Section 5.4. Human Syndromic Surveillance

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Objectives: To safely and ethically collect biological samples and data from humans in clinical settings.

This document was made possible by the generous support of the American people through the United States Agency for International Development (USAID) Emerging Pandemic Threats PREDICT program. It was drafted to support activities conducted under PREDICT and is intended for an audience of qualified professionals trained in standard, associated best practices. This guide is not intended for use by untrained individuals.

The authors assert that human surveillance and sampling should always occur in compliance with all applicable laws and regulations and should only be undertaken after securing all necessary permits and approvals, including ethical approvals.

For more information about the contents of this guide, please contact predict@ucdavis.edu.

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Section 5.4.1. Confirmation of Knowledge

When you are familiar with the information in this guide, take the PREDICT quiz ***Section 8.4.12. Human Syndromic Surveillance***.

PREDICT team members involved in the human surveillance activities described in this guide must be familiar with PREDICT's Institutional Review Board (IRB)-approved Master Protocol and related IRB obligations and should take and pass the quiz ***Section 8.4.18. PREDICT IRB Compliance and Monitoring***.

Section 5.4.2. Ethical and Training Considerations

All PREDICT activities involving human subjects must adhere to the most up-to-date version of the Master Protocol that has been approved by the UC Davis Institutional Review Board (IRB). The Master Protocol is available online through the PREDICT Operating Procedures e-Book under "Section 5.3" (https://eidith.org/Resources/PREDICTOperatingProcedureseBook.aspx). In addition, PREDICT activities involving human subjects may only be initiated after obtaining ethical approval from country institutional review boards.

Before implementing human subjects research related activities, documentation of all necessary country approvals along with attestations of trainings and adherence to ethical standards must be provided for review to UCD, and the UCD IRB as appropriate. These include

1) documentation of local IRB/ethical approvals and all approved documents (including the consent form and human questionnaire translated into the local language and any additional introduction letters and recruitment scripts planned for use);
2) completion of CITI training for all personnel listed on the country protocol (with training events documented in EIDITH);
3) training of project staff in procedures outlined in this SOP (with training events documented in EIDITH);
4) identification and documentation of local institutional biosafety committee (IBC) requirements (if any);
5) a consultation from a local expert summarizing risks to the area; and
6) an attestation that all personnel will adhere to USA and local government federal and state regulations regarding protection of human subjects research.

A checklist with both country IRB preparation guidance and post country IRB approval procedures relating to UC Davis IRB authorization has been created to assist country teams with this process (Appendix 1). Please review this checklist when preparing your application for

country IRB submission and to guide the final UCD IRB authorization process following local IRB approval. **The UC Davis IRB must approve each country's protocol before local activities are initiated.**

Effort will be made in all recruitment, consent, sampling, and interview activities to assure potential participants that their **participation in the study is completely voluntary** and that all information shared with researchers will be kept confidential. Every effort will be made to avoid coercion and ensure the privacy, respect, dignity, and freedom of each participant**.**

PREDICT staff named on the country protocol must complete Collaborative Institutional Training Initiative (CITI) training in human research ethics for biomedical researchers. In addition, PREDICT staff listed in the country protocol will need to ensure proper training of hospital/clinic POC(s) in study procedures, including recruitment, enrollment, informed consent, and sample collection, to ensure compliance with our Master IRB protocol and PREDICT practices.

When the staffing and implementation plans have been established, a plan should be developed to train clinic and hospital staff on protocol procedures to ensure implementation of agreed upon study design. Consideration should be given to how information will be presented, as not every facility staff member will need to know every detail of the PREDICT plan.

Section 5.4.3. Partnerships with Participating Health Facilities

Symptomatic patients will be recruited for syndromic surveillance in collaborating health facilities that have a catchment area that includes high-risk communities and PREDICT field sites where linked animal and human samples are being collected concurrently.

Syndromic surveillance of patients presenting to health facilities is necessary to identify symptomatic individuals. In order to optimize the chances of accessing the most relevant acute symptomatic individuals presenting at health facilities, appropriate selection and engagement of health facilities is key. While each individual site will require a slightly different approach, teams can be guided by the following methodology when looking to engage and maintain relationships with their sites in each country.

Assessment of the Health Facility

After initial engagement with key personnel, teams will need to work collaboratively with health facility personnel to consider the most optimal way to engage with clinical, laboratory and professional staff. A short form to assist with initial assessment of potential partners for syndromic surveillance is attached in Appendix 2 (Health Facility Screening Form).

Understanding Patient Flow

A thorough review of patient flow from arrival at the facility to discharge should be done by country teams through scoping site visits including:

- Where do patients normally present upon arrival to the facility and who would they first come into contact with for initial screening and assessment?
- What health professionals would potentially be involved in the assessment, diagnosis and treatment of individuals presenting with syndromes of interest throughout their stay at the health facility?
- If patients are not admitted to a health facility but might require follow-up care, what are the normal follow-up and discharge procedures?
- If patients are admitted to the health facility, what service units/departments might be involved in their care and treatment?

Understanding Staffing Needs

Understanding normal daily routine of staff and diagnostic practices, and identifying point of contact(s) (POC), will ensure that PREDICT procedures fit in as seamlessly as possible into the normal clinic routine.

- What is staff workload like?
- Who is your POC(s) to help identify symptomatic individuals?
- Who is your POC(s) for recruitment of appropriate individuals?
- Who may be best suited for assisting with study procedures, including sample collection and administration of questionnaire?
- Are these POC(s) likely to be the same person or different?
- What will be the best way to engage and train staff about study procedures and protocol?
- Are clinical staff skilled in proposed sampling procedures?
- How will costs for staff time at hospitals be covered and implemented?

The team should identify how PREDICT activities will fit into hospital workflow and develop an implementation plan that will need to be agreed upon with the hospital team. Decisions will need to be made about whether current hospital staff will be assigned additional duties or whether a new staff person(s) will be hired.

