MATRIX-007 Study-Specific Procedures (SSP) Manual Section 6 - Clinical and Safety Considerations

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6. Introduction

This section presents information on the clinical procedures, point-of-care (POC) testing, and safety considerations for MATRIX-007. The Schedule of Study Visits and Evaluations in Appendix I of the protocol and the study Visit Checklists indicate when specific clinical assessments are to take place.

6.1. Healthcare Provider Information and Medical Records Release

Essential to comprehensive and accurate data capture of study endpoints is access to the participant's medical record, including for antenatal, delivery, postnatal, infant, and any other relevant health care. Note that to be eligible for the study, participants must be willing and able to provide permission for the study team to contact their care provider(s) and for the study team to access medical records, including information about their infant at the time of delivery. These criteria are embedded in the Enrollment Informed Consent Form. Sites may need to obtain additional signed medical record release, memorandum of understanding (MOU), or other approval letter from health facilities/local MOH (or other documentation that allows for release of medical records), if required by local laws and regulations; this process, should be outlined in site SOPs.

Heath care provider information for participants will be captured on a **Health Care Provider Form**. This is a paper form identifiable by participant name and stored in the maternal participant's Name File; it records the names and locations of all health facilities where the participant (maternal and infant) seek care during study participation, including ANC, delivery, postnatal, well-baby, or any other specialized or hospital care. The form is initially completed at the Enrollment visit and should be reviewed and updated at each study visit. Changes or corrections are to be documented by hand per GCP.

Sites are encouraged to engage local health facilities where MATRIX-007 participants are anticipated to deliver before and during study implementation. In some instances, obtaining a permission letter from Ministry of Health or local municipality authorities may serve as a helpful introduction. Establishing and maintaining relationships with providers/management at health facilities where participants receive care will help facilitate access to medical records. Study staff can use the **CARE PrEP study factsheet** to sensitize health care facility staff to the study and the expectations for data abstraction.

Mothers are expected and should be encouraged to continue all routine antenatal care during their study participation. Similarly, once babies are born, adherence to well-baby care visits should be encouraged. Study visits do not replace routine care provision for mothers or their infants and this should be made clear to participants. It is also advised that study staff are aware of routine antenatal care and well-baby schedules (including immunizations) to remind participants to maintain regular care. These health care schedules should be outlined in SOPs.

Study staff may also access available HIV, syphilis, and pregnancy test results in the participant's hand-held records or client records at the health facility where CARE PrEP is linked. CARE PrEP should establish agreements with facility management to be able to access such records easily and in a timely manner. This system should be outlined in SOPs. See SSP section 6.9 below for guidance around HIV and pregnancy test result documentation.

6.2. Medical Record Abstraction

Participants should be encouraged to bring any hand-held medical records such as ANC passbooks, delivery records, and well-baby care books to study visits. As noted in the previous section, study staff will also attempt to access medical records directly from health facilities. This may include but is not limited to information from the ANC records, delivery registry, maternity ward records, transfer/referral register, and discharge records. The expectation is that the sites will attempt to review all delivery records to the extent possible. Data abstracted from medical records should be captured in relevant CRFs. This may mean that a CRF started at a study visit based on participant report is updated during medical record abstraction once records are reviewed from a health

facility. Any records reviewed should be indicated in the 'CRF Notes' field of a CRF and in participant chart notes.

Original medical records should not be removed from the health facility; abstraction into a CRF should occur at the health facility. Ideally, data is entered directly into CRFs within REDCap. See SSP section 7 Data Management for guidance on using REDCAP off-line. Alternatively, if there is no option to use REDCap, paper-based CRFs can be used and then transcribed into REDCap once back at the study site. Routinely making copies of records to keep as source documentation is not encouraged.

Records for which a certified copy must be created and filed are for documentation of HIV, syphilis, and or pregnancy test results when used to omit the need to perform the respective test at the study visit, and documentation of a non-study directed ultrasound record. See SSP section 6.9 and 6.4 below for more guidance on Point-of-Care (POC) testing and ultrasounds, respectively. These records must be a certified copy, identifiable only by PID, with the participant' s name redacted. See the **MATRIX GDP policy** for guidance on making certified copies.

There may be situations when study staff reviewing medical records (health facility records or hand-held records) may need assistance because a record is illegible or there are contradictions in the record that require further consideration. Options for assistance may be to ask a matron or other provider familiar with the record to assist with readability/interpretation, transcribe the record information into a note that can be shared with other study staff for input (note: no identifiable information should be recorded and the notes should be filed in the participant chart), or call another study staff and try to describe the record over the phone. A last resort would be to photocopy or take a photo of the record per the following steps and considerations.

6.2.1. Taking photos of medical records on an electronic device:

1. All personally identifiable information (PII) must be obscured prior to the photo being taken. This includes any participant names, age, address, facility name/location, dates (birth, visit dates, lab/test dates, etc.) or any other information that could identify the participant. Pieces of paper can be placed over such information before taking the picture. The PID should be included instead, which can be accomplished by placing a piece of paper with the PID written on it on/near the record before taking the photo.
2. Only take photos on study-approved, institutionally managed devices (phones or tablets). **Study staff should never use personal devices.** Devices should have restricted access to only study staff or other authorized institutional staff.
3. Upload photos immediately to the designated site location on the CARE PrEP Data SharePoint when accessible (as soon as internet connection is available), include the PID in the file name. Delete the photos from the device and any cloud back-up. Ideally, cloud back-up should be disabled for photos taken on the device.
4. If possible, have a second staff person check to ensure that the photo is appropriately uploaded, with no PII visible, and originals are deleted from the device.
    - If the photo needs to be edited to remove PII, do so electronically using an application such as Microsoft Paint and re-save the photo in a format that cannot be editable. Then delete all previous versions of the image from SharePoint.
5. No paper-based copy is necessary if the electronic version is securely saved on SharePoint.
6. Only share the photo with other authorized country team study staff or the Safety Sub-Committee. Share via a link from SharePoint only; never include the image in an email or text/SMS/message platform.

