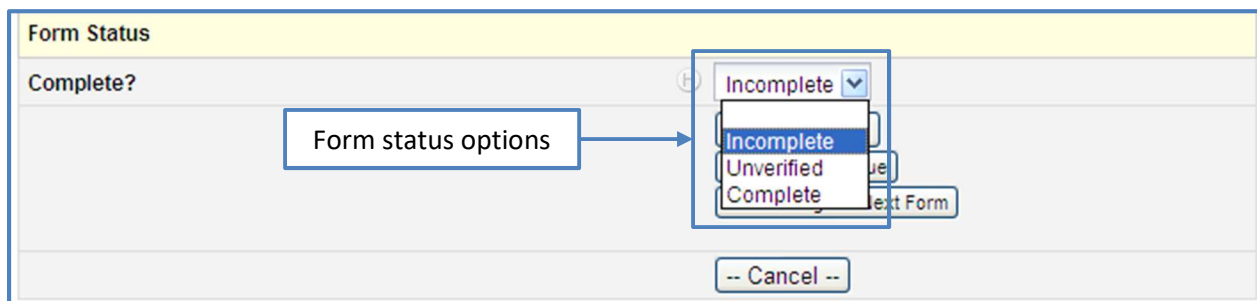
A red circle (●) corresponds to an Incomplete form status. This is the default value for all forms until the form status is updated. Use this option when no data has been entered on a form.

### Unverified


A yellow circle (●) corresponds to an Unverified form status. Use this option when not all data has been entered on a form, or when you still need to verify the data entered.

### Complete

A green circle (●) corresponds to a Complete form status. Use this option when all data has been entered and verified on a form.



Note: Even if a form status as **Complete**, it can be re-opened at a later time to modify or add data.

If a field is locked by the Data Manager, the icon will appear with a lock on the Dashboard:  This will not allow to edit the data in this field. In this case please email the AHRC Project Manager: [Rekha.Thomas@unityhealth.to](mailto:Rekha.Thomas@unityhealth.to) ) to request for the field to be unlocked.

### iii. Saving Data

After entering data, a form can be saved using one of the options:

#### Save & Exit Form/Save & Exit Record

Clicking on **Save & Exit Form** or **Save & Exit Record** will save the data on the form, and return you to the **Event Grid** for the current subject.

#### Save & Stay

Clicking on **Save & Stay** will save the data and refresh the form. This option allows you to continue entering data on the current form.

#### Save & Go to Next Instance

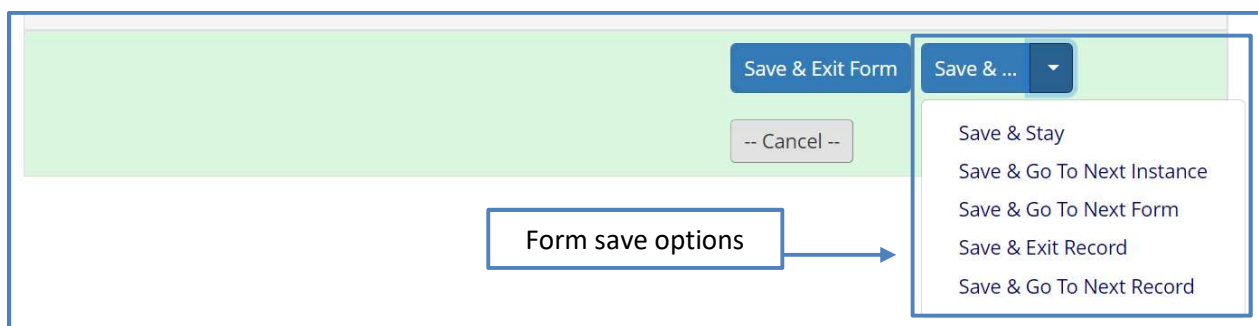
Clicking on **Save & Go to Next Instance** will save the data and advance to the next instance of a repeat form. If there is no next instance, a new instance of the repeat form will be created. This option is only present for repeat forms (e.g. Medications – Baseline).

#### Save and Go to Next Form

Clicking on **Save and go to Next Form** will save the data and advance to the next form in the visit. This option is not present for the last form in a visit, or if only one form is present for a visit.

#### Save & Go To Next Record

Clicking on **Save & Go To Next Record** will save the data and advance to the next patient at the site. This option is not present for the last patient at a site, or if only one patient is enrolled at a site.

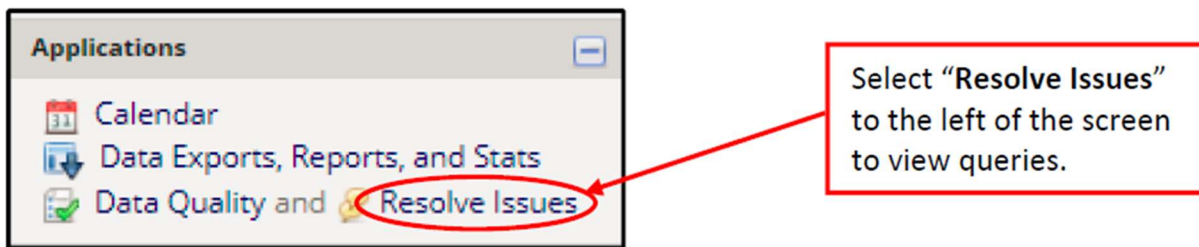


Note: Save data early and often. There is no auto-saving in REDCap™.

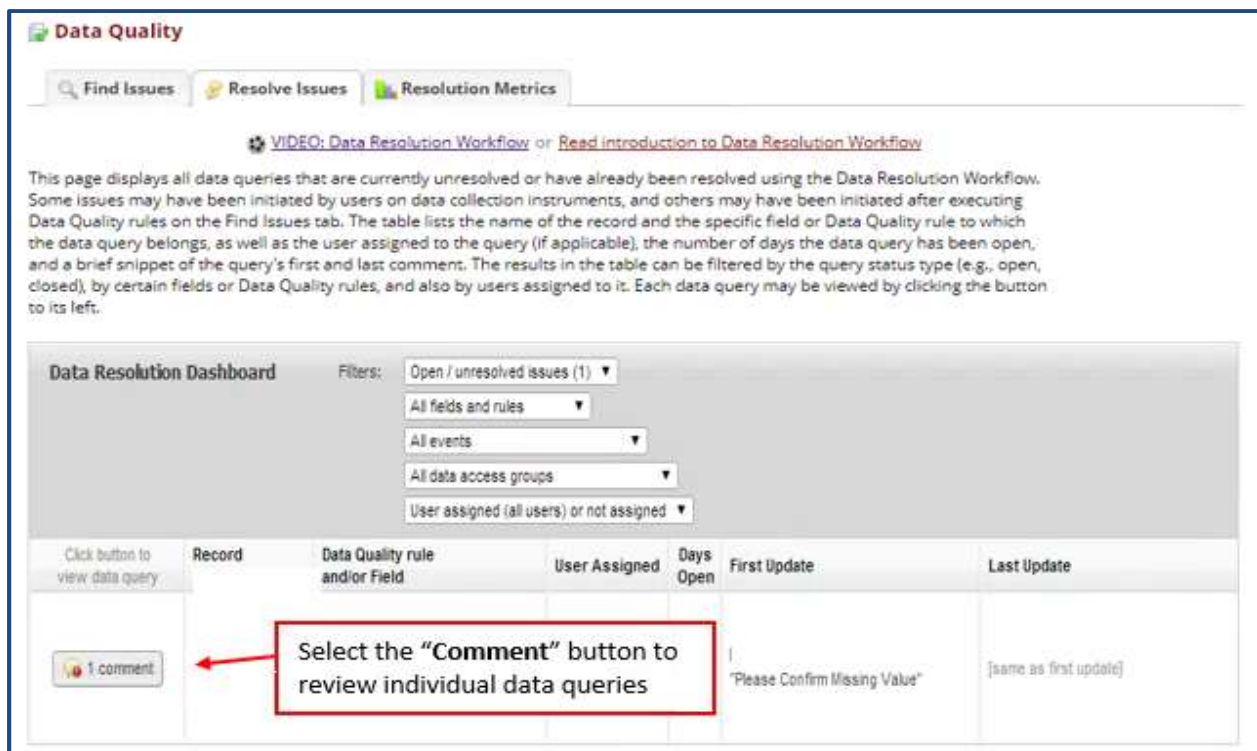
### iv. Answering Queries

Data queries will be managed within the eCRF system based on programmed validation rules built into the database, and also manually based on review by the AHRC data manager. These must be addressed in an ongoing and timely manner throughout the study. Queries must be addressed on an ongoing and timely manner throughout the study, at least once per week. In order to address

any queries that have been raised, click on the **Resolve Issues** icon located in the **Applications** section in the left hand toolbar.



In the **Data Quality** page, filter by query type using the **Filters** drop-down list.



Upon selecting the **Comment** button, a **Data Resolution Workflow** window will appear.

Select **Reply with response** (shown below), choose the response type for the query from the drop-down list, and complete the **Comments** box. Once finished, click the **Respond to query** button.

Date/Time	User	Comments and Details
07/25/2014 10:11am	Ispooner	Action: <b>Opened query</b> Comment: "Please Confirm Missing Value"
07/25/2014 11:01am		<input checked="" type="radio"/> <b>Reply with response:</b> <div style="border: 1px solid black; padding: 2px; display: inline-block;"> -- choose response --  -- choose response --  Corrected - Data missing  Corrected - Typographical error  Corrected - Wrong source used  Verified - Confirmed correct (no error)  Other </div> Upload file (optional): _____ <input type="radio"/> <b>Close the query</b> Comment: <input style="width: 100%;" type="text"/>

Select a **response type** from the list.

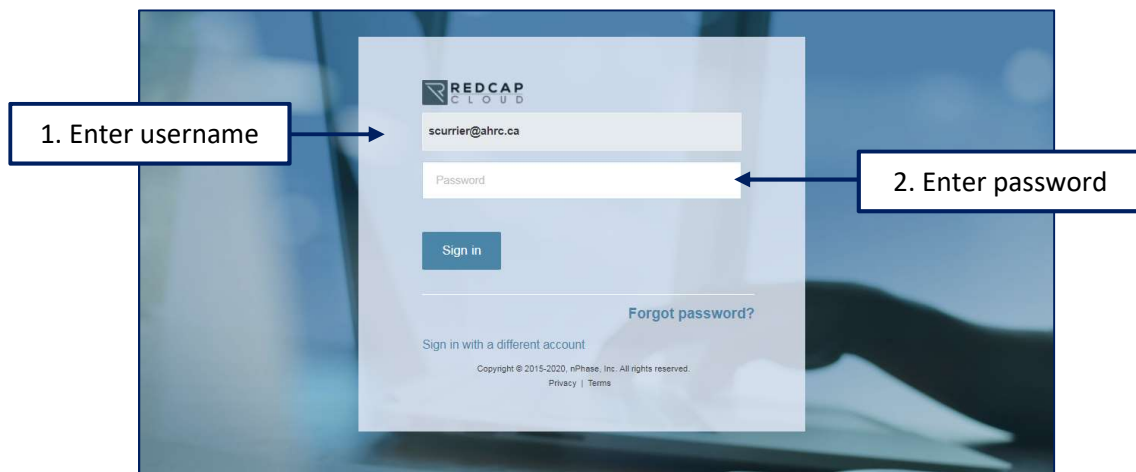
Complete "**Comment**" box.

Select the "**Respond to query**" button.

### 17.3 REDCap Cloud Data Entry Guidelines

These guidelines have been compiled to assist you with the data entry process for the CanTreatCOVID study.

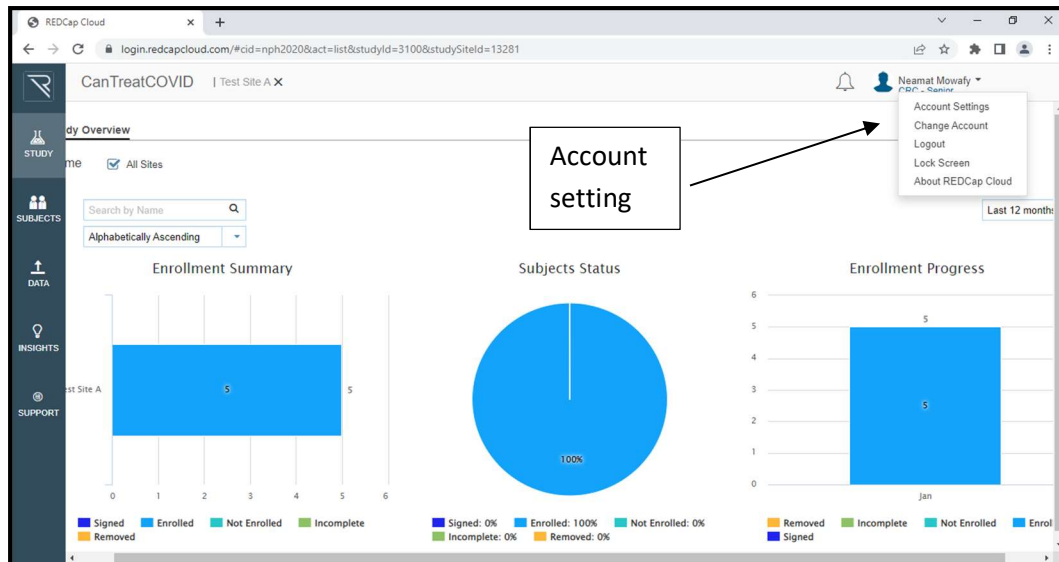
In order to access the REDCap Cloud database, an account is assigned for each individual. An account activation form, provided to by the AHRC Project Lead has to be submitted. Once access is granted to the study, a username and a generic password will be assigned, which will be required to be changed upon logging in for the first time.



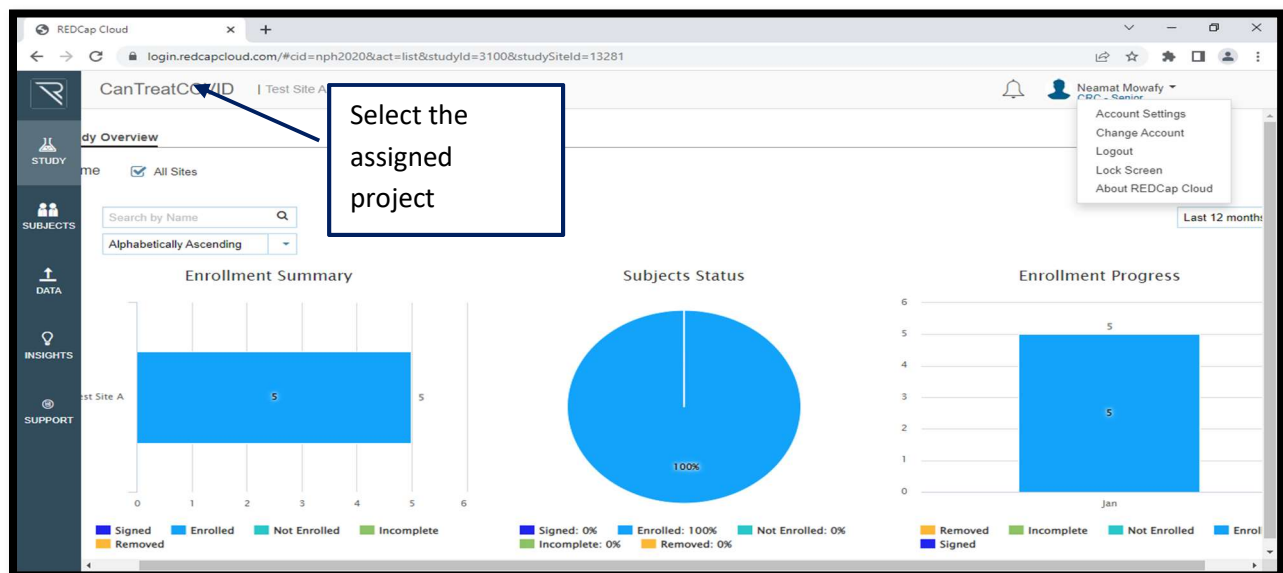
For forgotten password, the *Forgot password?* on the bottom right hand corner of the login page can reset the password.



In the Home page, at the top right hand corner of the home page, the *Account Settings* is located to view the username and email, and to update information.



A list of assigned projects will appear on the *My Studies* page. Select the **CanTreatCOVID** project.