A detailed implementation plan, taking into consideration the following issues, should be developed with participating hospital staff:

- What are some potential barriers to implementation?
- What level of visibility and follow-up will be appropriate to keep sites engaged for the duration of the study?
- How will you maintain clear and open communication with health facility staff?
- What is the plan if key personnel involved in implementation leave the health facility?
- How will you take into consideration any known or observed differences religious/ethnic/immigration status in targeting individuals for recruitment?
- How will you monitor for adverse events?

Section 5.4.4. Patient Recruitment in Hospitals and Clinics

PREDICT targets patients that have been recently admitted to clinics and hospitals with acute conditions that match the case definitions for undiagnosed febrile syndromes of likely viral origin. **The objective of PREDICT's testing strategy is to detect novel viruses that are causing diseases in patients without a known etiology.** PREDICT testing should not overlap or duplicate diagnostic testing already being conducted at the hospital.
In communications with clinic medical staff, clinic administration and patients who might be enrolled, it is critical to note that **PREDICT's testing strategy will not directly inform on patient diagnoses or treatment. Our testing strategy is exploratory at the community level and not designed as a point of care diagnostic platform for normative (known) diseases.**
Case definitions should be reviewed closely with hospital POC(s) in advance of study implementation to identify patients for enrollment. Patients for enrollment may be identified in the emergency room, in the ward, or in the intensive care unit of each participating clinic and hospital. The POC(s) at each location should use the **clinical case definitions below** to target potential participants**.** Case definitions for syndromes have been standardized with those commonly used by WHO and CDC to allow national health authorities to interpret data in an international context.

Syndromic Category Clinical Case Definitions

Surveillance should be designed to target specific syndromes as appropriate in each clinical setting. Identification of relevant syndromes for each facility should be done on a facility-by-facility basis with participating partners and facility staff. Selected syndromes should reflect 1) high priority undiagnosed syndromes with likely animal origins, and 2) the clinical caseload of the hospital or clinic so that a large number of patients with targeted syndromes can be enrolled. Additionally, targeted syndromes should take into account local needs and seek to not duplicate ongoing syndromic surveillance programs by other partners at the clinic or hospital.

In larger referral hospitals with high caseloads, enrollment of patients in the PREDICT study will most likely want to focus on the following three severe syndromes and clinical case definitions to better target individuals with potentially unknown viral pathogens of concern:

1. **Severe Acute Respiratory Illness (SARI) of unknown origin:**
Acute onset of a fever greater than or equal to 38°C (100.4 °F) within the last 5 days
AND cough
AND requires hospitalization (or referral to a hospital)
AND absence of a more likely clinical explanation.

2. **Acute Encephalitis Syndrome (AES) of unknown origin:**
Acute onset of a fever (greater than or equal to 38°C or 100.4 °F) within the last 5 days
AND clinical signs consistent with meningitis, encephalitis, acute flaccid paralysis, or other

acute signs of central or peripheral neurologic dysfunction, as documented by a physician or a health-care provider
AND absence of a more likely clinical explanation.

3. **Hemorrhagic fever of unknown origin:**
Acute onset illness with a fever greater than or equal to 38°C (100.4 °F) within the last 5 days in a severely ill patient
AND clinical findings of bleeding or hemorrhage with no apparent cause
AND one or more of the following clinical findings: 1) severe headache, 2) muscle pain, 3) rash on the trunk within 3–4 days after rash onset, 4) vomiting, 5) diarrhea, 6) abdominal pain, or 7) pharyngitis, as documented by a physician or a health-care provider
AND absence of a more likely clinical explanation.

See also http://wwwn.cdc.gov/nndss/script/casedef.aspx?CondYrID=893&DatePub=2010-01-01

In smaller rural clinics, with limited diagnostic capabilities and lower patient caseloads, it may be appropriate to enroll a broader range of patients with suspected illness of unknown origin. In these circumstances, the following 2 clinical case definitions, for less severe and less specific syndromes, may be appropriate to target in addition to the severe syndromes targeted above.

4. **Fever of Unknown Origin (FUO):**
A temperature greater than or equal to 38°C (100.4 °F) for more than 24 hours as reported or measured by the patient or a health-care provider
AND absence of a more likely clinical explanation or failure to reach a diagnosis.

5. **Influenza-like Illness (ILI) of unknown origin**:
Acute onset of a fever greater than or equal to 38°C (100.4 °F) within the last 5 days.
AND cough
AND absence of a more likely clinical explanation.

Be sure to follow the most up-to-date version of the PREDICT Master IRB protocol with respect to all procedures, including recruitment, enrollment, inclusion, and exclusion criteria, and sample sizes.

Additional Enrollment Criteria and Considerations

PREDICT and hospital/clinic staff must take special care to ensure that patient recruitment and enrollment is not adversely impacting patients seeking medical care, or hindering patients' ability or willingness to seek medical care in any way. Recruitment and enrollment of patients should only occur after patients have established access to health services. Patient recruitment for this study should not be linked to patient intake or admission. Enrollment must be completely voluntary.

Eligible individuals should be recruited as soon as safely possible after presentation to the health facility, and after initial screening to ascertain whether patients meet the above clinical case definition, in order to maximize the utility of the biologic specimen collected. Successful recruitment of syndromic individuals will require monitoring of incoming patients to health facilities. Recruitment from health facilities involves many coordinated steps, involving coordination between PREDICT and health facility staff.