6.2.2. Photocopy to paper

1. Copy the record. Immediately use a marker to remove all PII.
2. Certify the copy per the MATRIX GDP policy, making sure to write the PID on the document and file with the participant chart.
3. If the paper copy must be viewed by someone remotely (i.e. converted to electronic), follow relevant steps described above for photos taken on devices.

Please keep in mind that the copied medical records now become source documents and are required to be stored by the study (either physically in the participant chart or on SharePoint). Never delete or discard copies.

6.2.3. Medical Record Abstraction Considerations

Consider the following tips for abstracting data from medical records at a health facility.

1. Accessing and identifying records
    a. Most importantly understand the protocol, especially primary outcomes, and what data are captured in CRFs.
    b. If locally appropriate, contact the facility manager to let them know of your visit and work out the best time for you to access records.
    c. Make sure you are at the correct facility (some have similar names or multiple locations).
    d. Bring with you any relevant documentation: regulatory entity approvals, participant consents, or facility permission documents/letters.
    e. Bring relevant copies of completed or blank CRFs or have REDCap available with you to reference AS YOU REVIEW RECORDS. See SSP Section 5 for guidance in reviewing and completing CRFs at off-site.
    f. Use multiple identifiers (e.g., name and date of birth) to confirm you have the correct patient record.
    g. Follow facility rules for accessing and reviewing patient records. If you are having trouble reading or understanding a record, ask a familiar provider at the facility for assistance. If you must take a photo of the record, ask the facility for permission first (see SSP section 6.2.2 above for guidance).
2. Reviewing records
    a. Sit in a quiet, secure place where you can review records privately. Do not leave patient records or your study laptop/tablet unattended.
    b. Briefly review the data points that you will be looking for (i.e., review the CRF questions).
    c. Using tape flags or sticky notes, identify locations in paper record where episodes of care start and end for the index pregnancy or infant care. Remember to remove your notations once you are done.
    d. Read through each section of record in chronological order, covering all sections.
    e. If something seems pertinent as you are reviewing, flag it. (For example, the chart note mentions chorioamnionitis. Flag it.)
    f. Read ALL components describing patient care for the index pregnancy, e.g., chart notes, nursing documentation, theatre records, labor care guide (partograph), orders, laboratory results, etc.

g. Once you have reviewed the entire chart and understand the complete picture, complete relevant CRFs and return to your flags to be certain that all pertinent information is captured appropriately.
h. Note: It is recommended that you have a general understanding of the participant's clinical course before filling out CRFs. For example, you may see gestational hypertension mentioned in the chart first and then a reference to preeclampsia on the next page. Preeclampsia should be captured as a pregnancy complication. If you review the chart and understand the story of the encounter, it will make filling out CRFs easier and more efficient.

In addition to reading the chart thoroughly, study staff responsible for data abstraction are expected to have some clinical knowledge such that they might be able to infer a clinical diagnosis if the component parts are outlined in the chart. For example, if a pregnant person has multiple elevated blood pressures in the delivery record, is being induced, and is started on magnesium, it would be reasonable to assume that the delivery team is treating the patient for preeclampsia, even if the word "Preeclampsia" is not written in the patient's chart. Consequently, preeclampsia should be entered on the Medical Events/Conditions CRF and indicated as a complication on the Pregnancy Outcome CRF. If your assessment supports a pregnancy complication that is not explicitly written in the chart, provide the rationale for assuming the diagnosis in the 'CRF Notes' field of the CRF. In addition, notify the Safety Sub-committee (SSC) via an SSC Query Form that provides the diagnosis and the rationale for deciding the participant experienced this complication. Study staff can refer to the **Medical and Medications Guide** for definitions of common pregnancy complications. An SSC Query Form can also be submitted for consultation on ambiguous cases (See SSP section 6.15 below for SSC Query instructions).

6.2.4. Medical Record Proficiency

Abstracting pertinent information from the medical chart is inherently difficult and takes time and attention. It becomes easier with more practice and familiarity with the organization of the medical chart. Because the study's endpoints rely on the ability to abstract and interpret data, MATRIX-007 has developed a proficiency assessment to ensure study staff are able to capture essential information. This will involve passing a written evaluation of clinical knowledge and reviewing sample chart notes for pertinent data. All site study staff responsible for data abstraction and medical event/conditions assessment must complete this assessment as a requirement for delegation to data collection on the country Delegation of Duties (DoD). Reassessment may be requested at intervals throughout study implementation.

6.3. Maternal Medical Assessment

6.3.1. Baseline Medical Events/Conditions at Enrollment

The participant's baseline medical and obstetric histories are initially collected and documented at the enrollment visit on the **Medical History and Events CRF** and the **Obstetric Care and History CRF**. The goal of obtaining these histories at enrollment is to understand the participant's baseline risk factors for a pregnancy complication and any current known pregnancy complications for the index pregnancy.

Obstetric history will be assessed using the **Obstetric Care and History CRF** at the Enrollment Visit. In addition to data regarding prior pregnancies, the CRF also asks about genetic history, current pregnancy complications, alcohol/substance use, and environmental exposures, e.g., pesticides or other workplace chemicals. Importantly, questions regarding family history/ genetics

are intended to ask about a family history of structural abnormalities. For example, "heart" condition would include atrial septal defect, hypoplasia, etc.; it would not include a family history of hypertension. See CRF Completion Guidelines (CCGs) for details on CRF completion.

This **Obstetric Care and History CRF** will be filled out once at the enrollment visit and is considered a 'snapshot' of relevant obstetric history at study baseline. Should the information asked on this form change over time, it is not necessary to update the Obstetric Care and History CRF. The changes can be reflected in chart notes and other relevant CRFs. For example, if a participant reported at enrollment that she smokes but then in follow up relayed that she had stopped, this information would be captured on the 'tobacco use' entry on the **Medical Event/Conditions CRF** but need not be changed on the **Obstetric Care and History CRF**. If the participant states that she is not receiving antenatal care at the time of enrollment while answering questions on the **Obstetric Care and History CRF,** but in follow-up relays that she has started, that information should be updated on the **Healthcare Provider Form** and in chart notes; the **Obstetric Care and History** CRF should not be updated.