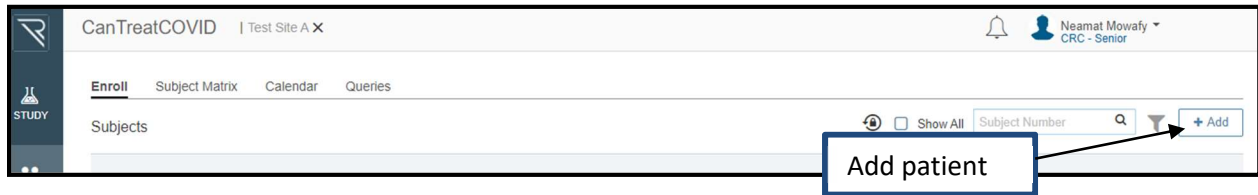
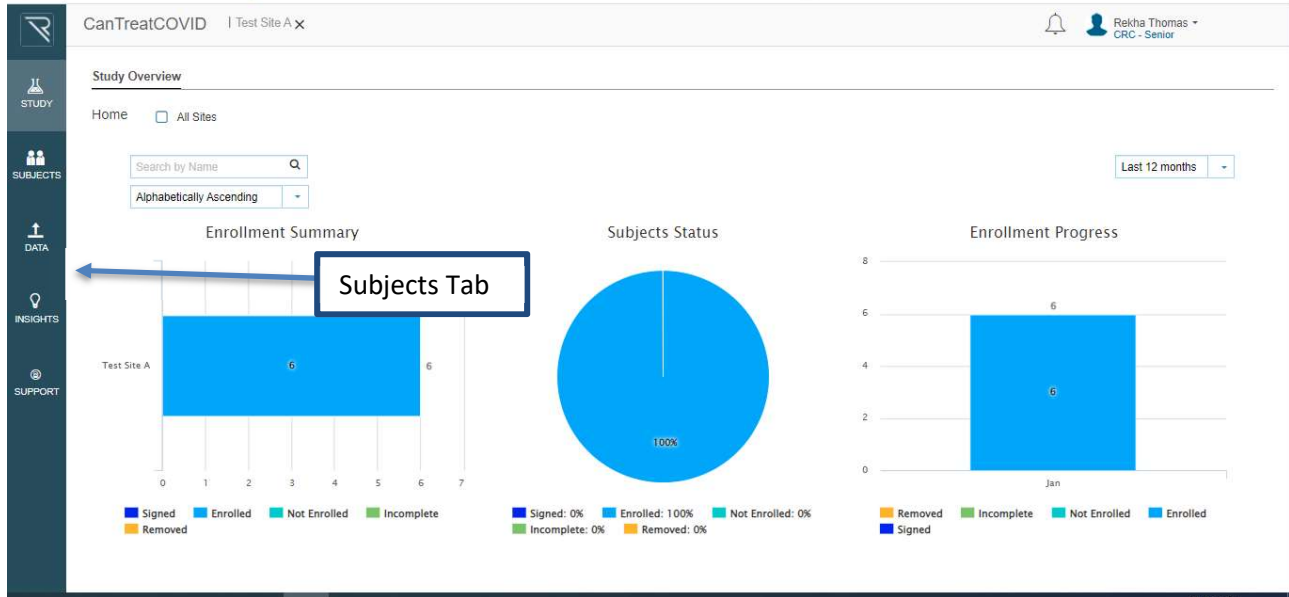


Once the project is selected, a site has to be selected to enter data into.

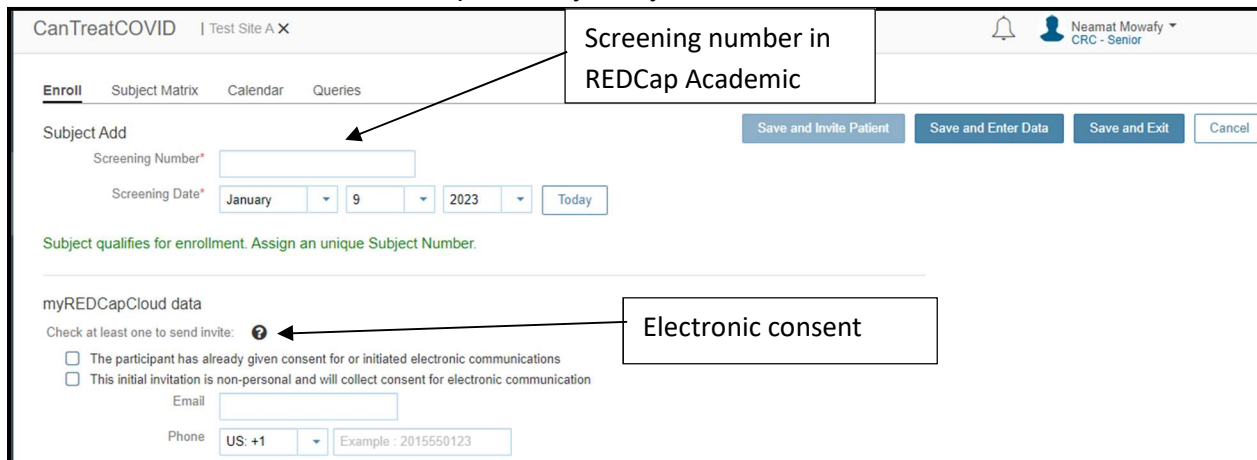
After selecting the site, the homepage is viewable with a set of graphics that indicates the progress of enrollment at the site

## ADDING SUBJECTS

Select 'Subjects' (on the left) to 'Add' to enter a new participant to the study.



Enter the Screening number (copy paste it as assigned in REDCap Academic), and screening date, and answer the question if patient have given consent or enter the email address to send the invitation for the Participant Daily Diary or Flu Pro Plus.

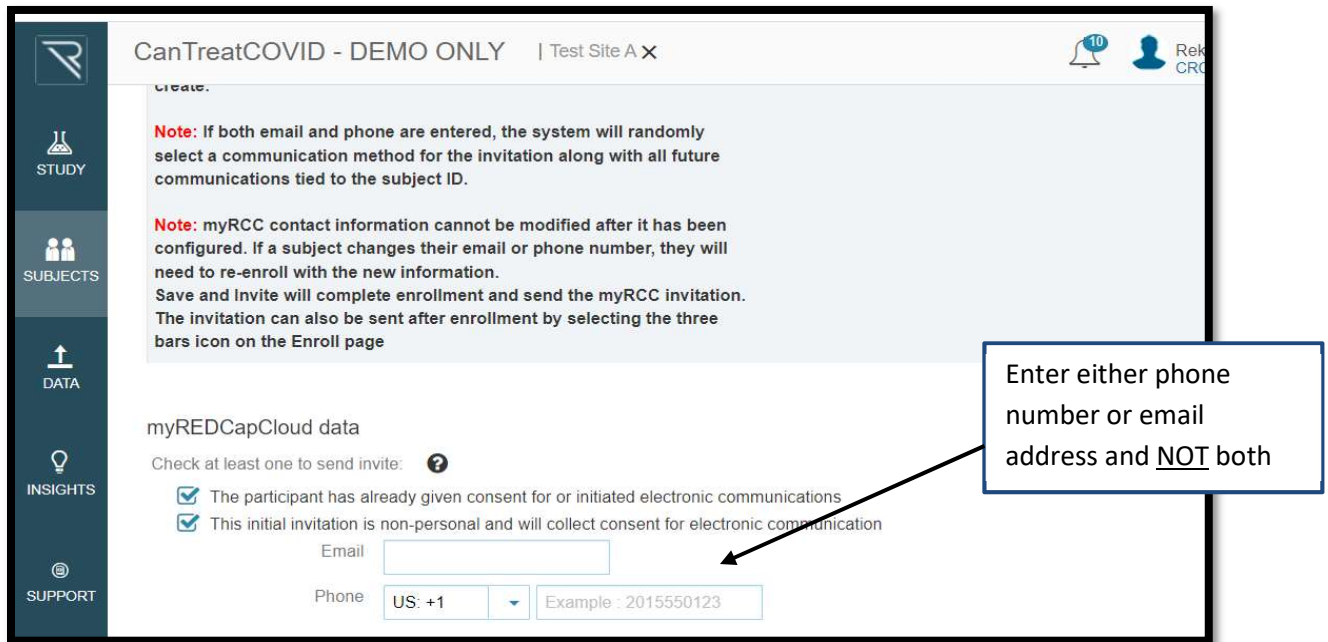


The screenshot shows the 'Subject Add' form in the CanTreatCOVID interface. The form includes the following fields and options:

- Screening Number\***: A text input field.
- Screening Date\***: A date picker set to January 9, 2023.
- Buttons:** Save and Invite Patient, Save and Enter Data, Save and Exit, Cancel.
- Message:** Subject qualifies for enrollment. Assign an unique Subject Number.
- myREDCapCloud data:**
  - Check at least one to send invite:  The participant has already given consent for or initiated electronic communications
  - This initial invitation is non-personal and will collect consent for electronic communication
  - Electronic consent:** A box highlighting the consent options.
  - Email:** A text input field.
  - Phone:** A dropdown menu set to US: +1 and a text input field with the example 2015550123.

For each participant enrolled into the CanTreatCOVID trial, this participant will have screening number (as assigned in REDCap Academic). The Subject Number is also the Enrolment Number of the participant as assigned in REDCap Cloud upon enrolment

In order to send the invitation to the participant to access the surveys in the Participant portal, check off the options and enter either the participant's phone number or email address. If both email address and phone number are added the system will send the invitation by default to the only the phone number via text.



**CanTreatCOVID - DEMO ONLY | Test Site A x**

**Create.**

**Note:** If both email and phone are entered, the system will randomly select a communication method for the invitation along with all future communications tied to the subject ID.

**Note:** myRCC contact information cannot be modified after it has been configured. If a subject changes their email or phone number, they will need to re-enroll with the new information. Save and Invite will complete enrollment and send the myRCC invitation. The invitation can also be sent after enrollment by selecting the three bars icon on the Enroll page

myREDCapCloud data

Check at least one to send invite: ?

The participant has already given consent for or initiated electronic communications

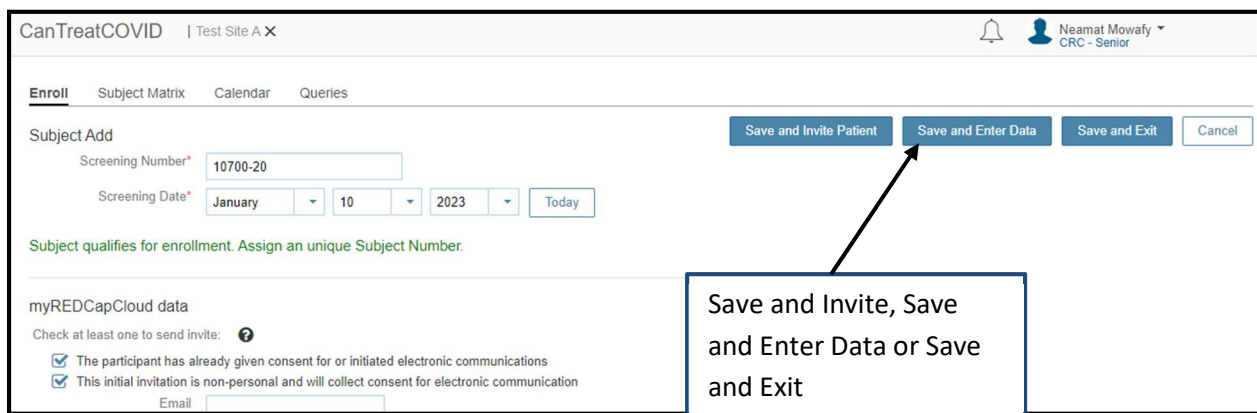
This initial invitation is non-personal and will collect consent for electronic communication

Email:

Phone: US: +1

Enter either phone number or email address and NOT both

Choose one of the options: Save and Invite patient, Save and enter data, Save and Exit



**CanTreatCOVID | Test Site A x**

Enroll Subject Matrix Calendar Queries

Subject Add

Screening Number\* 10700-20

Screening Date\* January 10 2023 Today

Subject qualifies for enrollment. Assign an unique Subject Number.

myREDCapCloud data

Check at least one to send invite: ?

The participant has already given consent for or initiated electronic communications

This initial invitation is non-personal and will collect consent for electronic communication

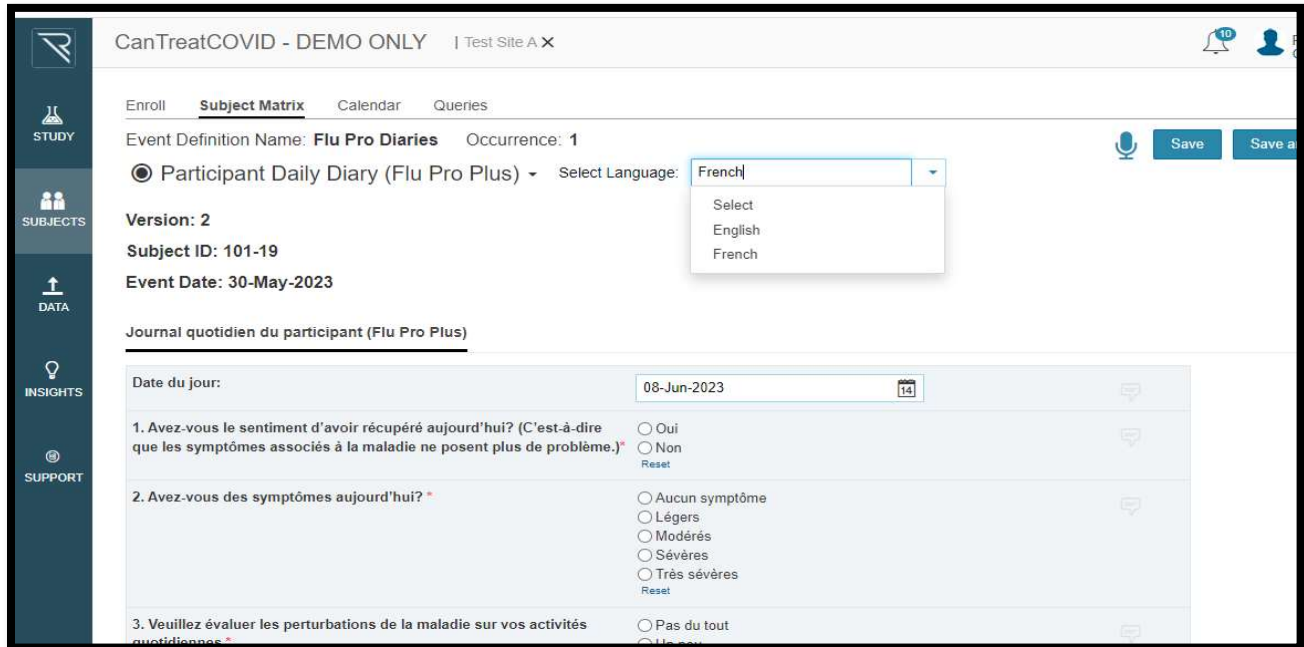
Email:

Save and Invite Patient Save and Enter Data Save and Exit Cancel

Save and Invite, Save and Enter Data or Save and Exit

For French Translation Please ensure to only select the language in the respective eCRFs (i.e. Daily Diary, Flu Pro Plus and Symptoms Burden Questionnaire) and not assign it in the Enrollment page. If the participant is assigned to a language in the Enrollment form the assigned language will

be set as default and the participant will not be able to change the language selection if needed in the future.