In addition to the clinical case syndromes identified above, inclusion and exclusion criteria outlined in the approved Master IRB protocol that must be applied to all PREDICT studies is reiterated below:

Additional Inclusion Criteria	***Exclusion Criteria***
1. Adults (18 years of age or greater) who provide informed consent	1. Individuals aged 18 years or older who refuse to provide informed consent, a parent or guardian of a child who refuses to provide consent on behalf of their child, or a child 12 years or older unable or unwilling to provide assent
2. Children (2 -17 years of age) * with an accompanying parent or guardian who is able to provide informed consent. Assent of children 12 years or older also required.	2. Adults unable to provide informed consent, including individuals with physiologically or medically induced cognitive impairments. **
3. Pregnant women	3. Children without an accompanying parent or guardian who is able to provide informed consent
	4. Children < 2 year of age
	5. Prisoners

**Children defined as 2-17 years unless the age of majority in a participating country differs. In these cases, the age range for children will be listed in the country specific IRB protocols.*

***Patients who are incapacitated and unable to provide informed consent may be enrolled if an appropriate patient representative (e.g., family member) is present, willing, and able to provide consent on the patient's behalf. If, in the course of study operations, such a patient become capable of providing informed consent, the patient will be directly consented.*

Section 5.4.5. Determining the Number of Patients to Enroll in Clinical Settings

Estimated sample sizes of patients approved in the Master IRB is a maximum of 1,620 in each country for syndromic surveillance activities over the course of the project. Any deviations from this total estimate will need to be reviewed and authorized by the UCD IRB (See Section 5.8.1b).

Patients meeting targeted case definitions should be enrolled systematically across the year so that the patient population is sampled across all relevant seasons. Monthly sample sizes throughout the year should reflect a consistent proportion of patients meeting targeted case definitions.

In general, patients should be enrolled using a quota system until approximately 20% of the participants are children < 18 years of age and 80% are adult. For larger hospitals and clinics, interval sampling will be implemented by selecting every N^{th} case at the site among those individuals who meet enrollment criteria. The interval should be determined by country teams based on an evaluation of the expected number of cases presenting at the site within a given year in order to best meet study design and sample size criteria. For example, in a large hospital with many patients meeting enrollment criteria, the first patient meeting criteria would be selected for study participation followed by selection of every 3^{rd} or 5^{th} individual (depending on the appropriate interval) until the maximum sample size is obtained.

Procedures for Patients in Hospitals and Clinics

Section 5.4.6. Overview of Procedures in Hospitals and Clinics

PREDICT and hospital/clinic staff should consider and make arrangements to conduct the following steps. These steps may need to be adjusted depending on the circumstances of each enrolled health facility. An overview is summarized below for ease of use in training PREDICT staff. Details for each procedure are described further below and in the IRB protocol.

Outline of Activities Involving Patients:

1. **Patient Triage and Intake**: Patients arrive at health facilities and present to patient triage and/or intake units. Clinic or hospital POC(S) will assess patient etiology as part of their normal routine. Following patient triage and intake, patients with presenting syndromes of interest will need to be actively referred to PREDICT POC(s). This active referral will deviate from the health facility staff's normal routine. Country coordinators will need to establish a protocol with the health facility staff prior to beginning recruitment and *ensure that this process does not negatively impact patient access to health services, or health facility workflow*.

2. **Administer Informed Consent**: Patients determined eligible via the Screening Form will be offered participation in PREDICT. Study staff will administer the informed consent form to interested patients. *No study procedures can be conducted without having first obtained informed consent.* Informed consent must happen in a private space and should not involve anyone other than research staff, the patient, a representative if the patient is incapacitated, an impartial witness if the participant is illiterate, and a

parent/guardian if the patient is a child. Once consented, the patient is considered an enrolled participant.

Note: The presence of clinical staff directly involved in patients' care during the consenting process should be construed as coercive. Patients may think they need to consent in order to continue receiving care. PARTICIPATION MUST BE STRICTLY VOLUNTARY.

3. **Collect PREDICT Specimens**: Once enrolled, PREDICT POC(s) will coordinate human biologic specimen collection. Samples may be taken concurrently when collecting samples for normative diagnostics or independently.

4. **Administer Human Questionnaire**: Study staff will administer the **standardized IRB approved human questionnaire to all enrolled participants** at a point in time that ensures patient privacy and is not disruptive to patient care. The human questionnaire must be administered to all patients from which a biologic specimen is collected.

   In clinical settings with critically ill patients, the full human questionnaire may not be possible or appropriate to administer. At a minimum, the "**Core Human Questionnaire" (pages 1-6 of Human Questionnaire)** and the **Human Hospital & Clinic Module** for Patients should be completed.

5. **Normative Diagnostics**: Throughout a patient's inpatient stay, a variety of normative diagnostics, if available, might be run by the health facility staff to determine patient etiology. If additional sampling procedures are conducted as part of normative diagnotics that do not overlap with PREDICT specimen types already collected, PREDICT may request that any unused or remaining diagnostic specimen types be saved from patients enrolled in the PREDICT study (such as cerebral spinal fluid, pleural fluid, etc) to expand the sample set for PREDICT testing.

   Once health facility staff obtain diagnostic results, patients' etiologies will be updated. This information can be used to prioritize samples for testing with PREDICT viral family protocols. If an etiology for fever or clinical syndromes is identified, samples from this patient are of lower priority, unless a novel viral infection is still suspected because the objective of PREDICT's testing strategy is to detect novel viruses that are causing disease in patients. PREDICT POC(s) will need to follow the inpatient progress of enrolled participants to know when etiologies are updated.

6. **Second PREDICT Serum Specimen Collected**: 7 days after the first sample collection or later, an additional serum sample (the discharge serum) should be obtained from participants when possible.

Section 5.4.7. Administering Informed Consent

Participation of human subjects in the study will be strictly voluntary and will require signed, informed consent. All consent discussions and procedures will be conducted in a private room or location with a trained staff member fluent in the local language. Only the PREDICT staff person/POC and the patient will be present during the consent process. Additionally, the patient's representative if the participant is incapacitated, an impartial witness if the participant is illiterate, and/or the patient's parent or guardian if the patient is a child, can be present during the consent process. CITI-trained PREDICT staff may occasionally observe consent procedures to ensure they are appropriately and thoroughly conducted.