In addition to the pregnancy specific data captured on the **Obstetric Care and History CRF**, other relevant (non-pregnancy related) medical history and current conditions must also be captured at baseline**.** Relevant events expected to be captured include chronic medical conditions, prior medical conditions requiring surgery or hospitalization, and clinically significant medical conditions which occurred/are occurring during the pregnancy. Clinically significant medical conditions are those which require medication for greater than 2 weeks (e.g., depression requiring daily anti-depressant) and/or may be associated with poor pregnancy outcome (e.g., substance use disorder, history of syphilis infection, or a history of herpes simplex virus infection). Transient events which are common during pregnancy, such as an episode of emesis or pelvic pressure, need not be captured. Study staff are encouraged to use their clinical experience and judgment to determine the best phrasing and approach to elicit complete and accurate information from the participant. In general, a gentle non-judgmental approach will have the greatest likelihood of success.

Study staff should use the **Medical and Medications Guide**, available on the MATRIX-007 website, as a more in-depth reference on what medical events, conditions and medications are relevant to document for this study for both maternal and infant participants. The guide also includes definitions of study-endpoint pregnancy complications and examples of how to document events, conditions and medications on relevant CRFs.

Any significant events or conditions identified during the medical baseline assessment are entered into a **Medical Events/Conditions CRF**. Relevant conditions or events that are indicated within the **Obstetric History and Care CRF** should also be detailed in a **Medical Events/Conditions CRF**. A new **Medical Event/Conditions CRF** should be completed for EACH independent event/condition. These CRFs will be viewable in a log-style format in REDCap for ease of reference and updating at subsequent visits. The **Medical Events/Condition CRF** will ask for a start/onset and stop/resolution date for each entry. Study staff should provide the most accurate dates possible and probe participants to find the best estimated date if the specific date cannot be recalled. See CRF Completion Guidelines and SSP section 7 for instructions on entering partial dates. If a medical event is ongoing, this can be marked on the CRF and the event should be followed up at each study visit until resolution can be documented (see SSP section 6.3.2 below).

While most information obtained during the medical and obstetric histories will be by self-report, the participant may have brought in medical records for review. It is important to review all medical records, including ultrasound results and antenatal care records when possible. Should a participant's self-report and a medical record conflict, the clinician should ask probing questions to ascertain the most accurate response. For example, if a participant reports that she had three full term deliveries, but her ANC card indicates that she had two full term deliveries and a preterm

delivery, the clinician should ask clarifying questions about the discrepant delivery. Ultimately, if a resolution cannot be reached, the information from the medical record should take precedent. The Safety Sub-Committee may also be consulted for assistance in triangulating different sources of available information.

6.3.2. Follow-Up Maternal Medical Events/Conditions

At each follow-up visit, any unresolved medical event/condition for a maternal participant already captured in a **Medical Events/Conditions CRF** should be reviewed and the current status assessed. It is possible that a previously identified problem now has a new diagnosis (for example, hyperemesis of pregnancy identified at enrollment was subsequently determined to be cholecystitis) or has resolved. In instances where the original data entry can be updated to reflect a more accurate assessment of the condition (e.g., change in diagnosis, current status of the event, medications now prescribed, for example), overwrite the prior entry with the updated information. Indicate in the 'CRF Notes' field at the end of the CRF what changes were made and why. Each open text entry in 'CRF Notes' should start with the date of entry and study staff initials (e.g., "12SEP24 TM: update resolution"); this will create a 'log' of changes over time for a specific event.

In addition to updating ongoing medical events/conditions, new medical/obstetric events/conditions that have occurred since the last visit or previously missed past events/conditions should be captured on a Medical Events/Conditions CRF. Study staff are encouraged to use their clinical skills to elicit this information from the participant but will find directive questions about changes in medical status, medications, and health care since the last visit on the **Antenatal Care CRF, Pregnancy Outcome CRF,** and **Post-natal Care CRF** according to the associated study visit. The **Medical and Medications Guide** indicates the relevant medical events/conditions to capture in the participant record, however, there is always some clinical discretion as to what qualifies as a significant medical event. If in doubt, it is recommended that the information be captured on the Medical Events/Conditions CRF and the Safety Sub Committee consulted as needed (See SSP section 6.15 below for guidance on querying the Safety Sub-Committee).

6.3.3. Maternal Medications

At enrollment and follow-up study visits, review and documentation of relevant medications used during the pregnancy and post-partum is required. All medications, except for PrEP, will be recorded on the **Medications CRF**, including PEP (See SSP section 6.3.3.1 below for guidance on documenting PrEP use.) Include prescribed/provider-directed medications for a reported medical event or condition. Over the counter medications used episodically to address common pregnancy complaints (for example, medications for pelvic pressure, reflux, or nausea) do not need to be documented unless they are used continuously for 2 weeks or longer. Also, individual medications used for anesthesia during a cesarean delivery do not need to be recorded individually; instead, it is acceptable to record "general anesthesia" or "regional anesthesia." See the **Medical and Medications Guide** for more specific guidance on relevant medications to record throughout study participation.

Similar to the Medical Event/Conditions CRF, the Medications CRF is a log-type CRF. A Medications CRF should be completed for EACH individual medication with indication, dose, unit, and start and stop/ongoing use recorded. Ideally the name of the medication should be recorded but if the participant doesn't know the name and/or it is not readily available, a description of the medication can serve as a placeholder until more information is gathered. For example, if a participant reports that she was prescribed antibiotics but doesn't recall the specific name, "antibiotic" can suffice until specific information is gathered.

Herbal medications to prepare for pregnancy are commonly used in some CARE PrEP communities. These medications should be captured on the Medication CRF as well. "Herbal medication to treat XXX" can be entered as the name of the medication on the CRF. Dosing frequency, start and stop dates, and route of administration should be completed as with any other medication.

Substance use is also an important exposure to collect. Rather than collecting alcohol or illicit substance use on the Medications CRF, "substance use disorder" should be recorded on the Medical Events/Conditions CRF. The specific drug and use pattern can be identified in the event description of the CRF.