CanTreatCOVID - DEMO ONLY | Test Site A X

Enroll **Subject Matrix** Calendar Queries

Event Definition Name: **Flu Pro Diaries** Occurrence: 1

Participant Daily Diary (Flu Pro Plus) Select Language: **French**

Version: 2  
Subject ID: 101-19  
Event Date: 30-May-2023

Journal quotidien du participant (Flu Pro Plus)

Date du jour: 08-Jun-2023

1. Avez-vous le sentiment d'avoir récupéré aujourd'hui? (C'est-à-dire que les symptômes associés à la maladie ne posent plus de problème.)\*

Oui  
 Non  
Reset

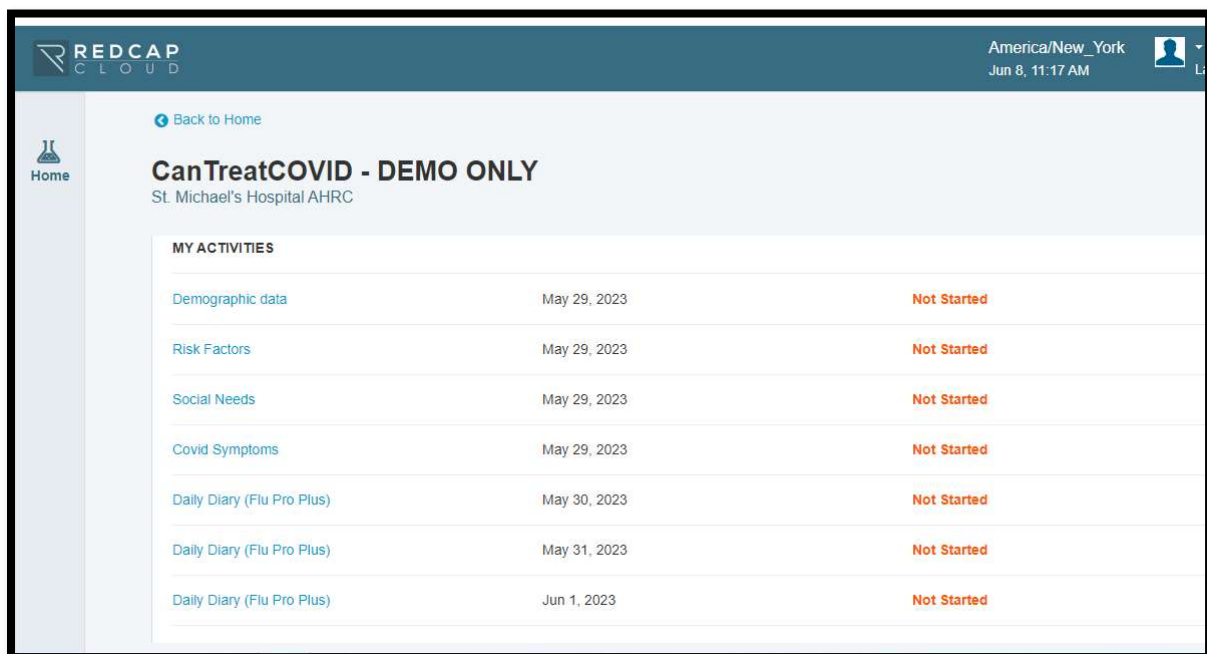
2. Avez-vous des symptômes aujourd'hui? \*

Aucun symptôme  
 Légers  
 Modérés  
 Sévères  
 Très sévères  
Reset

3. Veuillez évaluer les perturbations de la maladie sur vos activités quotidiennes. \*

Pas du tout  
 Un peu

## PARTICIPANT PORTAL



REDCAP CLOUD America/New\_York Jun 8, 11:17 AM

Back to Home

Home

**CanTreatCOVID - DEMO ONLY**  
St. Michael's Hospital AHRC

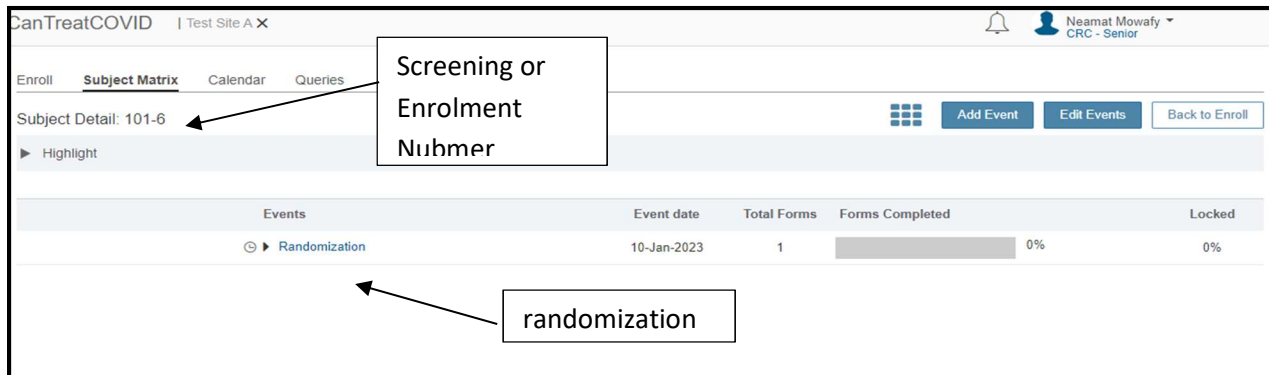
**MY ACTIVITIES**

Activity Name	Date	Status
Demographic data	May 29, 2023	Not Started
Risk Factors	May 29, 2023	Not Started
Social Needs	May 29, 2023	Not Started
Covid Symptoms	May 29, 2023	Not Started
Daily Diary (Flu Pro Plus)	May 30, 2023	Not Started
Daily Diary (Flu Pro Plus)	May 31, 2023	Not Started
Daily Diary (Flu Pro Plus)	Jun 1, 2023	Not Started

## RANDOMIZE SUBJECTS

If selecting Save and enter data, the participant will be assigned the Screening (or Enrolment) number in REDCap Cloud, and the Subject Matrix listing the forms for the participant will appear.

At first the Randomization form is the only one that is visible until randomization is completed.



CanTreatCOVID | Test Site A X

Enroll **Subject Matrix** Calendar Queries

Subject Detail: 101-6

Highlight

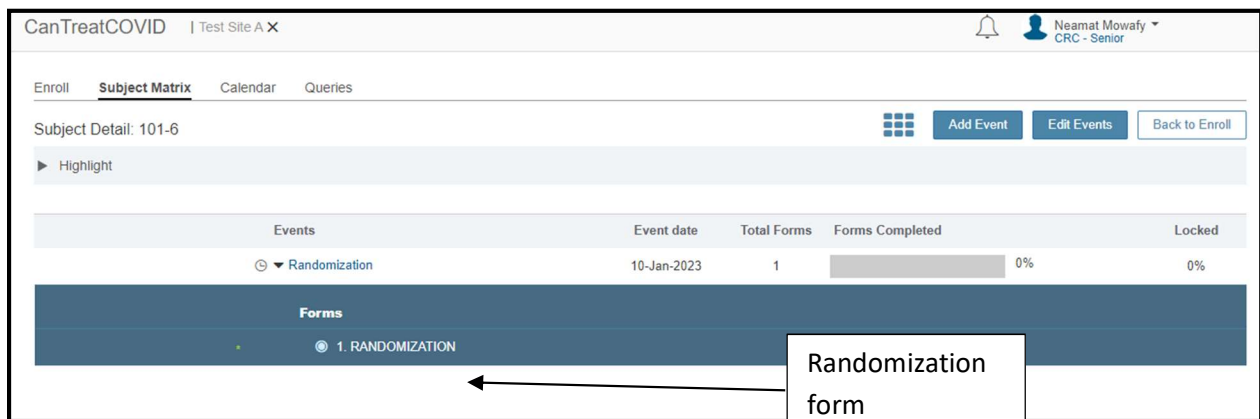
Screening or Enrolment Number

Events	Event date	Total Forms	Forms Completed	Locked
Randomization	10-Jan-2023	1	0%	0%

randomization

*Note: for this trial, The screening number listed in this guidance document are examples.*

The Randomization event will open populate the Randomization form to be completed.



CanTreatCOVID | Test Site A X

Enroll **Subject Matrix** Calendar Queries

Subject Detail: 101-6

Highlight

Events	Event date	Total Forms	Forms Completed	Locked
Randomization	10-Jan-2023	1	0%	0%

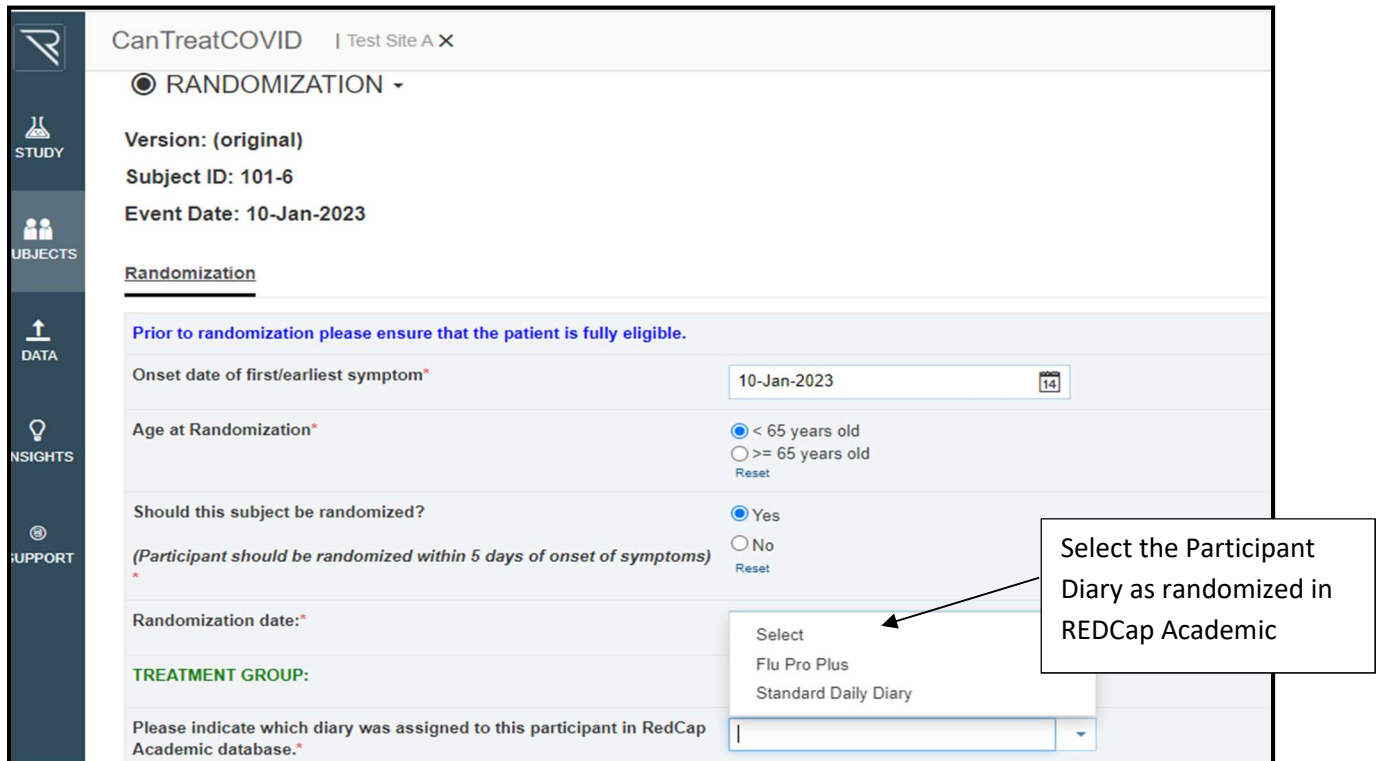
Forms

1. RANDOMIZATION

Randomization form

Enter all fields necessary to randomize the participant.

The Participant Diary should be selected as allocated on REDCap Academic to initiate the Flu Plus form or Standard participant diary for the participant to complete.



CanTreatCOVID | Test Site A X

**RANDOMIZATION**

Version: (original)  
Subject ID: 101-6  
Event Date: 10-Jan-2023

Randomization

Prior to randomization please ensure that the patient is fully eligible.

Onset date of first/earliest symptom\* 10-Jan-2023

Age at Randomization\*  < 65 years old  
 >= 65 years old  
Reset

Should this subject be randomized?  Yes  
 No  
(Participant should be randomized within 5 days of onset of symptoms)  
Reset

Randomization date:\*  
Select  
Flu Pro Plus  
Standard Daily Diary

**TREATMENT GROUP:**

Please indicate which diary was assigned to this participant in RedCap Academic database.\*

Select the Participant Diary as randomized in REDCap Academic

When all fields are entered, Save the form before in order for the Randomize button (on the upper right part of the screen) to be active.

Upon selecting Randomize the treatment group that the participant is assigned will automatically appear.

At the end of each form please remember to check the form as complete

**Randomization**

Prior to randomization please ensure that the patient is fully eligible.

Onset date of first/earliest symptom\* 10-Jan-2023

Age at Randomization\* < 65 years old

Should this subject be randomized? Yes  
*(Participant should be randomized within 5 days of onset of symptoms)*

Randomization date:\* 10-Jan-2023

**TREATMENT GROUP:** Usual Care

Please indicate which diary was assigned to this participant in RedCap Academic database.\* Standard Daily Diary

Mark Instrument as complete

Return

Participant will be randomized to Usual care or Paxlovid

Check the form as complete

Select Return to go back to the Subject Matrix where all the event forms will be populated

### STUDY EVENT FORMS

This page highlights all the forms to be completed for the participant in the duration of the study.

To complete each form, Select the Event and then open the appropriate form to be completed.

Enroll **Subject Matrix** Calendar Queries

Subject Detail: 101-6

Add Event Edit Events Back to Subject Matrix

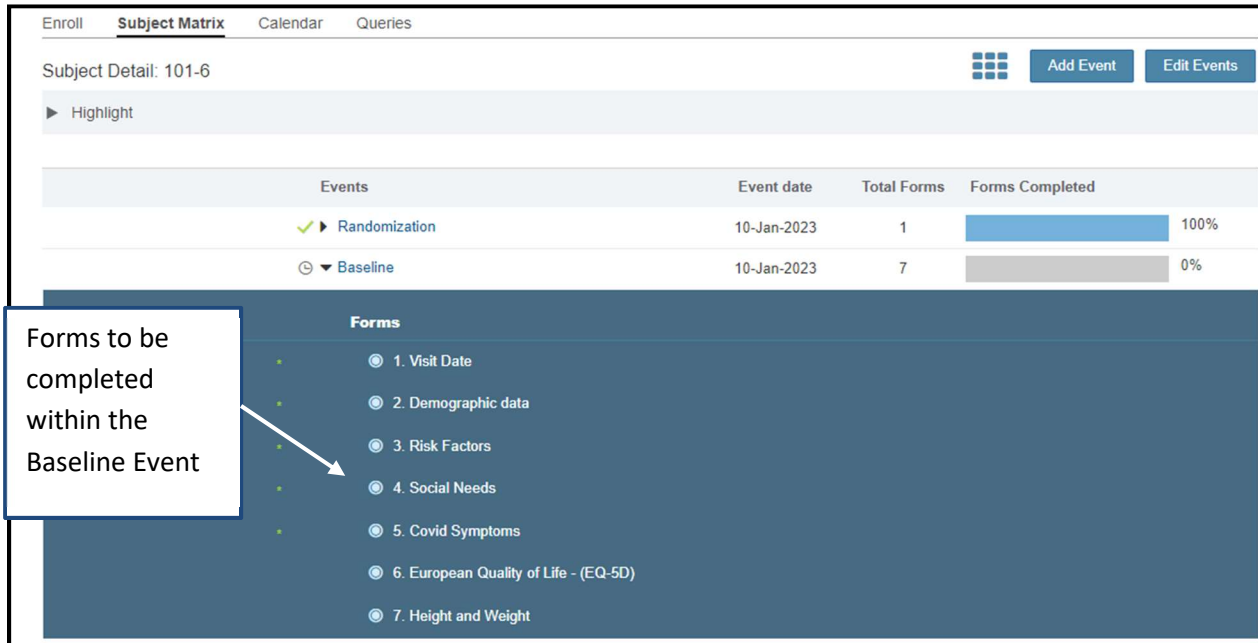
Highlight

Events	Event date	Total Forms	Forms Completed
✓ Randomization	10-Jan-2023	1	100%
⊙ Baseline	10-Jan-2023	7	0%
⊙ Day 1	11-Jan-2023	1	0%
⊙ Daily e-Diary		14	0%
⊙ Day 21	31-Jan-2023	1	0%
⊙ Day 28	07-Feb-2023	1	0%
⊙ Day 90	10-Apr-2023	5	0%
⊙ Week 36	19-Sep-2023	5	0%
⊙ Concomitant Medications	10-Jan-2023	1	0%
⊙ Adverse Events/SAEs	10-Jan-2023	1	0%
⊙ As Needed Forms	10-Jan-2023	7	0%

Click back to return to the Subject matrix listing all participants enrolled at the Site

## BASELINE EVENT

Click the Baseline Event to view all the forms listed for completion. Open each form to enter the required data.



The screenshot shows the 'Subject Matrix' interface for subject 101-6. It features a table of events and a list of forms to be completed.