All participants will be given an information sheet and consent form prior to being asked to participate in this study. Potential participants will review the information sheet and consent form with the PREDICT POC(s) and will be given time to ask questions. During the review, POC(s) will explain details of the study, including:

- Purpose of the study,
- Why they were selected,
- What will happen if they enroll in the study,
- Potential risks due to their participation,
- How their participation is beneficial to understanding viral pathogens in the community,
- That their participation is completely voluntary,
- How they can withdraw their participation at any time,
- How participation in the study will not interfere with, nor affect, their routine medical care in the health facility,
- How PREDICT testing is exploratory research, and not diagnostic, and this will not inform on patient diagnosis or treatment.
- Test results, these will not be directly communicated back to the participant

PREDICT Study staff POC(s) will review the consent form with participants, answering any questions participants have. It should be made clear to all participants that any data or information collected will be kept strictly confidential. Measures will be taken to ensure the respect, dignity, freedom, and privacy of each participant. PREDICT POC(s) involved in the enrollment and recruitment of participants must avoid coercion of any kind. The PREDICT representative conducting informed consent procedures will not enroll the participant in the study unless confident that the participant or his or her representative fully understands the study and all potential associated risks and benefits.

After reviewing the forms and discussing the study, individuals who agree to participate will sign and date two copies of the consent form, and the staff member conducting the consent discussion will also sign and date the consent forms. If the participant is a child, he or she will

be asked to provide assent to participate in the study and the patient's parent or guardian will sign and date the consent forms. If the patient is illiterate, the witness will sign and date two consent forms. If the patient is incapacitated, his or her representative will sign and date the consent forms. The patient will be given a copy of all consent documents.

Section 5.4.8. Brief Overview of PPE

Minimum PPE Required for Safe Human Specimen Collection
The minimum PPE used by healthcare professionals for human sampling should follow the CDC and other international guidelines for best practices and precautions.

The following are the minimum PPE requirements:

- Gloves
- Designated clothing (which may include gown, apron, long sleeve lab coat)
- Closed-toed shoes
- Eye protection (glasses or goggles), face mask or shield

(See the PREDICT ***Biosafety and PPE Guide (Section 4.1)*** for detailed instructions regarding PPE Use.)

Section 5.4.9. Collecting Clinical Specimens

Enrolled patients who satisfy inclusion criteria as described above (with signed consent form) will be asked to provide clinically relevant biological specimens based on clinical symptoms. To ensure patient privacy, no identifying information from patients will be stored with, or paired with, biological specimens or test results.

Patients should be enrolled with specimens and data collected within 3-5 days of onset of symptoms if possible, and not longer than 10 days after onset becase we are targeting viral etiologies. Critically, patients must have specimens collected as soon as possible after admission in order to ensure they are captured in the viremic phase and/or while they are still shedding the virus, if the illness turns out to be of viral origin. If feasible, hospitalized patients may have repeated serum samples collected at seven days after enrollment, or later before discharge.

Biological samples may only be collected by trained personnel certified by the country's authority for certification of medical professionals. All personnel collecting or handling PREDICT biological specimens must wear appropriate PPE and practice Universal Precaution procedures.

Study representatives should conduct activities in a secure location and a confidential

manner to ensure participant privacy. A barrier or private room should be utilized so that participants cannot be seen by outside observers while they are being sampled. During and immediately after sample collection, trained medical professionals and/or clinic staff will monitor specimen collection site(s) and treat any complications according to existing health facility protocols.

Summary of Clinical Specimen Types

The decisions about which specimens to collect should be based on the patient's clinical symptoms (eg. blood and oral/nasal swabs for respiratory patients;):

- 2 x Oral or Nasal or Oropharyngeal swabs - one in 500 µL VTM and one in 500 µL Trizol
- 2 x Whole blood samples - one with max of 500 µL of whole blood in 500 µL VTM and one with max of 500 µL of whole blood in 500 µL Trizol
- 2 x Serum samples - 2 x 500 µL aliquots, frozen without media
- 2 x Urogenital swab samples – one swab each in 500 µl VTM and 500 µl Trizol
  OR
  2 x Urine samples - one 500 µL urine sample each in 500 µL VTM and in 500 µL Trizol
- 2 x Rectal swabs - one swab in 500 µL VTM and one in 500 µL Trizol
  OR
  2 x Fecal samples - 0.5cc (pea size) feces in 500 µL VTM and 0.5cc (pea size) feces in 1 mL Trizol
- Additional samples or aliquots of specimens collected for standard normative diagnostic purposes by hospital staff may be requested, as appropriate and based on clinical symptoms (see below).

Whole Blood and Serum

Trained phlebotomists, doctors, or nurses will collect venous blood samples by standard venipuncture from the right or left antebrachium.

A minimum of two blood samples will be collected from each participant. Collect one sample into a vacutainer tube containing serum separator and the other into a vacutainer tube containing EDTA. For children aged 12 years or younger, collect a maximum of 6mL in each tube. From individuals aged 13 years and older, collect a maximum of 12mL per tube.

Ensure adherence to appropriate PPE while handling biological specimens.
Allow blood in the red top or serum separator tube to clot, then centrifuge. After clotting and centrifugation, aliquot a minimum of two (and up to four) 0.5 mL aliquots of serum into individual cryovials without Trizol or VTM.

From the EDTA lavender top tube, place up to 500 µL whole blood directly into 2 vials, one containing 500 µL VTM and one containing 500 µL Trizol. Mix each vial well.

Samples will be frozen immediately in liquid nitrogen and then transferred to an ultralow (-80°C) freezer as soon as possible for storage until analysis.

Note that two blood sampling events are warranted if feasible in a hospital or clinic setting, one on the day of enrollment and one seven days after enrollment or later (before discharge), to collect a serum sample only. If serologic assays are available for use for targeted viruses, a rise in IgM with convalescence might assist in establishing causality with disease syndromes.

Oral, Nasal, or Oropharyngeal Swabs

Each patient may have duplicate oral, nasal, or oropharyngeal swabs collected on the day of enrollment to the study.