As a reminder, participants may be reluctant to disclose that they are in the care of a traditional healer and likely even more hesitant to disclose substance use. Establishing rapport from the start of the study in addition to receiving information without judgment or rebuke is imperative. When such information is received, it is appropriate to thank the participant for entrusting the study team with this information, express appropriate concern when merited and offer referrals. **It is not appropriate to shame the participant under any circumstances.**

6.3.3.1. PrEP Use

Documenting PrEP use is critical for study endpoint analysis. The use of injectable CAB, PrEP ring, and/or oral PrEP during pregnancy and through the end of maternal study participation will be collected. Furthermore, because injectable CAB remains in the blood for up to a year after administration, injectable CAB use during the year prior to conception must also be ascertained. PrEP use will not be recorded on the Medications CRF. Instead, the **PrEP Use CRF** will be administered at every study visit. The **PrEP Use CRF** is completed log-style, with a new CRF to be completed for each month of the index pregnancy and post-natal period through study exit. For study analysis ONLY at the completion of the study, CARE PrEP will obtain PrEP use data from CATALYST which will provide more precise dates for CAB injections and PrEP ring and oral PrEP dispensing. Note: CATALYST data will not be used to *reconcile* PrEP use reported by participants during CARE PrEP study visits. Data will be treated independently during analysis. See SSP section 5 for more information on data sharing with CATALYST.

When a PrEP Use CRF is completed for the first time at the Enrollment Visit, answering "yes" to the question "Is this the first time filling out this CRF for this participant?" will open a series of questions about CAB use during the year prior to conception. Participants will be asked to estimate how many times they received an injection in that year (the reference date will auto populate in the CRF) and the date of the last injection prior to conception. Then the CRF should be completed for the first month of the pregnancy. Participants will be asked to estimate how often they used each of the three PrEP methods during that month. Actual initiation/refill dates are not collected. Participants will respond yes or no to having a CAB injection that month and indicate oral PrEP and PrEP ring use on a Likert scale. A new CRF should be completed for each subsequent month (in order) from the time of conception through the current month of the study visit. For the month occurring at the time of a study visit, assess PrEP use based on the days of the month completed thus far. For example, if the date is the 5th of March and ring was used continuously for the 5 days of March, the response would be 'Most or all of the time' for the current month. Ideally, include a CRF Note for each instance with brief explanation of the month's use.

At each follow-up visit, study staff should open the PrEP Use CRF for the last month reported, if the month was only partially assessed at the previous visit, and ask the participant again about PrEP use in that month. At this point, the entire month should be considered and the previous response should be updated in the CRF. Following on the example from above, if the participant's next visit is

in June, reassess the full month of March at that June visit. If the participant explains that they stopped using ring on 10 March, change the response to 'less than half of the time' or if they continued to use ring the whole month, keep as 'most of all of the time.' Always include a CRF Note explaining the outcome of a reassessed month i.e. response was changes form X to X or response was kept the same. Continue with data collection by opening a new CRF for the month of April and so on. See Figure 6-1 below for a CRF completion example and also the CCGs

To help participants recall PrEP use in previous months, it may be useful to have a paper calendar (both previous and current year), such as one with all months viewable on one sheet, where study staff and the participant can talk through specific dates such as holidays or other dates of significance (started school, accepted a new job, broke up with partner, etc.) to try to triangulate data regarding PrEP use.

Figure 6-1: PrEP Use CRF Completion Example

Complete a PrEP Use CRF for each month per the following visit schedule:

• **Enrollment Visit Date: 20 October 2024** (Date of conception: 15 Aug 2024)
  ○ **Aug:** New CRF. Assess CAB use in year prior to 15 Aug; assess all PrEP use in month of August
  ○ **Sept:** New CRF. Assess all PrEP use for entire month
  ○ **Oct:** New CRF. Assess all PrEP use through visit date

• **Antenatal Visit (102): 10 Jan 2025**
  ○ **Oct:** Reopen/update CRF. Reassess all PrEP use for the entire month
  ○ **Nov:** New CRF. Assess all PrEP use for entire month
  ○ **Dec:** New CRF. Assess all PrEP use for entire month
  ○ **Jan:** New CRF. Assess all PrEP use through visit date

• **Antenatal Visits (103): 9 April 2025**
  ○ **Jan:** Reopen/update CRF. Reassess all PrEP use for the entire month
  ○ **Mar:** New CRF. Assess all PrEP use for entire month
  ○ **April:** New CRF. Assess all PrEP use through visit date

• **Pregnancy Outcome Visit: 8 May 2025 (**Pregnancy Outcome 3 May 2025)
  ○ **April:** Reopen/update CRF. Reassess all PrEP use for the entire month
  ○ **May**: New CRF. Assess all PrEP use through visit date

• **Post-natal 3-Month (V202): 5 Aug 2025**
  ○ **May**: Reopen/update. Reassess all PrEP use for the entire month
  ○ **Jun:** New CRF. Assess all PrEP use for entire month
  ○ **Jul:** New CRF. Assess all PrEP use for entire month
  ○ **Aug:** New CRF. Assess all PrEP use through visit date

• **Post-natal 6-Month: missed (Lost to Follow-up)**

6.4. Ultrasounds

Per protocol, all maternal participants will have a study-directed ultrasound performed, ideally between 8-24 weeks gestation, for purposes of pregnancy dating. In addition, they may have an ultrasound performed for clinical indications through their clinical provider or as directed by the study. Of note, ultrasound examinations solely for the determination of fetal sex may not be ordered by study staff. Examples of appropriate clinical indications include but are not limited to the following: suspected growth restriction, vaginal bleeding, abdominal trauma. See Section 6.4.4 below for more details. Any ultrasound performed at the request of the study should be documented by the ultrasonographer using a paper-based **Ultrasound Results CRF.** Then the paper CRF can be transcribed onto an Ultrasound Results CRF in the participant's record in REDCap. If an ultrasound scan is done per clinical provider request, the results should also be captured on the Ultrasound Results CRF in REDCap. The following is guidance for scheduling, performing, and documenting ultrasounds. Clinically relevant results should be communicated to the participant's ANC provider(s) and/or maternity unit as appropriate.