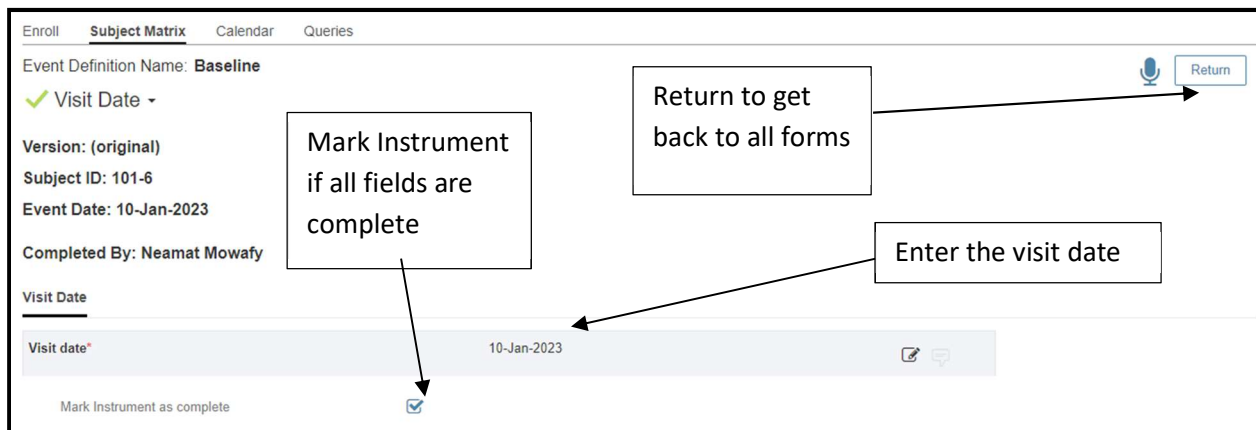
Events	Event date	Total Forms	Forms Completed
✔ Randomization	10-Jan-2023	1	100%
☹ Baseline	10-Jan-2023	7	0%

Below the table, a 'Forms' section lists the following items to be completed:

- 1. Visit Date
- 2. Demographic data
- 3. Risk Factors
- 4. Social Needs
- 5. Covid Symptoms
- 6. European Quality of Life - (EQ-5D)
- 7. Height and Weight

A callout box with an arrow points to the 'Forms' list, containing the text: "Forms to be completed within the Baseline Event".

## Visit date form



The screenshot shows the 'Visit Date' form within the 'Baseline' event. The form includes the following information:

- Event Definition Name: Baseline
- Version: (original)
- Subject ID: 101-6
- Event Date: 10-Jan-2023
- Completed By: Neamat Mowafy

The form field for 'Visit date\*' is populated with '10-Jan-2023'. A 'Return' button is visible in the top right corner.

Three callout boxes provide instructions:

- "Mark Instrument if all fields are complete" points to a checkmark icon at the bottom of the form.
- "Return to get back to all forms" points to the 'Return' button.
- "Enter the visit date" points to the 'Visit date\*' input field.

## Demographic data form

Please note to enter **15** for the Participant day of birth.  
Complete all fields of the form as provided by the participant.



**Demographics**

1. Please enter **15** for the participant DAY of the birth  
e.g. if the month is March and year is 1957 please enter as 15-Mar-1957\*

1a. Date of birth\*

1b. Age

1c. Current Vaccination Status?\*  
 Less than 2 doses  
 2 and more doses  
 None  
[Reset](#)

2a. What is your sex assigned at birth?\*

Male  
 Female  
 Intersex  
[Reset](#)

2b. What is your current gender identity?\*

Woman  
 Man  
 Gender fluid or Gender non-binary  
 Two-Spirit (Indigenous)  
 Other  
[Reset](#)

3a. Were you born in Canada?\*

Yes  
 No  
[Reset](#)

**SOCIO-DEMOGRAPHIC CHARACTERISTICS**

### Risk Factors form

If Yes for a chronic disease, select all conditions as reported by the participant.

Note: Enter the details of each condition in the Comorbidity Log of the participant

**Risk Factors**

1a. Have you been diagnosed, or do you currently have a chronic disease (a disease persisting for 3 months or more)?  
\*  Yes  No [Reset](#)

Please select all that apply

- Arthritis (excluding fibromyalgia)
- Asthma
- Bladder disorders (e.g., incontinence, overactive bladder, cystitis)
- Bowel disease (e.g., IBD, IBS, Crohn's disease, celiac, ulcerative colitis)
- Liver disease or cirrhosis (non-hepatitis)
- Cancer (excluding non-melanoma skin cancer)
- Cerebrovascular diseases (e.g., stroke, TIA)
- Chronic pain (e.g., fibromyalgia, back pain, migraines)
- COPD, chronic bronchitis, emphysema
- Dementia (e.g., Alzheimer's disease)
- Diabetes
- Epilepsy/seizure disorder
- GERD/reflux/peptic ulcer disease
- Arrhythmia
- Angina
- Past heart attack
- Heart failure
- Hepatitis B
- Hepatitis C
- HIV / AIDS
- High cholesterol

## Social needs

Enter data for all fields as reported by the participant

**Social Needs**

---

1. Will you or your household find it hard to pay for basic expenses in the next 4 weeks?\*

Yes  
 No  
[Reset](#)

2. Is there a risk you or your household won't have food or be able to pay for food in the next 4 weeks?\*

Yes  
 No  
[Reset](#)

3. Are you currently homeless or at risk of losing your housing in the next 4 weeks?\*

Yes  
 No  
[Reset](#)

4. Are you alone, and do not have family/friends who can help you during this time?\*

Yes  
 No  
[Reset](#)

5. Are you worried about your safety at home?\*

Yes  
 No  
[Reset](#)

**Household Food Security Module**

1. Within the past 12 months, you worried that food would run out before you got money to buy more.\*

Often True  
 Sometimes True  
 Never True  
 Don't know/Refuse to answer  
[Reset](#)

## COVID Symptoms

Enter data for all fields as reported by the participant

**Covid Symptoms**

---

1. Have you received any COVID vaccine?\*

Yes  
 No  
[Reset](#)

2. How are you feeling today?\*

No symptoms  
 Mild  
 Moderate  
 Severe  
 Very severe  
[Reset](#)

3. Please rate interference in daily activities due to illness:\*

Not at all  
 A little bit  
 Somewhat  
 Quite a bit  
 Very much  
[Reset](#)

4. How is your general health?\*

Poor  
 Fair  
 Good  
 Very good  
 Excellent  
[Reset](#)

Mark Instrument as complete

## European Quality of Life(EQ-5D)

The EQ-5D-5L is a standardized questionnaire, a self-assessment tool on health related and quality of life. The scale measures quality of life on a 5-component scale including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

<p><b>USUAL ACTIVITIES</b> (e.g. work, study, housework, family or leisure activities): *</p>	<p><input type="radio"/> I have no problems doing my usual activities  <input type="radio"/> I have slight problems doing my usual activities  <input type="radio"/> I have moderate problems doing my usual activities  <input type="radio"/> I have severe problems doing my usual activities  <input type="radio"/> I am unable to do my usual activities  <a href="#">Reset</a></p>
<p><b>PAIN / DISCOMFORT:</b>*</p>	<p><input type="radio"/> I have no pain or discomfort  <input type="radio"/> I have slight pain or discomfort  <input type="radio"/> I have moderate pain or discomfort  <input type="radio"/> I have severe pain or discomfort  <input type="radio"/> I have extreme pain or discomfort  <a href="#">Reset</a></p>
<p><b>ANXIETY / DEPRESSION:</b>*</p>	<p><input type="radio"/> I am not anxious or depressed  <input type="radio"/> I am slightly anxious or depressed  <input type="radio"/> I am moderately anxious or depressed  <input type="radio"/> I am severely anxious or depressed  <input type="radio"/> I am extremely anxious or depressed  <a href="#">Reset</a></p>
<p><b>Visual Analogue Scale (VAS)</b></p> <p>We would like to know how good or bad your health is TODAY.</p> <p>This scale is numbered from 0 to 100.</p> <p>100 means the <u>best</u> health you can imagine.  0 means the <u>worst</u> health you can imagine.</p>	<div style="border: 1px solid black; width: 100px; height: 20px; margin: 0 auto;"></div> <div style="border: 1px solid black; padding: 5px; margin-top: 10px; width: fit-content;">             Complete the Visual Analogue Scale         </div>
<p>Mark Instrument as complete <input type="checkbox"/></p>	

## Height and Weight form

Enter the height and weight and BMI will be calculated

<b>Height and Weight</b>	
<p><b>Height (cm)</b>* (90 / 220)</p>	<input type="text"/>
<p><b>Weight (kg)</b>* (40 / 200)</p>	<input type="text"/>
<p><b>BMI</b></p>	<input type="text"/>
<p>Mark Instrument as complete <input type="checkbox"/></p>	

## Day 1 form

Check 'Yes' for Visit performed for the remainder of the form to be populated.

Note: Follow up at Day 1 form can be administered after participant has taken at least the 1<sup>st</sup> dose of the study treatment. If randomized to usual care the Follow up Day 1 form can be administered the day after randomization

**Follow - up Visit at Day 1**

---

Was the visit performed?\*

Yes ← Select 'Yes' for the form to be populated

No

[Reset](#)

---

Date of visit\*

14

---

Did the participant experience any clinical events since last visit?\*

Yes

No

[Reset](#)

---

Did the participant receive the study drug?\*

Yes

No

Not Applicable (Usual care)

[Reset](#)

---

Is participant currently taking any new concomitant medications?\*

Yes ← If the participant maybe taking a new contraindicating Con-med the Pharmacist should be consulted.

No

[Reset](#)

If the participant reports and Clinical Events (i.e. Emergency room and/or Hospitalization and/or Adverse Event) the respective forms should be completed as listed in the 'As Needed Event Forms'


If the participant reports any new concomitant medication that maybe a contraindication with the Investigational Product, the Study Pharmacist should be consulted with to continue or withdraw the participant from the study. An email confirmation from the Pharmacist should be retained in the Participant's file.

## Daily Diary form

Participant will complete the Daily Diary or Flu Pro Plus form as assigned for 14 occurrences (i.e. 14 days). If the participant is unable to complete the form the Research Coordinator can assist in completing the form as reported by participant for the respective day.

Events	Event date	Total Forms	Forms Completed
🕒 ▼ Daily e-Diary		14	<div style="width: 0%;"></div> 0%
🕒 ▶ Occurrence: 1	11-Jan-2023		
🕒 ▶ Occurrence: 2	12-Jan-2023		
🕒 ▶ Occurrence: 3	13-Jan-2023		
🕒 ▶ Occurrence: 4	14-Jan-2023		
🕒 ▶ Occurrence: 5	15-Jan-2023		
🕒 ▶ Occurrence: 6	16-Jan-2023		
🕒 ▶ Occurrence: 7	17-Jan-2023		
🕒 ▶ Occurrence: 8	18-Jan-2023		
🕒 ▶ Occurrence: 9	19-Jan-2023		
🕒 ▶ Occurrence: 10	20-Jan-2023		
🕒 ▶ Occurrence: 11	21-Jan-2023		

**Participant Daily Diary**

Today's date:  

1. Do you feel you have recovered today? (i.e., Symptoms associated with the illness are no longer a problem).  
 Yes  
 No  
[Reset](#)

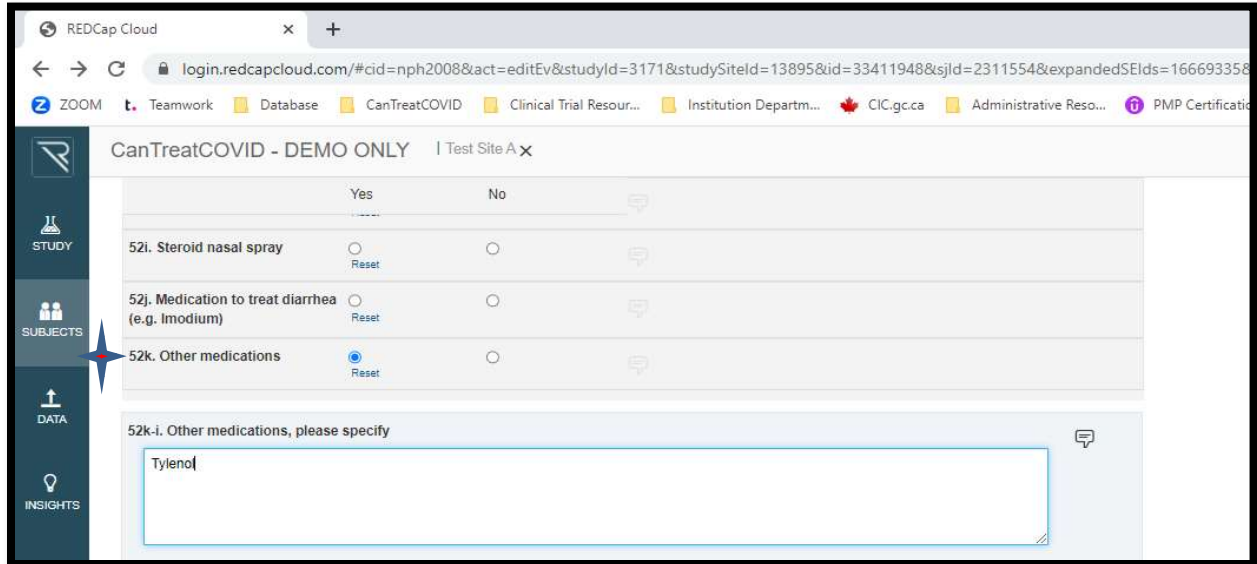
2. How are you feeling today?  
 No symptoms  
 Mild  
 Moderate  
 Severe  
 Very severe  
[Reset](#)

3. Please rate interference in daily activities due to illness:  
 Not at all  
 A little bit  
 Somewhat  
 Quite a bit  
 Very much  
[Reset](#)

4. How is your general health?  
 Poor  
 Fair  
 Good  
 Very good  
 Excellent  
[Reset](#)

Click Reset to delete the selected response

In the Daily Diary (I.e. Standard diary or Flu Pro Plus) if the participant selects 'Other medications' an alert will be sent to the Research Coordinator in order to follow-up with the participant to record its details in the Concomitant medication list.



### Day 21 form

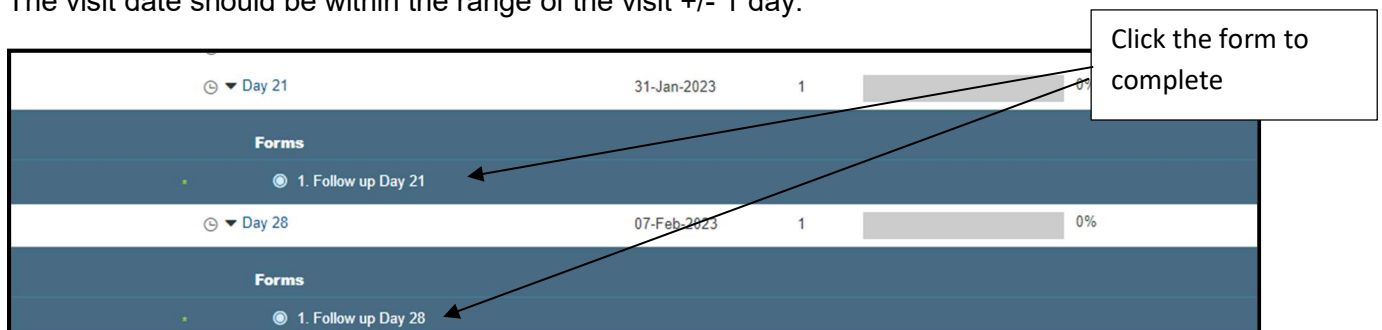
Open the Day 21 Event to view the forms for completion.

The visit date should be within the range of the visit +/- 1 day.

### Day 28<sup>th</sup> form

Open the Day 21 Event to view the forms for completion.