Oral and nasal swabs will be collected by applying a sterile, flexible, nylon-tipped swab to the appropriate tissue and gently rubbing for 2-5 seconds. Oropharyngeal swabs will be collected by medically trained personnel by gently inserting sterile, flexible, nylon-tipped swabs into the pharyngeal cavity for 2-5 seconds and rotating while removing, as is done for diagnostic procedures.

Place each swab into its own vial, one containing 500 µL VTM and one containing 500 µL of Trizol, mix each tube well, and freeze immediately.

Rectal Swab or Feces

Rectal swabs will be collected by gently inserting 2 sterile, flexible, nylon-tipped swabs into the anal canal, moving them from side to side, and rotating while removing. Place each swab into a vial, one containing 500 µL VTM and one containing 500 µL of Trizol. Mix each tube well and freeze immediately.

If patients are to provide a stool sample instead, they will be provided containers labeled with their individual ID number and instructions on how to collect an uncontaminated fecal sample, including appropriate guidelines for hand washing after sample collection.

Add 500 µL (a pea-sized piece) of feces directly into each of two vials, one containing 500 µL VTM and one containing 1ml Trizol. Mix each tube well and freeze immediately.

Urogenital Swab or Urine

A urine sample will be collected in a sterile universal container. Patients will be provided containers labeled with their unique ID numbers and instructions on how to collect an uncontaminated urine sample, including appropriate guidelines for hand washing after

sample collection.

Add up to 500 µL of urine directly into each of two vials, one containing 500 µL VTM and one containing 500 µL Trizol. Mix each tube well and freeze immediately.

If urine can't be obtained, collect two urogenital swabs and place into two vials, one containing 500 µL VTM and one containing 500 µL of Trizol. Mix each tube well and freeze immediately.

Additional Samples

For hospitalized patients, PREDICT also may receive remnants or aliquots of appropriate clinical specimens that have already been collected for diagnostic purposes. PREDICT testing should be conducted on remaining sample aliquots only after standard diagnostic procedures have been completed to ensure PREDICT activities do not interfere with patient care. These samples may include urogenital swabs, cerebral spinal fluid (CSF), pericardial fluid, pleural fluid, ocular swabs, or others. PREDICT should collect these remnants or aliquots in keeping with the respective participant's clinical symptoms, for instance, pleural fluid would be sourced from participants with respiratory distress, CSF from participants with encephalitis, etc. These samples can be frozen at −80 °C without Trizol or VTM. If additional PREDICT analyses are done on hospital diagnostic screening samples, results will not be communicated to patients or participating health facilities.

Section 5.4.10. Medical History and Behavioral Risk Data Collection in Clinical Setting

All enrolled patients will complete the required elements of the ***Human Questionnaire*** and the ***Human Hospital and Clinic Module for Patients***. If appropriate given the clinical setting and patient condition, the full PREDICT Human Questionnaire with all relevant modules can be completed.[1]

Questionnaire data will be collected by trained staff in a strictly confidential manner. Individual interviews will be conducted in private with no other individuals within a 10-foot distance, ensuring that others cannot hear the interviews. A barrier will be created so that no other individuals can view the participant while they are in their interview. Staff will take care to pair interviewers and respondents by sex to ensure protection of women and children and privacy

[1] To access the Human Questionnaire and desired module bubble forms, log in to EIDITH at https://connect.eidith.org/. Click the "Download Bubble Forms" button and select "Human Questionnaire" under the Choose Type drop-down menu. Select the Questionnaire or module you wish to download, indicate the number of forms you would like, and press "Submit." When prompted to do so, click on the word "here" to download your form/s. Additional instructions for completing and uploading the forms may be found in the Videos and Instructions menus on the connect.EIDITH.org dashboard.

and confidentiality of responses. Children will not be interviewed in the absence of a parent or guardian.

As many questions are sensitive in nature, the presence of support persons may make it difficult for participants to feel comfortable answering questions honestly. PREDICT POC(s) should liaise with clinical staff and family members for critically ill participants, as appropriate, to determine the most patient-centered means of collecting sensitive data, while still maintaining the accuracy of the data collection methods.

Where participants are intubated and unable to communicate verbally, but alert and appropriately communicative, POC(s) may administer the human questionnaire using paper and pencil with participants, if possible. Where patients are sedated and/or comatose, a shortened version of the questionnaire may be completed with a family member or substitute decision maker, if deemed appropriate by all parties. The human questionnaire must be completed if a biologic specimen is drawn; therefore, if the POC(s) is unable to complete the questionnaire for any reason with a participant, they will be excluded from the study. In all instances, the decision to complete the human questionnaire with critically ill individuals must weigh the benefits and downsides with family/friends, clinical staff, and the research team. The POC(s) must also consider patient privacy in immobile or critically ill participants and deem if there is appropriate space in which to conduct the questionnaire to ensure privacy and confidentiality.

Participants may be given a small token of appreciation for participation in the study that is appropriate with local culture and customs and valued at no more than $10 USD. Local research teams will determine the most appropriate item to give as a token of gratitude to research participants. This item should be given to participants after consent and baseline sampling and interviews are complete.

Section 5.4.11. Record Maintenance and Ensuring Participant Privacy

A study participant log should be maintained at each site to track participant enrollment. Information on new participant enrollments should be added to the log in a timely fashion after their consent; the enrollment of pregnant women and children, in particular, should be noted. If, after signing a consent form, a participant decides that they wish to withdraw from study activities, this information must be recorded in the participant log. In addition, each site may wish to maintain a confidential linking log that links participant names to their unique identification number; this log should also be maintained in an up-to-date manner, with information on study enrollees added shortly after their consent. An example participant log is attached in Appendix III.

No identifying information from patients will be stored with or paired with questionnaire data, biological specimens, or analytical test results. Further, identifying information must not be stored electronically and must be stored securely in locked drawers or cabinets in areas accessible only by PREDICT staff. When questionnaires are moved to the country headquarters,

they will contain only coded data to ensure the safety and confidentiality of participants and will be maintained in a secure database. The only document that will link the participant with a unique ID number is the consent form, which will be stored in a locked file separately from participant data in the offices of the Country Coordinator.