6.4.1. Ultrasound setup and coordination

Each CARE PrEP site will need to designate at least one ultrasonographer who will perform study-directed ultrasounds. Study teams can choose to work with local ultrasonographers within the health system, contract a study-specific ultrasonographer, or designate existing study staff (if qualified). All teams are encouraged to have a back-up ultrasonographer as well. Each study-designated ultrasonographer must demonstrate adequate credentials to perform study-directed ultrasounds. Contact the Safety Sub-committee if there are questions about credentials. Ultrasonographers can be offered the following resources and courses:

- https://obgyn.uw.edu/education/ultrasound
- https://www.isuog.org/education.html https://www.isuog.org/education.html

Sites will need to establish a relationship with ultrasonographer(s) and the health facilities where the scans will be performed prior to study activation. Costs to perform study-directed ultrasounds, including use of machines, ultrasonographers' time, and supplies, should be covered by the study. Teams can arrange a service payment mechanism whereby no direct payment is expected from participants. Study staff should sensitize any ultrasonographers expected to perform scans for CARE PrEP to the purpose of the scan (gestational dating), the expected minimum parameters of the ultrasound as indicated on the **Ultrasound Results CRF**, and instructions on how to coordinate scheduling scans, document results and provide results back to the study staff and the participant. All aspects of ultrasound coordination and facilitation should be outlined in site SOPs.

6.4.2. Ultrasound prior to enrollment: non-study directed

An ultrasound report dated within 5 days of the enrollment visit, which notes a viable pregnancy can be used as proof of pregnancy for eligibility purposes. This ultrasound will have been ordered presumably through the clinical provider. The study cannot direct or pay for any ultrasound to be performed on a participant who is not yet enrolled in the study. The report must meet the following criteria to be used for pregnancy confirmation:

- Report is available to study staff and clearly identifies the participant
- Date of scan is with 5 days of the participant's enrollment date
- Documented evidence of a viable intrauterine pregnancy:

- A viable intrauterine pregnancy is defined as a fetus within the uterine cavity with visualized cardiac activity (i.e. fetal heart tones detected). See SSP section 6.4.3 below.
- An important distinction to make between a positive pregnancy test and an ultrasound demonstrating intrauterine fetal cardiac activity (fetal heart tones) is the concept of "viability." A positive pregnancy test may be positive because of a viable pregnancy, a recent delivery, a pregnancy loss (recent or in progress), an abnormal pregnancy outside of the uterus (ectopic pregnancy), or a hormone secreting tumor. A positive pregnancy test is required for entry into CARE PrEP; a viable pregnancy documented within 5 days of enrollment can override the requirement to do a pregnancy test. See SSP section 6.4.2.1 below for determining a viable pregnancy.

- Estimated due date or gestational age documented

If the participant provides results of an ultrasound but it does not demonstrate a viable intrauterine pregnancy, it is appropriate to continue with enrollment procedures pending a positive urine pregnancy test; however, it would be advisable to counsel the participant appropriately and to seek guidance (see below) from the Safety Sub-Committee as necessary.

Note: Even if a participant brings a previous ultrasound report, they must still receive a study-direct ultrasound once enrolled.

6.4.2.1. Evidence of a viable pregnancy by ultrasound

The expected development of a fetus on ultrasound is as follows:

- gestational sac at 4.5 weeks
- yolk sac at 5 weeks
- fetal pole at 5.5 weeks
- fetal pole with heartbeat 6.5 weeks

It is only once the yolk sac is visualized inside the uterus that an intrauterine pregnancy can be confirmed (as opposed to an ectopic pregnancy). It is only once the heartbeat is visualized within the fetal pole that the pregnancy is considered viable.

6.4.3. Management of unexpected clinical ultrasound results at enrollment

The following scenarios are presented as examples and are not intended to be inclusive of all possible scenarios.

1. Fetal demise: Ultrasonographers are sometimes able to diagnose a fetal demise or early pregnancy loss based on certain measurements of the pregnancy. If the participant provides an ultrasound report with a documented fetal demise (that is, the report clearly states a fetal demise), *she can still be enrolled into the study with a positive urine pregnancy test,* but her participation in the study will be quite limited (enrollment and pregnancy outcome visits). She should not be discouraged from enrolling in the study. She should be counseled that the ultrasound indicates a fetal demise. Presumably the provider who ordered the ultrasound should have a clinical care plan outlined, but if not, the participant should be counseled that she can expect to pass the pregnancy within the next several weeks. It is important to highlight symptoms that should prompt immediate evaluation in the emergency room: fever, chills, heavy bleeding (saturating a pad every hour), passage of large blood clots, severe abdominal pain,

lightheadedness, dizziness, nausea/emesis, and extreme fatigue. Septic abortion (infection of pregnancy tissue in the uterus) is a leading cause of maternal death.

2. Pregnancy of Unknown Location (PUL): If an ultrasound does not show an intrauterine pregnancy developing in the uterus (as evidenced by at least a yolk sac), it is important to counsel the participant about possible explanations: very early normal pregnancy, ectopic pregnancy, or early pregnancy loss. *She can be enrolled into the study with a positive urine pregnancy test*, and the site should make every effort to schedule her study directed ultrasound for as close to 8 weeks as possible. Note, "8 weeks" will be based on the estimated due date identified on the ultrasound at hand or her LMP if the ultrasound does not indicate an EDD. The gravest concern in this situation is that the participant may have a developing ectopic pregnancy, which can be life threatening. Signs and symptoms of an ectopic pregnancy include vaginal spotting, pelvic and/or abdominal pain, light headedness, unusual rectal pressure, or change in consciousness. A participant with a PUL should be familiarized with these warning signs and instructed to seek emergency healthcare should she experience any.

   See SSP section 6.4.5 below for guidance on counseling participants about unexpected clinical findings from ultrasounds.