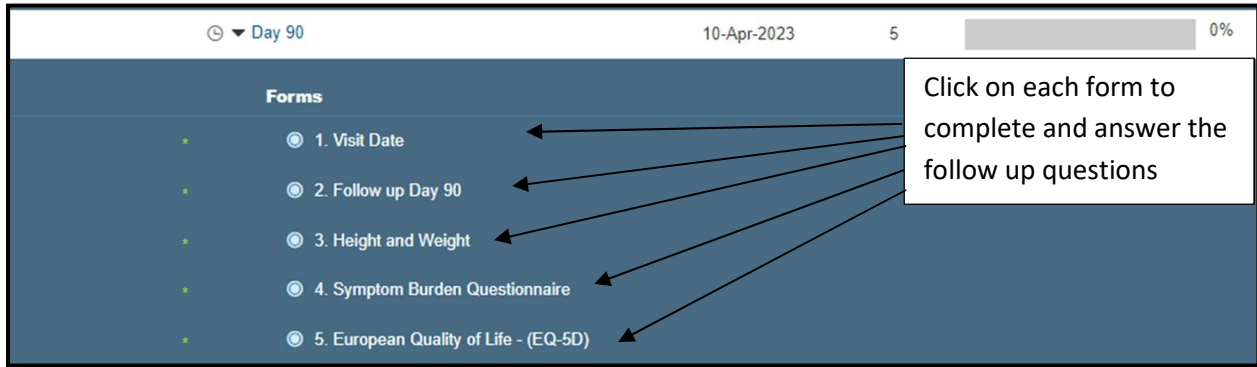
The visit date should be within the range of the visit +/- 1 day.



Event	Date	Count	Progress
Day 21	31-Jan-2023	1	0%
<b>Forms</b>			
1. Follow up Day 21			
Day 28	07-Feb-2023	1	0%
<b>Forms</b>			
1. Follow up Day 28			

### Day 90 form

Click the Day 90 Event to view all the forms listed for completion. Open each form to enter the required data.



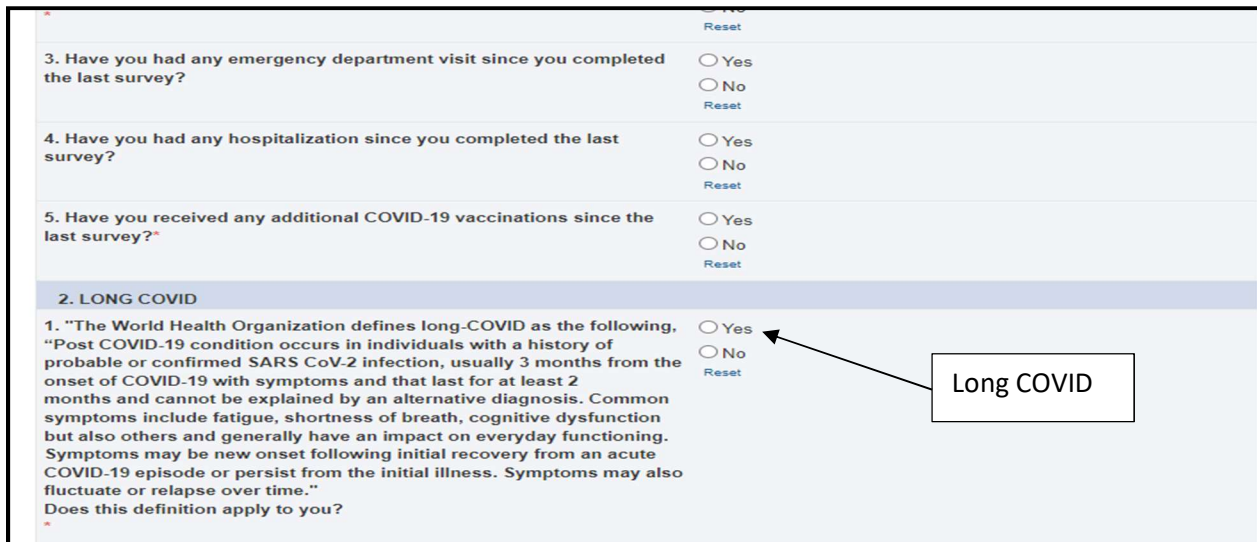
Day 90 10-Apr-2023 5 0%

**Forms**

- 1. Visit Date
- 2. Follow up Day 90
- 3. Height and Weight
- 4. Symptom Burden Questionnaire
- 5. European Quality of Life - (EQ-5D)

Click on each form to complete and answer the follow up questions

The Day 90 follow-up includes the questionnaire on Long COVID.



3. Have you had any emergency department visit since you completed the last survey?  Yes  No [Reset](#)

4. Have you had any hospitalization since you completed the last survey?  Yes  No [Reset](#)

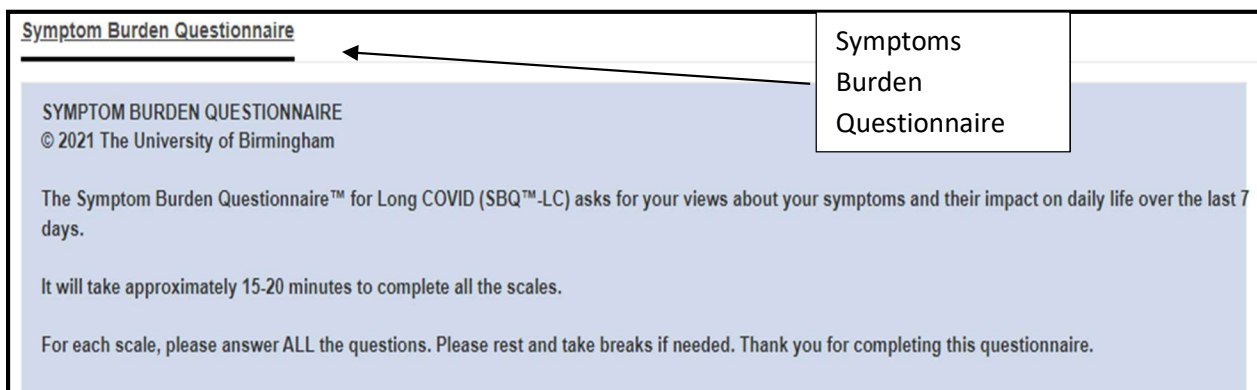
5. Have you received any additional COVID-19 vaccinations since the last survey?  Yes  No [Reset](#)

**2. LONG COVID**

1. "The World Health Organization defines long-COVID as the following, "Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time." Does this definition apply to you?  Yes  No [Reset](#)

Long COVID

The Symptoms Burden questionnaire includes questions on Breathing, Pain, Circulation, Fatigue, Memory, Thinking and communication, Memory, Sleep, Ear, Nose and Throat, Stomach and Digestion, Muscles and Joints, Mental health and Wellbeing, Skin and Hair, Eyes, other symptoms, and the impact on daily life



Symptom Burden Questionnaire

SYMPTOM BURDEN QUESTIONNAIRE  
© 2021 The University of Birmingham

The Symptom Burden Questionnaire™ for Long COVID (SBQ™-LC) asks for your views about your symptoms and their impact on daily life over the last 7 days.

It will take approximately 15-20 minutes to complete all the scales.

For each scale, please answer ALL the questions. Please rest and take breaks if needed. Thank you for completing this questionnaire.

Symptoms Burden Questionnaire

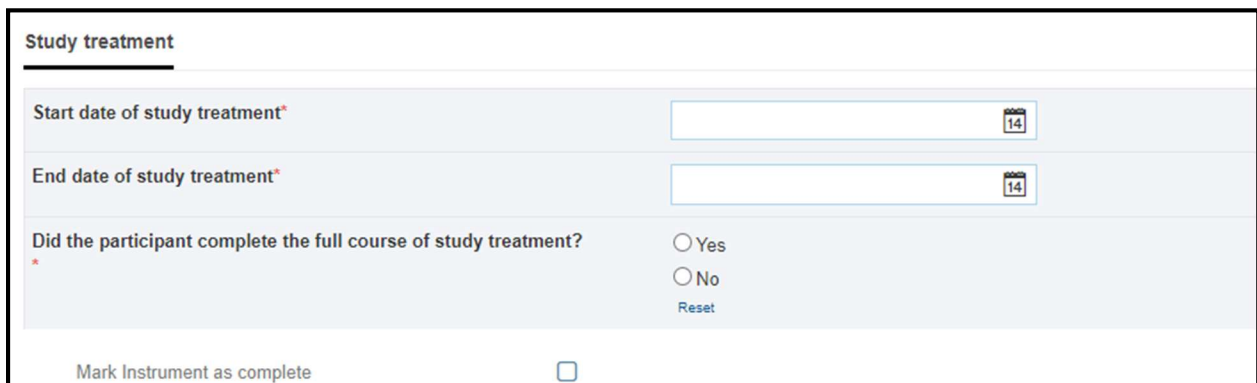
### Week 36 form

Click the Week 36 Event to view all the forms listed for completion. Open each form to enter the required data.

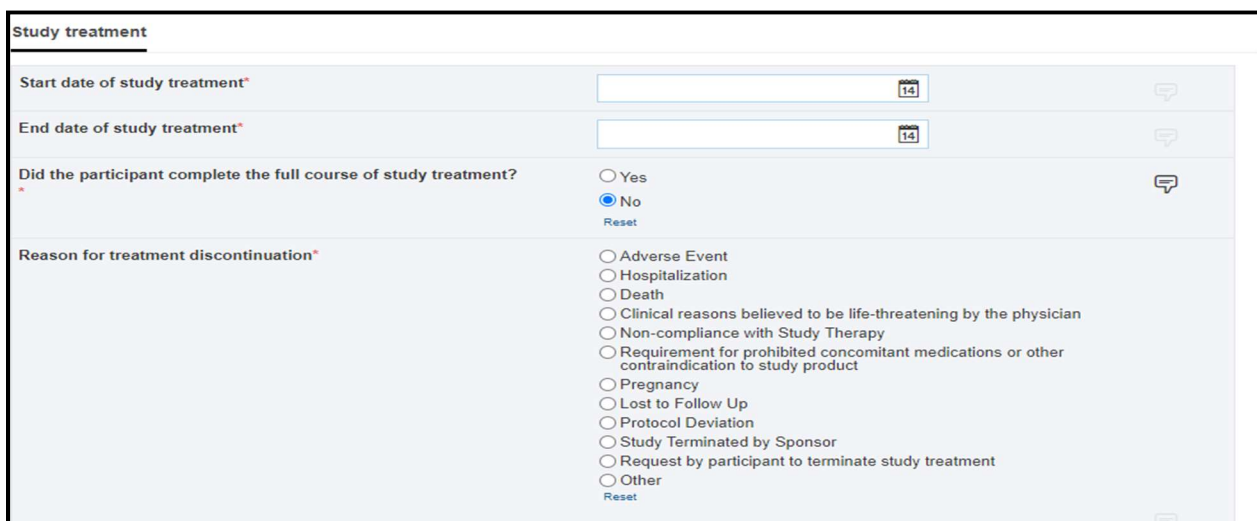


## Study Treatment (Paxlovid)

This form will only be available for participant's randomized Intervention arm



If the participant did not complete the full course, indicate the reason from the drop down list



## Concomitant Medication form

Complete if the participant is taking any medication



● Concomitant Medication Log ▾

**Version: (original)**  
**Subject ID: 101-6**  
**Event Date: 10-Jan-2023**

**Medications**

Is participant taking any medications?\*

Yes  
 No  
[Reset](#)

Mark Instrument as complete

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● Concomitant Medication Log ▾ Select Language:

**Version: 2**  
**Subject ID: 101-19**  
**Event Date: 30-May-2023**

**Medications**

Is participant taking any medications?\*

Yes  
 No  
[Reset](#)

**Medications**

Row No.	Med name:*	Obtained at which time point*	Primary reason for therapy:*	Indication:*	Route of administration:*	Other Route, specify:	Dose:
1	<input type="text" value="ibuprofen"/>	<input type="text" value="Select"/>	<input type="text" value="Select"/>	<input type="text"/>	<input type="text" value="Select"/>	<input type="text"/>	<input type="text"/>

[+ Add](#)

[+ Add](#)

If Yes, for taking any medication the table to detail the medication will appear.

Any new medication will be added by selecting the 'Add' button

Note - If Dose of medication is unknown enter '999'

### Adverse Events/Serious Adverse Event form

Complete all fields related to the reported Adverse Event

If an Adverse Event categories as 'Serious' events AE, the initial SAE is created by the system. Any additional SAE form has to be manually created.

**Adverse Events**

Did the participant experience any adverse events?\*

Yes  
 No  
[Reset](#)

Click yes if patient experienced AE

Mark Instrument as complete

Did the participant experience any adverse events?\*

Yes  
 No  
Reset

For any AE that became Serious, please complete a new SAE form.

Row No.	Adverse Event Term:*	AE Serious:*	Start Date:	Is this event an adverse drug reaction (ADR)?*	Intensity:*	Relatedness to study treatment:*	Action Taken Study Treatment:*
1	MI	<input type="radio"/> Yes <input type="radio"/> No Reset	<input type="text" value="14"/>	<input type="radio"/> Yes <input type="radio"/> No Reset	Select	Select	Select

**Annotations:**

- If Yes, popup window will open to enter AE details (points to the 'Yes' radio button)
- Click yes if serious (points to the 'Yes' radio button in the table row)
- If the Participant has more than one event, click Add to enter it (points to the 'Add' button)

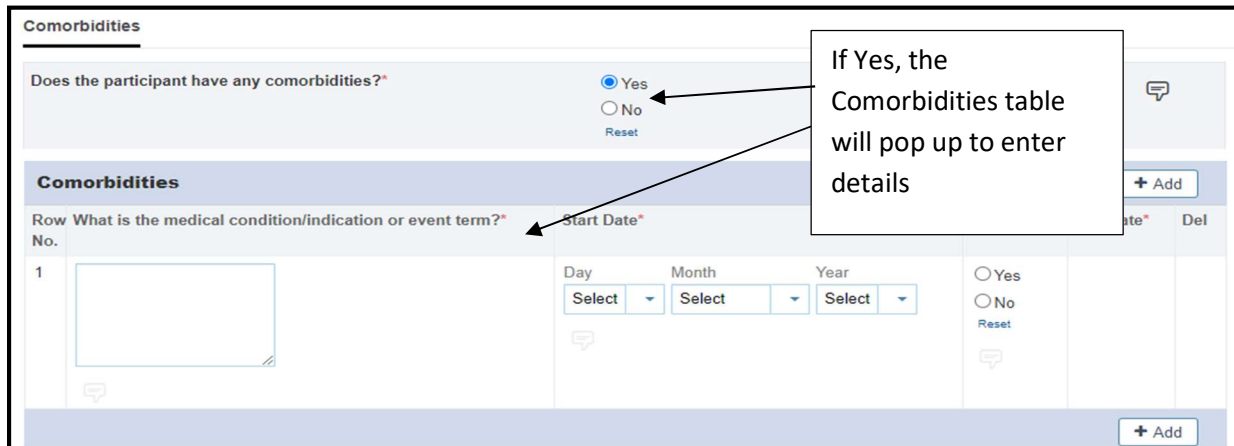
### As needed Form

This section lists all the forms that will be needed throughout the Participation of the study.

Events	Event date	Total Forms	Forms Completed
<ul style="list-style-type: none"> <li>As Needed Forms</li> </ul>	10-Jan-2023	7	0%
<b>Forms</b>			
<ul style="list-style-type: none"> <li>1. Comorbidity Log</li> <li>2. Vaccination for COVID-19</li> <li>3. Emergency Department Visit Log</li> <li>4. Hospitalization Log</li> <li>5. Death Form</li> <li>6. Protocol Deviation Log</li> <li>7. Phone Contact Visit</li> </ul>			

### 1- Comorbidity Log

To be completed if the Participant has any Comorbidities before or during participation in trial



**Comorbidities**

Does the participant have any comorbidities?\*

Yes  
 No  
Reset

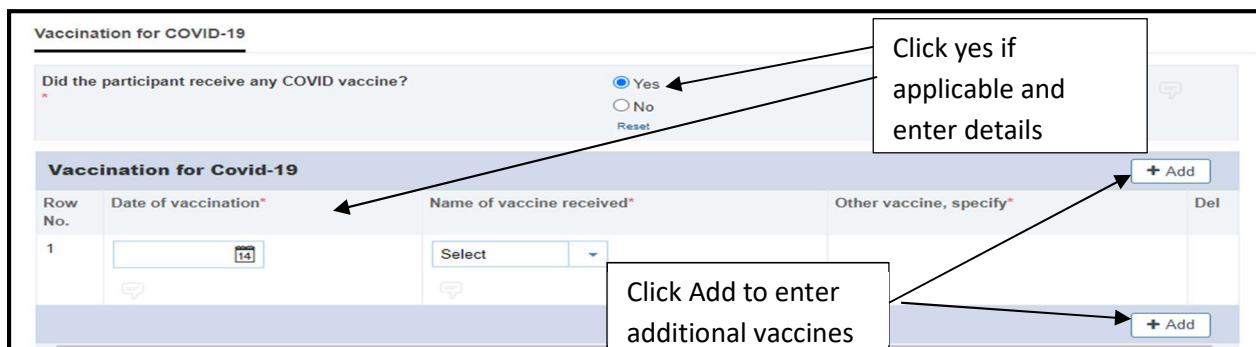
**Comorbidities**

Row No.	What is the medical condition/indication or event term?*	Start Date*	Yes/No	Del
1	<input type="text"/>	Day: <input type="text"/> Select Month: <input type="text"/> Select Year: <input type="text"/> Select	<input type="radio"/> Yes <input type="radio"/> No Reset	

+ Add

If Yes, the Comorbidities table will pop up to enter details

## 2- Vaccination for COVID-19



**Vaccination for COVID-19**

Did the participant receive any COVID vaccine?\*

Yes  
 No  
Reset

**Vaccination for Covid-19**

Row No.	Date of vaccination*	Name of vaccine received*	Other vaccine, specify*	Del
1	<input type="text"/> 14	<input type="text"/> Select		

+ Add

+ Add

Click yes if applicable and enter details

Click Add to enter additional vaccines

## 3- Emergency Department Visit Log

Complete if the participant has any reported Emergency room visit during participation in the trial.