Section 5.4.12. Reporting Results

The PREDICT team will inform collaborating partners of the aggregate patient test and behavioral risk findings as well as provide information about viral detection and zoonotic diseases detected, as appropriate. One key benefit of this study to participating clinics and hospitals is to enhance understanding of viruses that could be causing syndromes in local people but that have previously gone undiagnosed. This information will inform participating clinics and hospitals about viruses common in target patient communities and may lead to practices that could reduce exposure and health risks.

Report summaries of interpreted data generated from the project will be provided to the Ministry of Health for approval for release. Following approval for release, report summaries from the project can be shared with other in-country collaborating investigators and hospitals. Adverse events or serious adverse events will be included in report summaries provided to Ministries of Health upon request.

Section 5.4.13. Protocol Deviations, Unanticipated Problems, and Adverse Events

For complete information on protocol deviations, unanticipated problems, and adverse events, see the PREDICT Compliance and Monitoring Guide.

Protocol Deviations
Country teams and hospital and clinic POCs responsible for conducting PREDICT surveillance activities must be familiar with PREDICT's IRB protocols and knowledgeable about expected human surveillance operations. If, during the course of study activities, a team member becomes aware that any human surveillance activities have not been conducted in accordance with protocols or training guides, the team member should promptly inform the country field coordinator/human surveillance officer (if one is active in the country) or Country Coordinator about the deviation. The Country Coordinator should promptly contact the regional lead and complete any documentation, including developing any Corrective and Protective Action plans.

Unanticipated Problems
Unanticipated problems are events that are **unexpected** and **related to the research study** and that put one or more study participants at **greater risk of harm**. Unanticipated problems can include events or issues arising during standard research operations that may not cause detectable harm or adverse effects to research participants, but nonetheless raise the level of

risk associated with research participation (e.g., stolen consent forms or linking logs; breaches of privacy during research interviews). All problems meeting the three criteria above must be reported to the Operations Officer (predict@ucdavis.edu) within 24 hours (if the unanticipated problem is serious) or 72 hours (if the problem is not serious) using the form in Appendix IV.

Adverse Events and Serious Adverse Events

It is possible that during the course of study activities, a participant may experience discomfort or distress. Certain discomforts, such as pain at the site of blood collection and discomfort answering sensitive questions, are expected and detailed in the study protocol. Additional possible risks to study participation may be identified for a given site upon consultation with a local risk expert.

If, during the course of study operations, a participant reports or exhibits one of these anticipated adverse reactions to study participation (be it physical, mental, emotional, or social), that adverse reaction, or "adverse event," should be documented and reported to the human surveillance/field coordinator (if one is active in the country) and Country Coordinator promptly, but no later than within five working days (see the Reportable Information, Unanticipated Problem, and Adverse Event Reporting Form, Appendix IV). Once the Country Coordinator learns of the Adverse Event, he or she should report it to the Lead PREDICT PI (Dr. Mazet) and Operations Officer (predict@ucdavis.edu) within **72 hours**.

In the event a participant reports or exhibits a ***serious*** adverse event that is ***unexpected,*** that is likely ***related*** to study activities, and that implies the ***level of risk to all study participants may be higher than previously expected***, that serious adverse event should be reported to the human surveillance/field coordinator (if one is active in the country) or Country Coordinator within five working days. The human surveillance/field coordinator should report the event to the Country Coordinator, and the Country Coordinator should report the event to the Lead PREDICT PI (Dr. Mazet) and Operations Officer (predict@ucdavis.edu) **within 24 hours**.

The Lead PREDICT PI and Operations Officer are responsible for notifying the UCD IRB within the same time frame (72 hours for adverse events; 24 hours for serious adverse events). The Country Coordinator should report these adverse events to the in-country IRB or ethical committee if and as required to do so.

After becoming aware of any adverse event, the Country Coordinator should confer with their regional lead, the PREDICT global team, and relevant IRBs/ethical boards to determine what steps, if any, should be taken to address the adverse event and prevent similar future events.

Section 5.4.14. Site Monitoring

Each in-country team should work together in the first year to implement key procedures from the PREDICT IRB Compliance and Monitoring Guide on site monitoring and reporting (summarized in Appendix 5). Country Coordinators will be expected to work with PREDICT POCs at hospital and clinic sites to develop a regular system for transferring key study documents, reviewing records for completion, and addressing issues or concerns that arise during study activities.

As part of monitoring and reporting plans, at the completion of each surveillance period, generally on a calendar year schedule, a data and safety review will be conducted by a representative of the PREDICT global or regional management team. At this review, safety information and adverse events collected during the performance period will be discussed and addressed. Data may include case report forms, notes from study visits, and or any telephone calls to the PI from participants.

Section 5.4.15. References

CDC – Guideline for Isolation Precautions 2007. Healthcare Infection Control Practices Advisory Committee. Retrieved from:
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http://www.ncbi.nlm.nih.gov/books/NBK138665/http://www.ncbi.nlm.nih.gov/books/NBK138665/

Influenza Specimen Collection, U.S. Department of Human and Health Services, Centers for Disease Control and Prevention. Retrieved from
http://www.cdc.gov/flu/pdf/freeresources/healthcare/flu-specimen-collection-guide.pdf

Section 5.4.16. Appendix I. PREDICT IRB Checklist for UC Davis Submission

Before initiating human surveillance activities described in the Master Protocol, the following items must be submitted to the PREDICT Global Team via predict@ucdavis.edu prior to submission to local IRBs or ethical committees. The Global Team will conduct a rapid internal review of these documents to ensure plans comply with project objectives and global IRB approvals.

Following local IRB or ethics committee approval, additional materials must also be shared with the Global Team to forward onto the UC Davis IRB for final review and approval of country activities.

The most current drafts of global IRB-approved documents, including the currently approved protocols, consent forms, and questionnaires, are available at: http://eidith.org/Resources/PREDICTIRBProtocols.aspx (EIDITH login required).