6.4.4. Ultrasound performed for pregnancy dating or clinical indication: study-directed

The study-directed ultrasound is instrumental for establishing an accurate estimated date of delivery (EDD) and, by extension, determining the pregnancy outcome. This dating ultrasound should be scheduled at the enrollment visit with the goals of completing the ultrasound: 1) before the first Antenatal Visit and 2) between 8 and 24 weeks of estimated gestation (see SSP section 6.5 below for pregnancy dating guidance). The earlier the ultrasound can be performed, the more accurate the assessment of gestational age. When possible, schedule the ultrasound as soon as possible after 8 weeks (based on the information available at enrollment). For participants who are estimated to be between 24 and 34 weeks at enrollment, an ultrasound should still be scheduled, again the earlier in gestation, the better.

Ultrasounds may also be performed for clinical indications in addition to the one-time study-directed dating ultrasound. Study staff should use their clinical judgement to schedule another study-directed ultrasound based on a suspected pregnancy complication. In addition, the Safety Sub-Committee should be notified via an SSC Query Form, but there is no need to wait for a response before performing the ultrasound. (See SSP section 6.15 below of query for guidance). Signs and symptoms that would raise suspicion of a suspected pregnancy complication include but are not limited to vaginal bleeding, uterine size substantially larger or smaller than expected for gestational age, severe pelvic or abdominal pain, or physical examination suspicious for fetal malpresentation at or after 36 weeks gestation.

All study-directed ultrasounds (dating and otherwise) done by study-designated ultrasonographers should be documented using the paper-based **Ultrasounds Results CRF** and then transcribed into the electronic version of the CRF in REDCap. A separate CRF should be completed for every ultrasound conducted during the participant's pregnancy. If the ultrasound is done outside of the study, study staff should attempt to get the results and complete a new Ultrasound Results CRF directly into the participant's REDCap record, to the extent possible. The original results should be made into a certified copy and filed in the participant chart (See SSP section 6.2 above for guidance). Participants should be reminded to bring all antenatal documents to their clinic visits and alert study staff to any additional testing/procedures done as part of clinical care. Any significant

ultrasound findings (fetal or maternal) should be documented on the **Medical Event/Conditions CRF** in the maternal REDCap record as relevant (for example, placenta previa or intrauterine growth restriction).

The following are specific considerations and expectations:

- The dating ultrasound should be scheduled ideally between the Enrollment Visit and first Antenatal Care Visit. If feasible and desirable for the participant, the scan can be done directly after the Enrollment Visit (when participant is enrolled) or immediately before the study Antenatal Visit.
  - Ideally site staff will accompany the participant to the ultrasound appointment to facilitate accurate documentation of the scan. When scans are not performed within or nearby the site, study staff will need a plan to ensure that the documentation is completed appropriately and returned back to the study staff.
  - Ultrasonographers must document results on a paper Ultrasound Results CRF while the participant is present.
  - The information required for the top portion of the paper Ultrasound Results CRF, including the participant's name, age, and LMP, must be filled in by study staff before the ultrasound CRF is provided to the ultrasonographer.
  - The above 2 points are more easily accomplished if the site staff accompany the participant to the ultrasound appointment.
  - Study staff should have a reliable system to retrieve the completed paper CRF from the ultrasonographer and review it for completeness.
- For multifetal gestations, the paper-CRF can accommodate information for up to 3 fetuses.
- Ideally, all fields on the paper CRF will be completed, but the following are required. If they are not present on the CRF, site staff should communicate with the ultrasonographer and have it completed.
    - Biometric data required for accurate dating
      - For a first trimester (up to and including 13 6/7 weeks of gestation), the report must include the gestational age at the time of the ultrasound and the crown rump length (CRL).
      - For a second and third trimester ultrasound the biparietal diameter (BPD), the head circumference (HC), the abdominal circumference (AC), and the gestational age (GA) at the time of the ultrasound based on the above measurements must be documented.
      - Estimated due date (EDD) based on ultrasound must also be completed by the ultrasonographer.
      - If the ultrasonographer is unable to provide this level of detail, an alternate facility must be explored
    - The scan, while primarily for dating purposes, is also an opportunity for the ultrasonographer to note any unusual findings. All unusual findings should be noted on by the ultrasonographer on the paper CRF.
- The paper CRF completed by the ultrasonographer should include the participant's name (no PID should be included at this point).
- If the study-directed ultrasound result will be used for determining the final EDD, study staff should determine EDD and complete the 'Final EDD' field at the bottom of the original paper CRF. See SSP section 6.5 for determining the final EDD.
- Study staff should make a certified copy of the original paper CRF with the name is obscured (blacked out) and the PID written on the CRF instead. This copy should be filed in the participant's chart.

- The original paper CRF (by participant name) can be given to the participant. Because ultrasounds provide valuable information that may affect clinical care, study staff should ask the participant if another copy (by participant name) may be given to the participant's clinical team (ANC) and/or encourage the participant to bring their copy to their next clinical care appointment.
    - If a complication is identified on ultrasound (placenta previa) or a clinically significant finding uncovered (twin gestation), it would be prudent for the study staff to contact the participant's clinical team directly and discuss this new information if given permission by the participant. Participant permission to discuss the clinical finding with the care team must be documented in the chart notes. In addition, all contact with a participant's clinical providers must be chart noted. Any medical event/conditions should also be documented on a **Medical Event/Conditions CRF**.
- The paper CRF should be transcribed into the maternal participant's record in REDCap. If a multifetal gestation, complete an **Ultrasound Results CRF** for each fetus. Within the CRF you will be able to assign a Fetal ID (A, B, C, etc.). Use this ID when documenting any future ultrasounds and data capture for a non-enrolled infant.

6.4.5. Participant Counseling for Unexpected Ultrasound Findings

Regardless of the type of finding, dialogue with participants regarding study-ordered ultrasounds should follow these general guidelines:

- Describe the findings, including the gestational age and any abnormalities at a comprehension level appropriate for the participant
- Describe any recommended follow-up to the findings
- Confirm that the participant understands any follow-up actions that she must take, e.g., reporting to maternity, having a follow-up scan, avoiding intercourse (e.g., in the case of placenta previa)
- Address the participant's concerns and allow her space to grieve regarding any adverse findings
- Provide the participant with resources for support if these are desired.