If more than one visit, enter each separately.

### Note:

- Every ED visit, hospitalization, and death must be reviewed by two clinicians. They won't have access to any PHI, so there's no need for a separate clinician at each hub.
- For every ED visit or hospitalization, the Research coordinator must call the participant to gather more information. This could include the date of visit/admission, patient's chief complaint, reason for the ED visit/hospitalization, a description of the event, and so forth. The procedure would be similar in the event of a patient's death, where the patient's next of kin would be contacted (where possible) to provide more information
- After the first part of this process is completed, the clinicians will be automatically notified to prompt them to review the form and assess whether the event was related to COVID-19
- In the event of discrepancies between the clinicians' assessments—for example one deems the event as related to COVID-19 and the other considers it unrelated or "unclear"—the study monitor will be notified automatically to review the event and provide the final determination
- All procedures for the provincial team to follow are automated in the ED Log, Hospitalization Log, and Death Form in the database

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**Emergency Department Visit**

Did the participant have any Emergency room visits?\*

Yes  
 No  
Reset

**Emergency Department Visit**

Row No.	Date of presentation*	Was the participant under observation for > 12 hours?*	Chief complaint*	Reason for ER visit *	Description of the event*	Participant understanding of discharge diagnosis*	Was the participant hospitalized following the emergency room visit?*
1	<input type="text"/>	<input type="radio"/> Yes <input type="radio"/> No Reset	<input type="text"/>	<input type="radio"/> Complications related to COVID-19 <input type="radio"/> Any other cause <input type="radio"/> Unclear Reset	<input type="text"/>	<input type="text"/>	<input type="radio"/> Yes <input type="radio"/> No Reset

Click yes if applicable, and enter details

#### 4- Hospitalization log

Complete if the participant has any Hospital incidence during participation in the trial.

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**Hospitalization Log** - Select Language: Select

Version: 2  
Subject ID: 101-19  
Event Date: 30-May-2023

**Hospitalization Form**

Was the participant hospitalized during the study?\*

Yes  
 No  
Reset

**Hospitalization** + Add

Admission date at facility / hospitalization*	Chief complaint*	Reason for hospitalization*	Description of the event*	Participant understanding of discharge diagnosis*
<input type="text"/>	<input type="text"/>	<input type="radio"/> Progression or complications related to COVID-19 <input type="radio"/> Any other cause <input type="radio"/> Unclear Reset	<input type="text"/>	<input type="text"/>

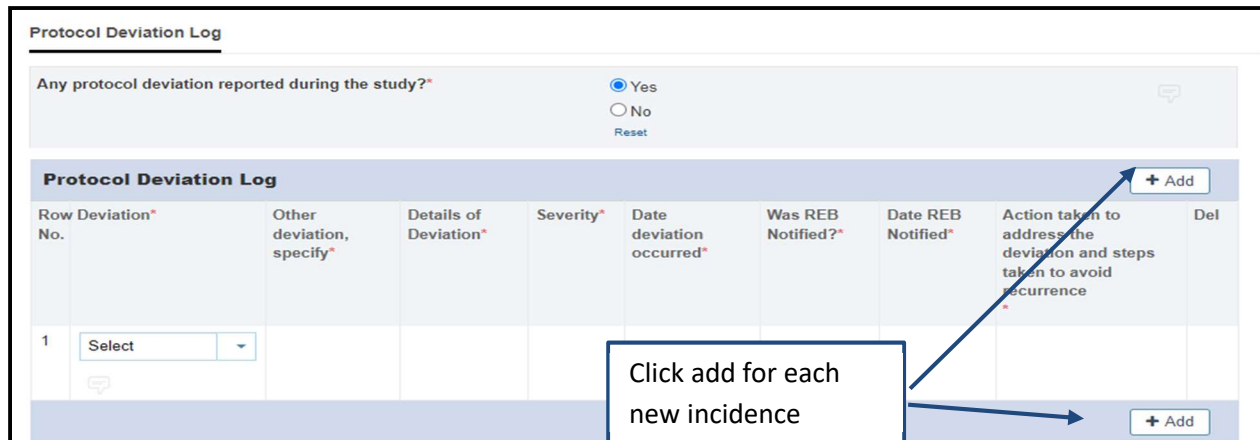
Click yes if applicable, and enter the data required

## 5-Protocol Deviation Log

Complete this form if there is Protocol Deviation

The **Protocol Deviations** form should record all Protocol Deviations. This form is setup as a repeating form, similarly to the Adverse Event/SAE form. Additional forms are created as new protocol deviations arise

If more than one protocol deviation, please enter each in separate field



**Protocol Deviation Log**

Any protocol deviation reported during the study?\*

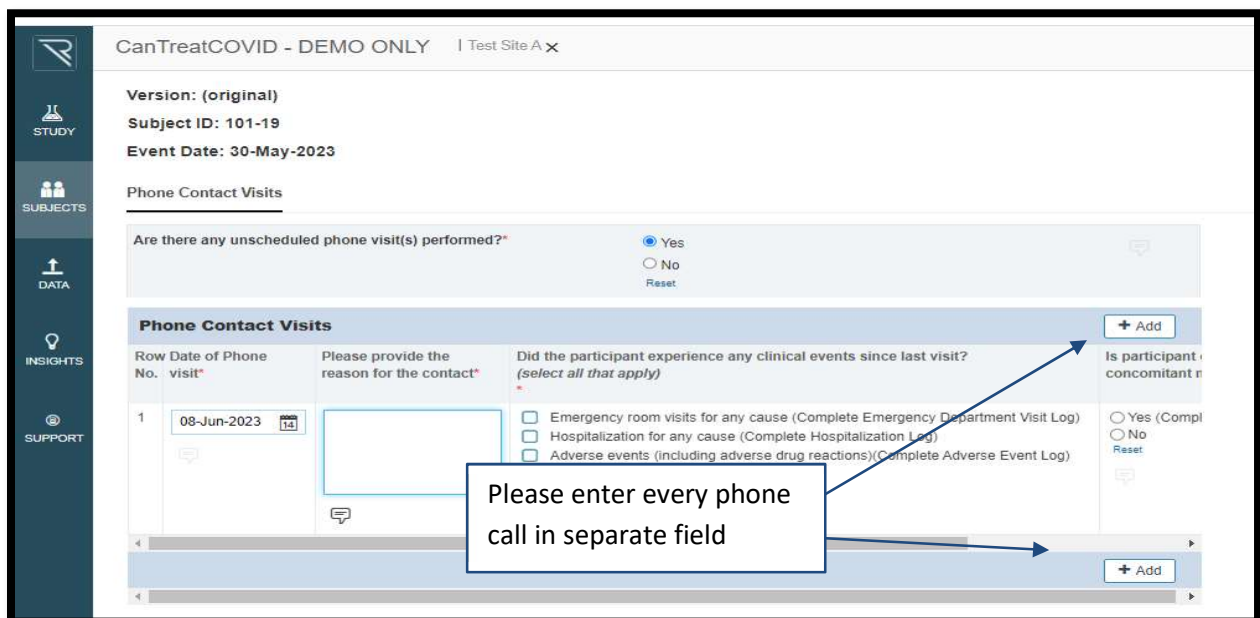
Yes  
 No  
Reset

Row Deviation No.	Other deviation, specify	Details of Deviation	Severity	Date deviation occurred	Was REB Notified	Date REB Notified	Action taken to address the deviation and steps taken to avoid recurrence	Del
1	Select							

Click add for each new incidence

## 6- Phone Contact Visit

Any unscheduled phone visits (i.e. outside of the study events) should be documented in the Phone Contact Visit Log



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Version: (original)  
Subject ID: 101-19  
Event Date: 30-May-2023

**Phone Contact Visits**

Are there any unscheduled phone visit(s) performed?\*

Yes  
 No  
Reset

Row No.	Date of Phone visit	Please provide the reason for the contact	Did the participant experience any clinical events since last visit? (select all that apply)	Is participant concomitant
1	08-Jun-2023		<input type="checkbox"/> Emergency room visits for any cause (Complete Emergency Department Visit Log) <input type="checkbox"/> Hospitalization for any cause (Complete Hospitalization Log) <input type="checkbox"/> Adverse events (including adverse drug reactions)(Complete Adverse Event Log)	<input type="radio"/> Yes (Complete) <input type="radio"/> No Reset

Please enter every phone call in separate field

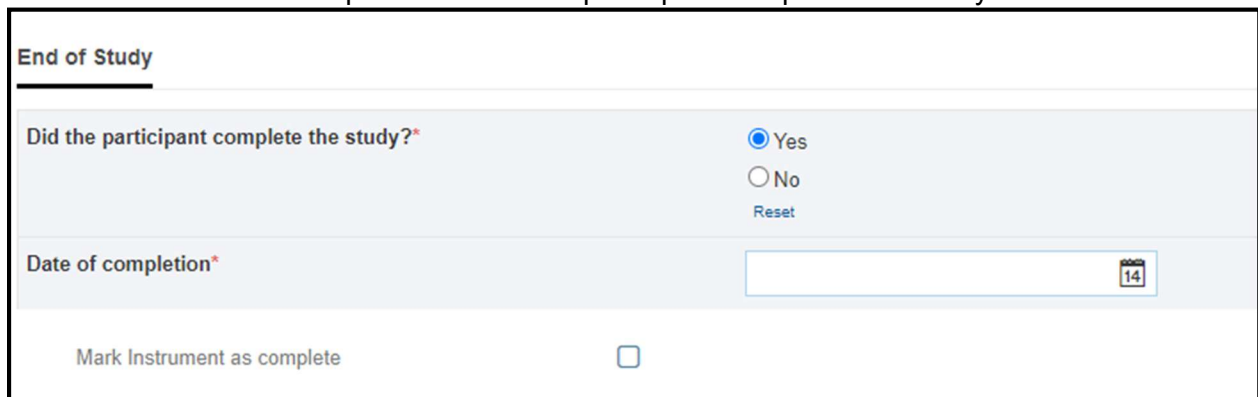
## Study Completion / Termination

The **Study End** folder contains one form: **Study Completion/Termination**. This form should be completed when a participant completes the study per protocol, or terminates the study early.

Note: End of Treatment form is completed for participants randomized to **the Interventional arm**


End of Study Completion/Termination

- Date of completion is the date participant completed the study



**End of Study**

Did the participant complete the study?\*  Yes  No   
 [Reset](#)

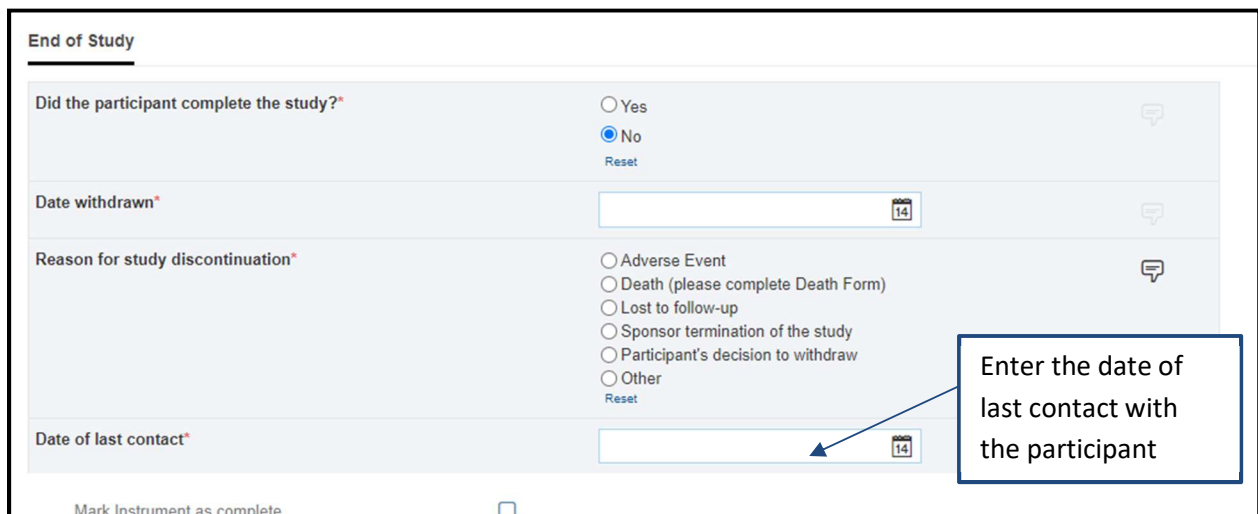
Date of completion\*  

Mark Instrument as complete

If the participant did not complete the study (first question is answered “No”), the reason for discontinuation and date of last contact should be entered.


Note:

- Date withdrawn – is the date the participant was withdrawn from the study (as deemed by the Study team)
- Date of last contact – is the date the Study team was last contacted the participant




**End of Study**

Did the participant complete the study?\*  Yes  No   
 [Reset](#)

Date withdrawn\*  

Reason for study discontinuation\*   
  Adverse Event   
  Death (please complete Death Form)   
  Lost to follow-up   
  Sponsor termination of the study   
  Participant's decision to withdraw   
  Other   
 [Reset](#)

Date of last contact\*  

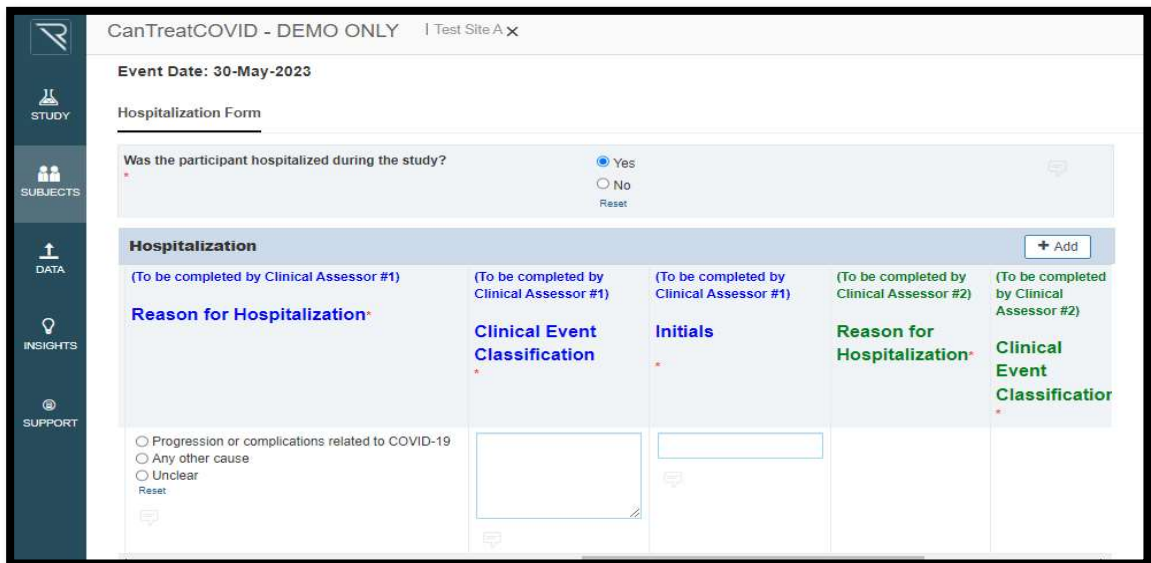
Enter the date of last contact with the participant