Submission Checklist:

☐ 1. Submitted a bulleted list of changes made to all global document(s) to predict@ucdavis.edu.

☐ 2. Shared the country plan developed on the PREDICT global protocol template (using Track Changes as descried in the instructions) with predict@ucdavis.edu.

☐ 3. Used the most recent version of the Master Protocol documents (available at http://eidith.org/Resources/PREDICTIRBProtocols.aspx) to develop in-country materials.

☐ 4. Submitted English language versions of the country protocol, written consent form, verbal consent form, introductory script, and human questionnaire (Word.doc preferred) to predict@ucdavis.edu. Provided English language versions of any printed advertising materials to predict@ucdavis.edu.

☐ 5. Provided in-country IRB submission requirements (in copy or by web link, or if not in English via a document explaining the requirements) to predict@ucdavis.edu.

☐ 6. Clearly listed all Country Coordinators, Human Surveillance Coordinators, Global Leads, and key US-based staff involved in the study in the country protocol personnel list. These individuals will require CITI training.

Following Country-Level Approval – The Post-Submission Checklist:

☐ 1. Submitted all documentation of local IRB/ethical approvals to predict@ucdavis.edu. *All countries to submit this documentation.*

☐ 2. Provided all translated documents to predict@ucdavis.edu. For countries using town hall recruitment methods, this includes (a) translated study introduction letter(s) and recruitment script(s).

☐ 3. Submitted CITI training certificates for all personnel listed in the country protocol to predict@ucdavis.edu and entered all CITI training events to the EIDITH training app for monitoring (EIDITH app: http://training.eidith.org).

☐ 4. Trained all members of the human subject research team (training conducted by CITI-certified personnel) in human research ethics, and entered documentation of training events into the EIDITH training app (http://training.eidith.org). *Please maintain a record of all personnel involved in the study to allow monitoring of training status via the EIDITH Training Dashboard.*

☐ 5. Trained all relevant staff in PREDICT biological specimen safety protocols and entered documentation of all training events into the EIDITH training app (http://training.eidith.org). In addition, identified all local requirements for biological specimen safety (if any) and communicated requirements with study staff.

☐ 6. Identified and addressed local IBC requirements (if any) and shared a document outlining these requirements with predict@ucdavis.edu.

☐ 7. Conducted a consultation with a local expert on risks of human subject research in the study area; communicated these risks to the global and human surveillance teams for consideration.

☐ 8. Submitted a signed attestation form to predict@ucdavis.edu (see instructions) indicating that all personnel will adhere to all US federal and state regulations related to the protection of human research subjects.

Section 5.4.17. Appendix II. Health Facility Screening Form

Health Facility Screening Form

Facility Description

Type of Facility:
- ☐ Clinic
- ☐ Hospital
- ☐ Other_____

Facility Operating Hours:

Sunday	☐ Closed	☐ 24-Hrs	☐ ____ Hrs
Monday	☐ Closed	☐ 24-Hrs	☐ ____ Hrs
Tuesday	☐ Closed	☐ 24-Hrs	☐ ____ Hrs
Wednesday	☐ Closed	☐ 24-Hrs	☐ ____ Hrs
Thursday	☐ Closed	☐ 24-Hrs	☐ ____ Hrs
Friday	☐ Closed	☐ 24-Hrs	☐ ____ Hrs
Saturday	☐ Closed	☐ 24-Hrs	☐ ____ Hrs

Direct Disease Reporting:
- ☐ Regional Reporting
- ☐ Country Reporting
- ☐ International Reporting

On-Site Facilities:
- ☐ Inpatient Unit (_____ beds)
- ☐ Emergency Department (_____ beds)
- ☐ Intensive Care Unit (_____ beds)

Facility Departments:
- ☐ Chemistry Lab
- ☐ Microbiology Lab
- ☐ Radiology Department
  - ☐ CT Scanner
  - ☐ MRI Machine
  - ☐ Ultrasound Machine
  - ☐ X-ray Machine
- ☐ Transfusion Medicine Department

On-Site Personnel:
- ☐ Physicians (_____ staff)
- ☐ Nurses (_____ staff)
- ☐ Infectious Disease (_____ staff)
- ☐ Phlebotomy Team (_____ staff)

Health Care System

Coverage of Care:
- ☐ Fixed-Cost for Patients
- ☐ Sliding-Scale for Patients
- ☐ Free for Patients
- ☐ Supplemented Only if Patient has Private Insurance
- ☐ Location-Specific

Patients Served

Geographic Areas Served by Medical Facility:
- ☐ _____
- ☐ _____
- ☐ _____
- ☐ _____
- ☐ _____
- ☐ _____

Presentation of Syndromes of Interest (Last Month):
- ☐ Fever of Unknown Origin (_____ patients)
- ☐ Fever with Rash (_____patients)
- ☐ Fever with Diarrhea (_____patients)
- ☐ ILI/SARI (_____patients)
- ☐ Encephalitis (_____patients)
- ☐ Hemorrhage (_____patients)

Diagnostics

Health Facility Screening Form

Normative Diagnostics:

Chikungunya	☐ On-Site Rapid	☐ Serology Testing	☐ Off-Site	☐ None
Cholera	☐ On-Site Rapid	☐ Stool Culture	☐ Off-Site	☐ None
Dengue	☐ On-Site Rapid	☐ Serology Testing	☐ Off-Site	☐ None
Hantavirus	☐ On-Site Rapid	☐ Serology Testing	☐ Off-Site	☐ None
Influenza	☐ On-Site Rapid	☐ Culture	☐ Off-Site	☐ None
Japanese Encephalitis	☐ On-Site Rapid	☐ Cerebrospinal ELISA Test	☐ Off-Site	☐ None
Malaria	☐ On-Site Rapid	☐ Microscopic Examination	☐ Off-Site	☐ None
Tuberculosis	☐ On-Site Rapid	☐ Culture	☐ Off-Site	☐ None
Typhoid	☐ On-Site Rapid	☐ Culture	☐ Off-Site	☐ None
Yellow Fever	☐ On-Site Rapid	☐ PRNT Test	☐ Off-Site	☐ None