6.5. Pregnancy Dating

CARE PrEP's primary endpoint of pregnancy outcome is dependent on gestational dating, and to ensure the highest quality data possible, paying close attention to pregnancy dating is vital. The "due date" is referred to as Estimated Date of Confinement (EDC) or Estimated Date of Delivery (EDD). They all reference the same thing: the best estimate for when the pregnant person will reach 40 weeks (280 days) gestation.

In pregnancy care, there is a working EDD and a final EDD. The working EDD is the estimated date of delivery based on the pregnant person's best estimate of their last menstrual period (LMP) or date of conception. A final EDD is confirmed after the first ultrasound when the gestational age based on the LMP can be compared to the gestational age based on fetal growth measurements from the ultrasound. Once a final EDD is set, it is never changed. For example, if a final EDD is set and several months later the baby is measuring very, very small (i.e., for the currently understood gestational age), the EDD is **not** changed. Instead, a fetus is given a diagnosis of intrauterine growth restriction if the estimated fetal weight or abdominal circumference is less than the 10th percentile for gestational age. Another example: if a final EDD is set and two days before the final

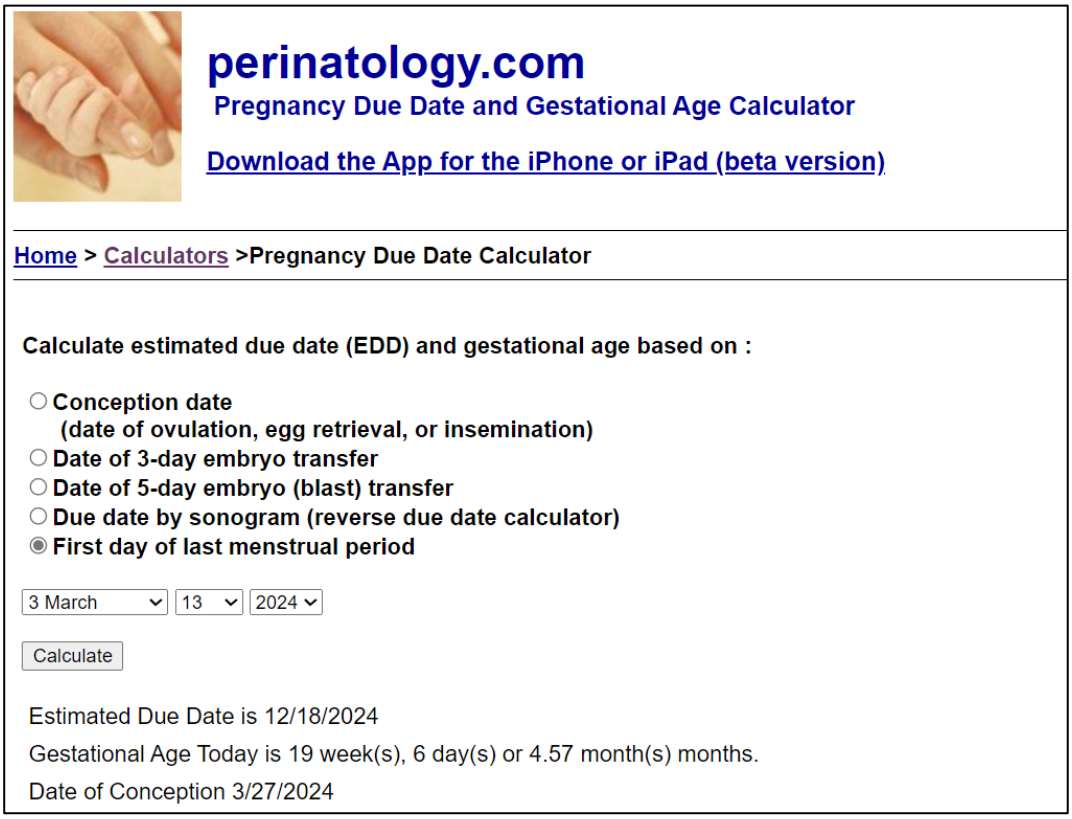
EDD the participant delivers, the EDD does **not** change. Rather, the participant delivered at 39 weeks and 5 days (2 days before 40 weeks). The final EDD is the best estimate possible for 40 weeks gestation, either based on the LMP or the ultrasound, which is explained below.

Because accurate dating is central to the CARE PrEP protocol, there are several tools and steps to ensure this is done correctly. This section and the **Pregnancy Dating Guide** are intended to explain these tools and the process of establishing both a working and a final EDD.

6.5.1. Pregnancy Dating at Enrollment

Study eligibility depends in part on gestational age at enrollment and PrEP use in relation to the pregnancy (based around date of conception). The **Eligibility CRF** includes a section on pregnancy dating. During enrollment, the LMP, working EDD, date of conception, and estimated gestational age (GA) will be documented on this CRF; this is done with the aid of an online calculator. The **Estimated Due Date (EDD) CRF** will also be completed at the Enrollment visit (after enrollment is confirmed); at this point, because a dating ultrasound has not yet been performed, the EDD is considered a working EDD. The Eligibility CRF will direct study staff to the gestational age calculator on the Perinatology.com website (https://perinatology.com/calculators/Due-Date.htm). *Note: The website is US-developed, therefore all dates provided are in the format of MM-DD-YYYY. Study staff MUST convert the dates to DD-MM-YYYY when entering them into study CRFs.* On the website, you will need to choose what input to use to calculate the working EDD ("Calculate estimated due date (EDD) and gestational age based on:") with the options of LMP, date of conception or due date by sonogram (ultrasound). By selecting one of these options and entering the corresponding value, the website will 'calculate' the working EDD as well as the other inputs options. See example in Figure 6-2 below.

Figure 6-2: Perinatology Website - EDD and GA



The following is guidance on how to select which input to use in the calculator.

1. Using LMP on the perinatology website

For most people, the last menstrual period is the easiest and most accessible starting point for determining the working EDD. By convention, the first day of the last menstrual period is considered the first day of blood flow. If a participant is not able to readily identify the first day of the last menstrual period, these questions might facilitate a best estimate.