Mark Instrument as complete

## Clinical Assessment Section

### 1- Emergency Visit/Hospitalization

- In the event of Emergency Visit/Hospitalization the Research Coordinator initiates recording the event in fields (Date, Chief complaint, Reason, Description of event, Participant understanding of discharge diagnosis, was participant hospitalized following ER visit) as reported by the participant
- The Clinical Assessor 1 & 2 sections (i.e. Reason for ER visit/hospitalization, Clinical Event Classification, Initials) are to be completed by the respective Assessors.
- If the 'Reason for ER visit/hospitalization' is categorized differently by Clinical Assessor 1 & 2 then Clinical Assessor 3 section will populate to be completed by Clinical Assessor 3 as the final adjudication of the event



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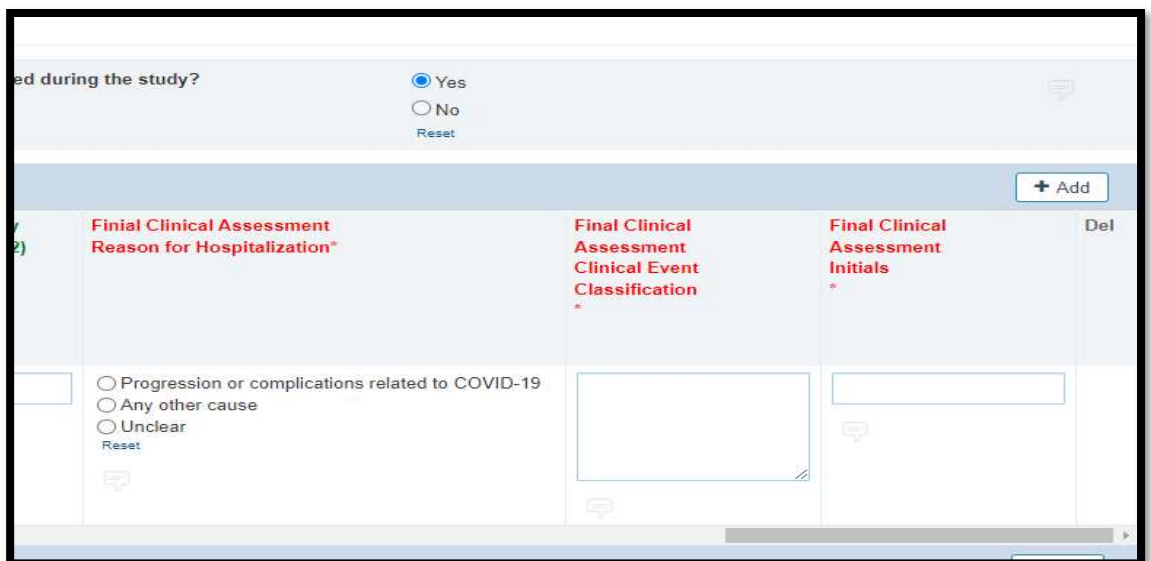
Event Date: 30-May-2023

Hospitalization Form

Was the participant hospitalized during the study?  Yes  No   
Reset

**Hospitalization** + Add

(To be completed by Clinical Assessor #1)	(To be completed by Clinical Assessor #1)	(To be completed by Clinical Assessor #1)	(To be completed by Clinical Assessor #2)	(To be completed by Clinical Assessor #2)
<b>Reason for Hospitalization*</b>	<b>Clinical Event Classification</b>	<b>Initials</b>	<b>Reason for Hospitalization*</b>	<b>Clinical Event Classification</b>
<input type="radio"/> Progression or complications related to COVID-19 <input type="radio"/> Any other cause <input type="radio"/> Unclear Reset				



ed during the study?  Yes  No   
Reset

**Final Clinical Assessment** + Add

(To be completed by Clinical Assessor #1)	(To be completed by Clinical Assessor #1)	(To be completed by Clinical Assessor #1)	Del
<b>Final Clinical Assessment Reason for Hospitalization*</b>	<b>Final Clinical Assessment Clinical Event Classification</b>	<b>Final Clinical Assessment Initials</b>	
<input type="radio"/> Progression or complications related to COVID-19 <input type="radio"/> Any other cause <input type="radio"/> Unclear Reset			

## 2- Death

- In the event of Death the Research Coordinator initiates completion of the fields (Date of Death, Was death related to SAR-COV2 disease? Cause of death, Description of event) as obtained.
- The Clinical Assessor 1 & 2 sections (i.e. Reason for death, Clinical Event Classification, Initials) are to be completed by the respective Assessors.
- If the 'Reason for death' is categorized differently by Clinical Assessor 1 & 2 then Clinical Assessor 3 section will populate to be completed by Clinical Assessor 3 as the final adjudication of the event

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**To be completed by Clinical Assessor #1**

**Reason for Death**

Mortality due to pulmonary complications  
 Cardiovascular mortality  
 Mortality from any other causes  
 Unclear  
 Reset

**Clinical Event Classification**

test

**Initials**

RCC1

**To be completed by Clinical Assessor #3 for Final Clinical Assessment**

**Reason for Death**

Mortality due to pulmonary complications  
 Cardiovascular mortality  
 Mortality from any other causes  
 Unclear  
 Reset

**Clinical Event Classification**

**Initials**

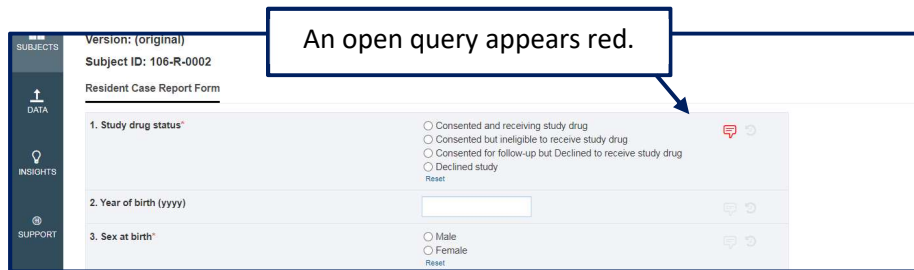
Mark Instrument as complete



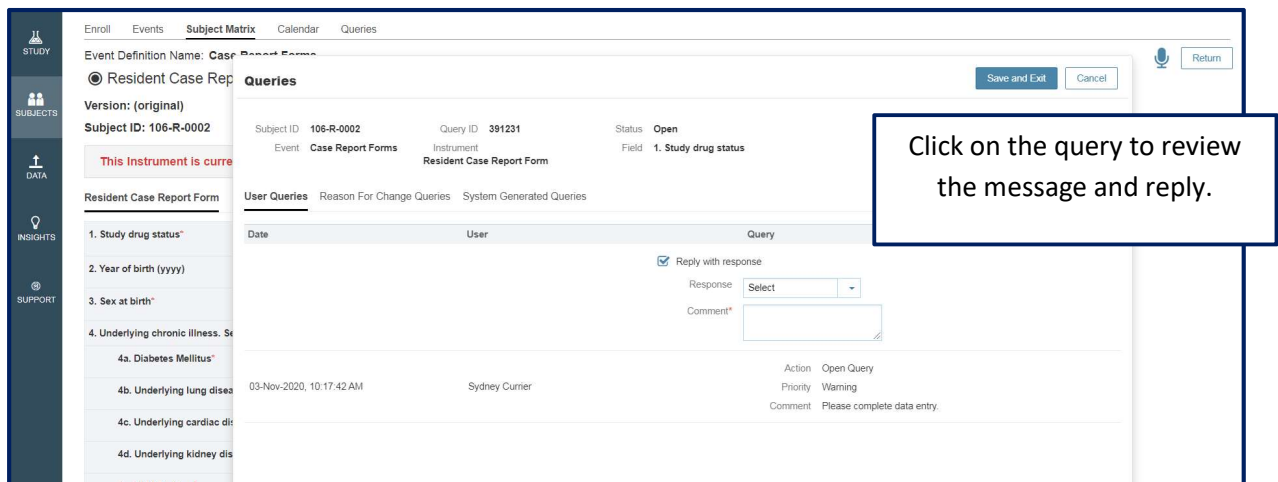
## Other Information

### 1- Queries

Queries can be opened by the Data manager, or they can be system generated queries (e.g. if a future date is entered, if a value is outside a specified range). When a query is opened, it will appear red. When a query has been responded to and is closed, it will appear green.



By clicking on the query, description of the query will be provided for action.

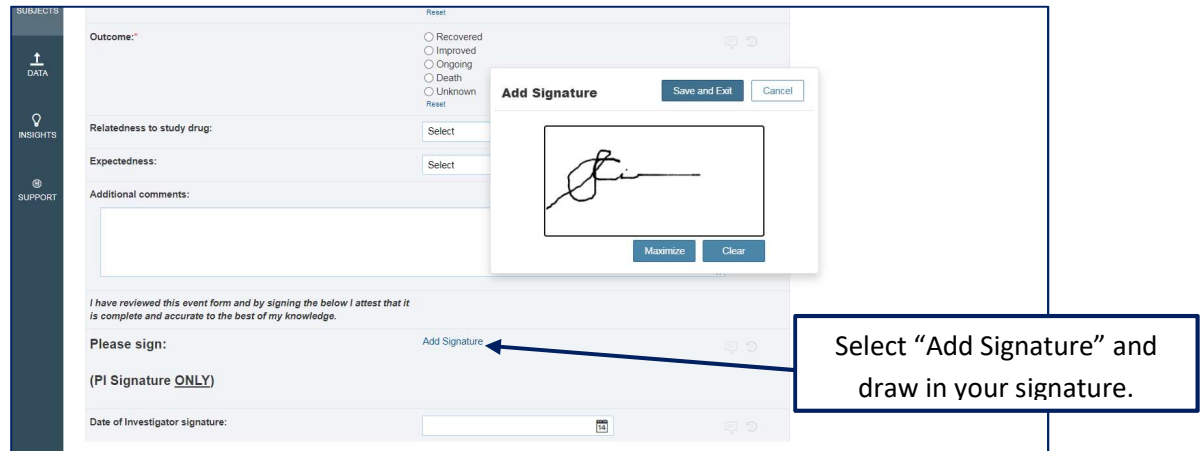


When the query is responded and actioned the query icon will appear in green. The Data Manager will review and close the query at a later time.

### 2- Investigator Signature on Serious Adverse Event form

Signatures are required on the **Adverse Events/SAE** Form when the event met the criteria for a SAE. The Qualified Investigator must be the one to sign this form.

The SAE form can be signed by clicking *Add Signature* in the signature field at the bottom of the page. Draw the signature, and click "Save and Exit". Enter in the date of signing as well.



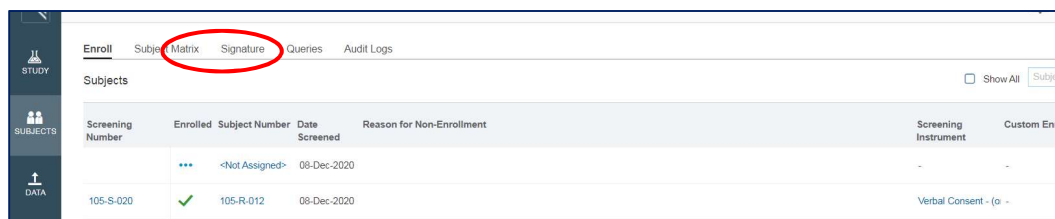
Be sure to save the data after signing, otherwise the signature won't be saved.

When a change is made to the SAE information, click the edit icon, and re-sign the form. The form must be re-signed when new information is available. Click on "edit signature" to update the signature.



The audit trail will provide a time-stamped list of signatures and updates to the form.

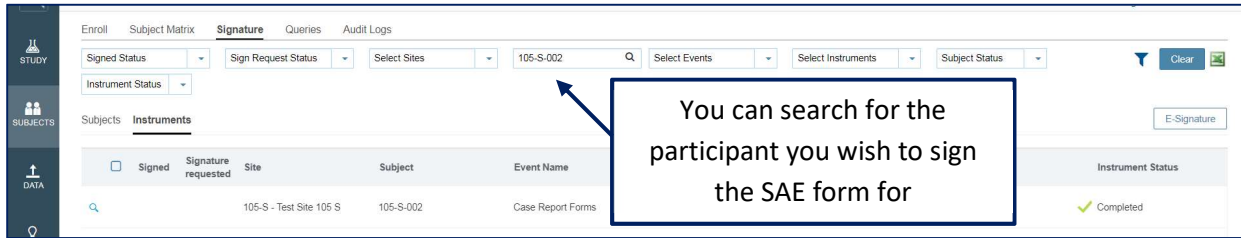
Once the SAE form is the final report, the form should be to e-sign the form. In order to do so, select **Subjects** in the left hand panel, and go to the top of the page and select "Signature".



There are two tabs: Subjects, and Instruments. In order to sign the SAE form, select the latter.

Go to the SAE form intended to sign, and click on the pencil icon to sign the form.

*Note: To edit the form at a later time the signature should be erased.*



Enroll Subject Matrix **Signature** Queries Audit Logs

Signed Status Sign Request Status Select Sites 105-S-002 Select Events Select Instruments Subject Status Clear

Instrument Status

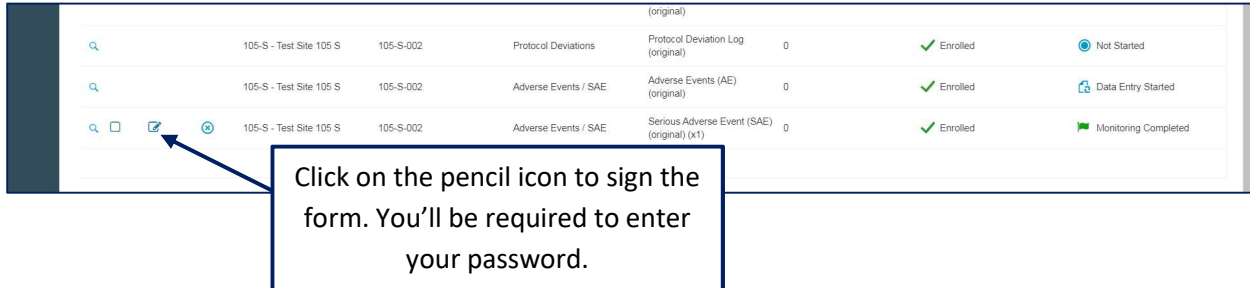
Subjects Instruments

Signed	Signature requested	Site	Subject	Event Name
<input type="checkbox"/>		105-S - Test Site 105 S	105-S-002	Case Report Forms

E-Signature

Instrument Status

Completed



Search	Site	Subject	Event Name	Count	Status	Actions
	105-S - Test Site 105 S	105-S-002	Protocol Deviations	0	Enrolled	Not Started
	105-S - Test Site 105 S	105-S-002	Adverse Events / SAE	0	Enrolled	Data Entry Started
<input type="checkbox"/>	105-S - Test Site 105 S	105-S-002	Adverse Events / SAE	0	Enrolled	Monitoring Completed

Click on the pencil icon to sign the form. You'll be required to enter your password.

The form can only be e-signed once Data management has been completed. E-signature will occur on the final SAE form.

The investigator will also be asked to sign the entire eCRF once it is completed. This will be done in the same way as described above, once all data management and monitoring has been completed. When the CRF is ready for investigator signature, the DM will request the signature. Signature is completed in the same way – navigate to the **Signature** page, go under the **Subject** tab and click the pencil icon for the appropriate participant.

### 3- Running Reports

To run reports, go to the left hand panel and click *Insights*. This will bring you to a list of reports that can be run, which are pre-programmed: e.g. a report of the queries, and CRF status.

To run a custom report, select "*Report Wizard*" at the top of the page. Follow the link for the *CRF Report Wizard*, and you will be brought to a page where you can select the form(s) you'd like to run a report on, or select certain fields. You can also run a report on participant's where a field has a certain value, by using the filters option.