If Off-Site, Where?_____

Specimen Collection Capability

Fluid Collection
- ☐ Blood Sample
- ☐ Fecal Sample
- ☐ Urine Sample

Mucosal Collection
- ☐ Nasal Swab
- ☐ Nasopharyngeal Swab
- ☐ Oropharyngeal Swab
- ☐ Anal Swab

Other Samples
- ☐ Ocular Swab
- ☐ Sputum Sample
- ☐ Cerebrospinal Fluid
- ☐ Pericardial Fluid
- ☐ Pleural Fluid

Patient Care

Referral Process:

Are Patients Ever Referred Out for Care?
☐ No ☐ Yes (where: _____)

If Yes, Is There Active Patient Follow-Up?
☐ No ☐ Yes

Patient Health Records:
- ☐ Paper
- ☐ Electronic

Research Capacity

Experience with Research:

Facility Actively Conducts Research
☐ No ☐ Yes

Facility Collaborates with External Researchers
☐ No ☐ Yes

On-Site Cold Storage:
- ☐ Refrigerator (4C)
- ☐ Freezer (-20C)
- ☐ Deep Freezer (-80C)

Section 5.4.18. Appendix III Sample PREDICT Participant Enrollment Log

Participant ID Number	Consent / Enrollment Date	Pregnant Woman? (Y/N)*	Child / Minor? (Y/N)*	Date Human Questionnaire Completed	Biological Samples Provided? (Y/N)	Ethnographic Interview? (If Yes, date)	Focus Group? (if Yes, date)	Withdrawn consent? (Y/N)	Withdrawn due to AE?** (Y/N)

*If a participant is **both** pregnant **and** a minor, they should be marked in the child/minor category **ONLY**
**AE – Adverse Event

Enrollment Log Page Number _____

Section 5.4.19. Appendix IV PREDICT Reportable Information, Unanticipated Problem, and Adverse Event Reporting Form

Form is embedded in PDF document (pp. 26a and 26b, below) and available as a standalone document in the PREDICT EIDITH online Operating Procedures EBook.

PREDICT Reportable Information, Unanticipated Problem, & Adverse Event Reporting Form

Reportable information (RI), unanticipated problems (UPs), adverse events (AEs), and serious adverse events (SAEs) arising in the course of PREDICT operations must be documented and reported to PREDICT Global staff at UC Davis. These reports help PREDICT and ethical review boards ensure that study participation does not pose unacceptable levels of risk to participants. This form should be used to report one instance of reportable information, one unanticipated problem, or one adverse event. The form may also be used to provide new, additional information on an existing report.

If providing new information on an existing report, please reference the date and provide a brief description of the previous report.

Please report all RI, UPs, AEs, and SAEs to your country coordinator within THREE (3) business days if the event is not serious and ONE (1) day if the event is serious (see reverse for definitions).

Country coordinators should report RI, UPs, AEs, and SAEs to predict@ucdavis.edu within THREE (3) days (if not serious) or ONE (1) day (if serious).

1. The report following describes (please check all that apply)

☐ Reportable Information ☐ an Unanticipated Problem ☐ an Adverse Event

☐ New information from a previous report.

Original report date: _____

2. Date of report: _____

3. Date(s) of event: _____

4. Date of event discovery: _____

5. Please provide a brief description of the event:

6. Did any of the following occur? (Check all that apply)

- ☐ Non-compliance with IRB requirements or determinations, or allegations of such non-compliance*
- ☐ Protocol deviation due to the action or inaction of the investigator or research staff*
- ☐ Breach of confidentiality*
- ☐ Death of participant
- ☐ Event is life threatening/places the subject at immediate risk of death
- ☐ Inpatient hospitalization or prolongation of existing hospitalization
- ☐ Persistent or significant disability/incapacity
- ☐ Congenital anomaly/birth defect
- ☐ Subject's health in jeopardy; may require medical, counseling, or surgical intervention to prevent one of the other outcomes listed above
- ☐ Criminal or civil liability or damage to the subject's financial standing, employability, or reputation.

7. Relatedness to study procedures, by principal investigator (PI) determination (Please select one)

- ☐ Unrelated: cause of problem is known; problem is not related to study procedures
- ☐ Possibly related: Less than likely (≤ 50%) chance of relatedness to study procedures; relation to study procedures is unclear but cannot be ruled out.
- ☐ Probably related: More than likely (≥ 50%) chance of relatedness to study procedures;
- ☐ Definitely related to study procedures: clear association in time with study procedures; no likely alternative cause

8. Outcome

- ☐ Resolved with no further problem/complaint
- ☐ Resolved with additional problem/complaint
- ☐ Hospitalization
- ☐ Death
- ☐ Unresolved at time of study close-out

Definitions:

Reportable Information includes **any new information that indicates the rights, safety, or welfare of participants or others has been or may be compromised** by something that occurred or did not occur in relation to study activities. Reportable information may include (but is not limited to) protocol deviations, participant complaints, safety monitoring reports, and changes to research conditions that pose safety risks.

Unanticipated problems are problems that are **unexpected**, that are **related or probably related** to the study, and that suggest research participation involves a **higher level of risk than was previously anticipated.**

Unexpected means that the **nature**, **severity**, and/or **frequency of the problem was not anticipated** given the study population and the nature of the IRB-approved study procedures. In reference to an AE, "unexpected" means that the nature, severity, or frequency of the problem is inconsistent with the natural progression of any underlying disease, disorder, or condition that the subject may have or with the participant's predisposing risk factor profile for the AE.

Adverse events are any **unfavorable occurrences** (including physical, mental, emotional, and social) that the participant experiences during or as a result of study activities.

*Requires additional completion and submission of a Corrective and Preventive Action (CAPA) Plan.

Signature _____ Date _____

Section 5.4.20. Appendix V. IRB Compliance Responsibilities and Expectations

(PENDING)