The screenshot shows the 'Report Wizard' interface in the 'CONTROL-COVID' system. The interface includes a top navigation bar with 'Reports', 'Dashboards', 'Report Wizard', and 'My Reports'. A sidebar on the left contains 'STUDY', 'SUBJECTS', 'DATA', 'INSIGHTS', and 'SUPPORT'. The main content area is titled 'Report Wizard CRFs' and contains instructions, a 'Global Filters' section, and three steps: 'Step 1 - Fields to include in report', 'Step 2 - Filters (optional)', and 'Step 3 - Order the Results (optional)'. At the top right, there are buttons for 'Submit Report', 'Save', 'Schedule Report', and 'Cancel'. The user's name 'Sydney Currier\_cra' and role 'CRA-Monitor' are displayed in the top right corner.

**2. Go to "Report Wizard"** (Callout pointing to the 'Report Wizard' tab in the top navigation bar)

**1. Select Instrument** (Callout pointing to the 'Add all fields from Instrument' button in Step 1)

**5. Run report or save report** (Callout pointing to the 'Submit Report', 'Save', and 'Schedule Report' buttons at the top right)

**4. Add any filters** (Callout pointing to the 'Value' input field in Step 2)

**1. Select "Insights"** (Callout pointing to the 'INSIGHTS' menu item in the left sidebar)

## 18. Appendix I : Essential Document Management and Retention

According to the ICH-GCP E6R2 Section 8.0 the following lists the essential documents for the Conduct of Clinical Trials

<b>ESSENTIAL DOCUMENT CHECKLIST</b>				
<b>Prior to Clinical Trial Implementation</b>				
<b>ICH-GCP Section</b>	<b>Title of Document</b>	<b>Purpose</b>	<b>Located in Files of Investigator or Institution</b>	<b>Located in Files of Sponsor</b>
8.2.1	Investigator's Brochure	To document that relevant and current scientific information about the investigational product has been provided to the investigator.	X	X
8.2.2	Signed protocol and amendments, if any, and sample case report form (CRF)	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF.	X (copy)	X (original)
8.2.3	Information given to trial subject - Informed consent form (Including all applicable translations)	To document the informed consent.	X	X
	- Any other written Information	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent		
	Advertisement for subject recruitment (if used)	To document that recruitment measures are appropriate and not coercive.	X	
8.2.4	Financial aspects of the trial	To document the financial agreement between the investigator/institution and the sponsor for the trial.	X	X
8.2.5	Insurance statement (where required)	To document that compensation to subject(s) for trial-related injury will be available.	X	X

8.2.6	<p>Signed agreement between involved parties, i.e.:</p> <ul style="list-style-type: none"> <li>Investigator/institution and sponsor</li> <li>Investigator/institution and CRO</li> <li>Sponsor and CRO</li> <li>Investigator/institution and authorities (where required)</li> </ul>	To document agreements.	X	X (where required)
8.2.7	<p>Dated, documented approval of IRB of the following:</p> <ul style="list-style-type: none"> <li>Protocol and any amendments</li> <li>CRF (if applicable)</li> <li>Informed consent form(s)</li> <li>Any other written information to be provided to the subject(s)</li> <li>Advertisement for subject recruitment (if used)</li> <li>Subject compensation (if any)</li> <li>Any other documents given approval</li> </ul>	To document that the trial has been subject to IRB review and given the version number and date of the approval. To identify document(s).	X	X
8.2.8	Institutional review board/independent ethics committee composition	To document that the IRB is constituted in agreement with GCP.	X	X (where required)
8.2.9	Regulatory authorities authorization/approval/notification of protocol (where required)	To document appropriate authorization/approval/notification by the regulatory authority (ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s).	X (where required)	X (where required)
8.2.10	Curriculum vitae and/or other relevant documents evidencing qualifications of investigator(s) and sub-investigators	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects.	X	X
8.2.11	Normal value(s)/range(s) for medical/laboratory/technical procedure(s) and/or test(s) included in the protocol	To document normal values and/or ranges of the tests.	X	X

8.2.12	Medical/laboratory/technical procedures/tests and Certification or Accreditation or Established quality control and/or external quality assessment or Other validation (where required)	To document competence of facility to perform required test(s), and support reliability of results.	X (where required)	X
8.2.13	Sample of label(s) attached to investigational product container(s)	To document compliance with applicable labeling regulations and appropriateness of instructions provided to the subjects.		X
8.2.14	Instructions for handling of investigational product(s) and trial-related materials (if not included in protocol or investigator's brochure)	To document instructions needed to ensure proper storage, packaging, dispensing, and disposition of investigational products and trial-related materials.	X	X
8.2.15	Shipping records for investigational product(s) and trial-related materials	To document shipment dates, batch numbers, and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability.	X	X
8.2.16	Certificate(s) of analysis of investigational product(s) shipped	To document identity, purity, and strength of investigational products to be used in the trial.		X
8.2.17	Decoding procedures for blinded trials	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment.	X	X (third party if applicable)
8.2.18	Master randomization list	To document method for randomization of trial population.		X (third party if applicable)
8.2.19	Pre-trial monitoring report	To document that the site is suitable for the trial.		X
8.2.20	Trial initiation monitoring report	To document those trial-related procedures were reviewed with the investigator and investigator's trial staff.	X	X
<b>During the Conduct of the Trial</b>				



8.3.1	Investigator's Brochure updates	To document that investigator is informed in a timely manner of relevant information.	X	X
8.3.2	Any revisions to: <ul style="list-style-type: none"> <li>• Protocol</li> <li>• CRFs</li> <li>• Informed consent form</li> <li>• Any other written information provided to subjects</li> <li>• Advertisement for subject recruitment (if used)</li> </ul>	To document revisions of these trials- related documents that take effect during the conduct of the trial.	X	X
8.3.3	Dated, documented approval of institutional review board (IRB) of the following revisions: <ul style="list-style-type: none"> <li>• Protocol amendment(s)</li> <li>• Informed consent form</li> <li>• Any other written information to be provided to the subject</li> <li>• Advertisement for subject recruitment (if used)</li> <li>• Any other documents given approval</li> <li>• Continuing review of trial</li> </ul>	To document that the amendment(s) and/or revision(s) have been subject to IRB review and were given approval. To identify document(s) version number and date of the revision and/or approval.	X	X
8.3.4	Regulatory authority(ies) authorizations/ approvals/notifications where required for protocol amendment(s) and other documents	To document compliance with applicable regulatory requirements	X (where required)	X
8.3.5	Curriculum vitae for new investigator(s) and/or sub-investigators	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects.	X	X
8.6.6	Updates to normal value(s)/range(s) for medical laboratory/technical procedure(s)/test(s) included in the protocol	To document normal values and ranges that are revised during the trial.	X	X



8.3.7	Updates of medical/laboratory/technical procedures/tests, Certification or Accreditation or Established quality control and/or external quality assessment or Other validation (where required)	To document that tests remain adequate throughout the trial period.	X	X
8.3.8	Documentation of investigational product(s) and trial-related materials	To document all inventory, including detailed information regarding amounts, descriptions, shipping, receiving and return dates.	X	X
8.3.9	Certificate(s) of analysis for new batches of investigational products (sponsor only)			X
8.3.10	Monitoring visit reports	To document site visits by, and findings of, the clinical trial monitor.		X
8.3.11	Relevant communications other than site visits <ul style="list-style-type: none"> <li>• Letters</li> <li>• Meeting notes</li> <li>• Documentation of telephone calls</li> </ul>	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting.	X	X
8.3.12	Signed informed consent forms	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission.	X	
8.3.13	Source documents	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject.	X	
8.3.14	Signed, dated, and completed case report forms (CRFs)	To document that the investigator or authorized member of the investigator's staff confirms the observations recorded.	X (copy)	X (original)
8.3.15	Documentation of CRF corrections	To document all changes/additions or corrections made to CRF after initial data were recorded.	X (copy)	X (original)

8.3.16	Notification by originating investigator to sponsor of serious adverse events and related reports	Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with 4.11 of ICH GCP.	X	X
8.3.17	Notification by sponsor and/or investigator, where applicable, to regulatory authority(ies) and IRB(s) of unexpected serious adverse drug reactions and of other safety information	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB(s) of unexpected serious adverse drug reactions in accordance with ICH GCP 5.17 and 4.11.1 and of other safety information in accordance with 4.11.2 and 5.16.2.	X (where required)	X
8.3.18	Notification by sponsor to investigators of safety information	Notification by sponsor to investigators of safety information in accordance with ICH GCP 5.16.2.	X	X
8.3.19	Interim or annual reports to IRB and authority(ies)	Interim or annual reports provided to IRB in accordance with ICH GCP 4.10 and to authority (ies) in accordance with 5.17.3.	X	X (where required)
8.3.20	Subject screening log	To document identification of subjects who entered pre-trial screening.	X	X (where required)
8.3.21	Subject identification code list	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/institution to reveal identity of any subject.	X	
8.3.22	Subject enrollment log	To document chronological enrollment of subjects by trial number.	X	
8.3.23	Investigational product(s) accountability at the site	To document that investigational product(s) have been used according to the protocol.	X	X
8.3.24	Delegation of Authority log	To document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.	X	X



8.3.25	Record of retained body fluids/tissue samples (if any)	To document location and identification of retained samples if assays need to be repeated.	X	X
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## 19. Appendix II: Serious Adverse Event Reporting Forms

Note: All SAEs should be inputted in the eCRF and additionally detailed in this form and reported to the AHRC within 24 hours of site becoming aware of the event.

Email: [rekha.thomas@unityhealth.to](mailto:rekha.thomas@unityhealth.to); [Andrew.pinto@utoronto.ca](mailto:Andrew.pinto@utoronto.ca); [Benita.hosseini@unityhealth.to](mailto:Benita.hosseini@unityhealth.to)  
(Please notify the above team members via email upon completing the SAE reporting form)

<b>Site investigator:</b>		<b>Site #:</b>	<b>Type of report:</b> Choose an item.	
<b>Name of person completing this form:</b>			<b>Date of report:</b> Click here to enter a date.	
<b>Phone #:</b> (    ) -    ext:		<b>Email:</b>		
<b>PATIENT INFORMATION</b>				
<b>Patient ID:</b>		<b>Patient initials:</b>	<b>Date of birth:</b> Click here to enter a date.	
<b>Sex:</b> Choose an item.		<b>Height:</b> Choose an item.		<b>Weight:</b> Choose an item.
<b>Ethnicity (check all that apply):</b>				
<input type="checkbox"/> Aboriginal	<input type="checkbox"/> Arab	<input type="checkbox"/> Black	<input type="checkbox"/> Chinese	<input type="checkbox"/> Korean
<input type="checkbox"/> East Asian	<input type="checkbox"/> Filipino	<input type="checkbox"/> Japanese	<input type="checkbox"/> Jewish	<input type="checkbox"/> Latin American/Hispanic
<input type="checkbox"/> South Asian	<input type="checkbox"/> Southeast Asian	<input type="checkbox"/> West Asian	<input type="checkbox"/> White	<input type="checkbox"/> Other ethnic group
<input type="checkbox"/> Don't know	<input type="checkbox"/> Patient preferred not to answer			
<b>Date of randomization/enrollment:</b> Click here to enter a date.			<b>Study treatment assignment:</b> Choose an item.	

### DETAILS OF SERIOUS ADVERSE EVENT

<p><b>Date AE met serious criteria:</b></p> <p>Click here to enter a date.</p>	<p><b>Serious adverse event name (medical term):</b></p>
<p><b>Date investigator became aware of SAE:</b></p> <p>Click here to enter a date.</p>	<p><b>Grade/Severity:</b></p> <p>Choose an item.</p>
<p><b>Serious due to (check all that apply):</b></p> <p><input type="checkbox"/> Death</p> <p><input type="checkbox"/> Life-threatening situation</p> <p><input type="checkbox"/> New in-patient hospitalization</p> <p><input type="checkbox"/> Prolongation of hospitalization</p> <p><input type="checkbox"/> Persistent or significant disability or incapacity</p> <p><input type="checkbox"/> Congenital anomaly or birth defect</p> <p><input type="checkbox"/> Other important medical event (specify):</p>	<p><b>Description of the SAE:</b></p>
<p><b>Date of resolution:</b></p> <p>Click here to enter a date.</p> <p>OR <input type="checkbox"/> ongoing</p>	

**STUDY MEDICATIONS**

Treatment	Dosage	Start Date	Stop Date	Relationship to the Study Medication	Expectedness
Choose an item.	Choose an item.	Click here to enter a date.	Click here to enter a date.	Choose an item.	Choose an item.
Choose an item.	Choose an item.	Click here to enter a date.	Click here to enter a date.	Choose an item.	Choose an item.

Choose an item.	Choose an item.	Click here to enter a date.	Click here to enter a date.	Choose an item.	Choose an item.
Choose an item.	Choose an item.	Click here to enter a date.	Click here to enter a date.	Choose an item.	Choose an item.
Choose an item.	Choose an item.	Click here to enter a date.	Click here to enter a date.	Choose an item.	Choose an item.

**Other medication required?** Yes

If yes, specify:

Medication Name	Reason for Use	Dosage/Unit	Start Date	Stop Date (if available)
			Click here to enter a date.	Click here to enter a date.
			Click here to enter a date.	Click here to enter a date.
			Click here to enter a date.	Click here to enter a date.

**Any other action taken?** Choose an item.

If yes, specify:

**Additional comments:**

<b>Qualified Investigator's Signature:</b>	<b>Date (dd/mm/yyyy):</b>
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Health Canada Reporting Forms

CIOMS FORM

<b>SUSPECT ADVERSE REACTION REPORT</b>	

**I. REACTION INFORMATION**

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION <input type="checkbox"/> PATIENT DIED <input type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION <input type="checkbox"/> INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY <input type="checkbox"/> LIFE THREATENING
		Day   Month   Year	Years		Day   Month   Year	
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)						

**II. SUSPECT DRUG(S) INFORMATION**

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	

**III. CONCOMITANT DRUG(S) AND HISTORY**

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

**IV. MANUFACTURER INFORMATION**

24a. NAME AND ADDRESS OF MANUFACTURER		
	24b. MFR CONTROL NO.	
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE <input checked="" type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input type="checkbox"/> HEALTH PROFESSIONAL	
DATE OF THIS REPORT	25a. REPORT TYPE <input type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP	

### Adverse Drug Reactions (ADRs) for Clinical Trials Expedited Reporting Summary Form

Drug Code, Generic, or Brand Name:	Sponsor of Clinical Trial:	
	(CR) File Number:	
Report Submitted By:	Contact Name and Telephone Number:	
Protocol Title / Protocol Number (if applicable):		
Sponsor's Identification Number for the case:	Date of ADR Onset:	
<input type="checkbox"/> Fatal or Life-Threatening Unexpected ADR <input type="checkbox"/> All other serious and unexpected ADRs	Is there an ongoing clinical trial for this drug in Canada? Yes                      No <input type="checkbox"/> <input type="checkbox"/>	
<b>FOR DETAILED INFORMATION ON ADVERSE DRUG REACTIONS SUBJECT TO EXPEDITED REPORTING REFER TO PART C DIVISION 5 OF THE FOOD AND DRUG REGULATIONS AND E2A 'CLINICAL SAFETY DATA MANAGEMENT: DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING' HC / ICH GUIDELINES, 1995</b>	Is this a followup to a previous report? Yes                      No <input type="checkbox"/> <input type="checkbox"/>	
Reported ADR occurred in:	If yes, date of previous report (s):	
<input type="checkbox"/> Phase I - III study  <input type="checkbox"/> Phase IV study  <input type="checkbox"/> Spontaneous ADR	Has the drug been or is it currently marketed in Canada? If yes, provide DIN.	DIN:
ADR Country of Origin	Has the drug ever been released under the Special Access Programme/ Emergency Drug Release?	Yes                      No <input type="checkbox"/> <input type="checkbox"/>
<input type="checkbox"/> Canada <input type="checkbox"/> Other	Is there a clinical trial application for this drug under review in Canada?	Yes                      No <input type="checkbox"/> <input type="checkbox"/>
Signature:	Date:	Is there a new drug submission for this drug under review in Canada? Yes                      No <input type="checkbox"/> <input type="checkbox"/>
<b>ADR Reports must be provided by the following deadlines:</b>  <b>Fatal and Life Threatening Unexpected ADRs</b> 1. Initial Report within 7 calendar days 2. Comprehensive Report within an additional 8 calendar days		
<b>All Other Serious and Unexpected ADRs</b> 1. Comprehensive Report within 15 calendar days		

For Pharmaceutical Drugs: Please fax to: (613) 941-2121:

For Biologics and Radiopharmaceuticals: Please fax to: (613) 957-0364

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Adverse Drug Reaction (ADR) Expedited Reporting Summary Form (01-03)