- Do you remember what you were doing when you had your last period?
- Where you were? Who you were with?
- Was it before or after XXX holiday/birthday?
- Do you record this information somewhere? Your phone, in a journal?

An LMP value can be entered into the perinatology website even if the participant is very uncertain. If a participant is only able to relay the month of the last menstrual period, enter the 15th of the month. Within the Eligibility CRF, the LMP entered must be indicated as 'certain' or 'uncertain.' The goal at the enrollment visit is to provide the best estimate of an EDD as possible while acknowledging it may be very inaccurate. Once the study-directed dating ultrasound is done, a more accurate EDD can be established.

In some instances, people become pregnant during a time of amenorrhea (no menstruation cycle). The most common example of this is falling pregnant while using DMPA. If a participant reports that the last menstrual period was years ago, asking about the last negative pregnancy test may provide clues about when the pregnancy was conceived. For example, if a participant reports that she has been amenorrheic for years but had a negative pregnancy test 2 months ago, you can deduce that she achieved pregnancy within the last 2 months. In this instance, use the estimated date of the negative pregnancy test as the LMP.

2. Using Date of Conception on the Perinatology website

In a typical menstrual cycle, the egg is released during ovulation and conception occurs within the next couple of days. The date of conception is generally considered to be about 2 weeks after the last menstrual period for a regular menstrual cycle. For the purposes of pregnancy dating, the date of conception can be helpful in situations when sexual contact was limited to a discrete time. For example, imagine a participant who has only one sexual partner who is a truck driver and he was home for only one night six weeks ago. Prior to that it had been three months since the participant had intercourse (and an intervening menses). You can assume that conception happened during this sexual encounter 6 weeks ago. "Conception date" is an option for estimating the EDD on the perinatology website and may be the best entry point, especially if LMP is uncertain, there were limited sexual encounters, and/or the participant's menstruation cycle is not consistent.

3. Using an ultrasound on the perinatology website

It is expected to be a rare occurrence that a prior ultrasound is available for review at enrollment. However, if the results of a prior ultrasound are available which clearly state the EDD, entering the "Due date by sonogram" will provide the best input. Please see SSP section 6.5 for additional information regarding establishing a final EDD with a non-study directed ultrasound performed BEFORE the study-directed ultrasound.

If more than one option is available as an entry point for this first question on the perinatology website, the order of preference is: ultrasound, certain conception date, and then LMP.

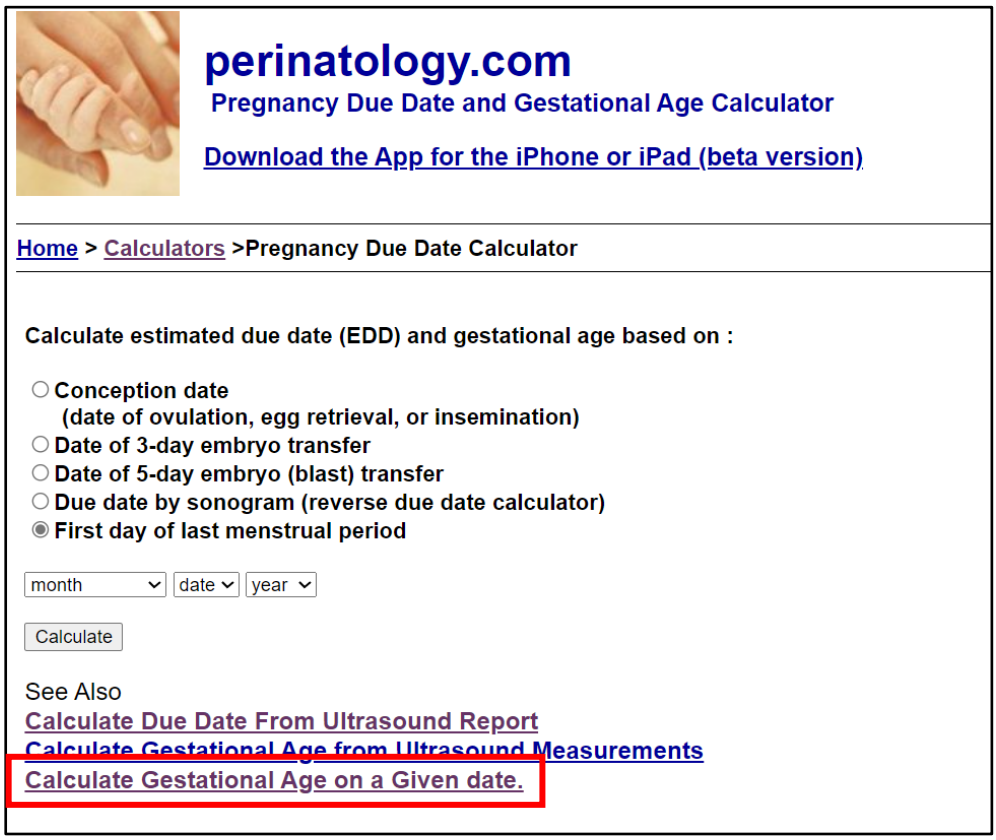
Note: The other options to the first question on the Perinatology website [Date of 3-day embryo transfer and Date of 5-day embryo (blast) transfer] are dates derived during In Vitro Fertilization and not expected to be relevant to our study population.

Once you choose the most reliable data to enter into the Perinatology website (ultrasound, conception, or LMP), select 'Calculate". A number of dates will be generated below the question based on your input. The generated data that will be entered on the Eligibility CRF are "Estimated Due Date" "Gestational Age Today" and "Date of Conception."

The completed calculator must be printed to create a source document of the input and outputs that can be used for data entry onto CRFs and filing in the participant chart. After printing, remember to write the PID on the document along with staff initials and date of when the document was created.

The perinatology calculator can also provide the GA on a certain date. See Figure 6-3 below for the link under the 'Also See' section of the website. The website will ask for the 'Estimated Due Date' and the 'Date To Calculate the Gestational Age On.'

Figure 6-3: Perinatology website - GA on a Given Date



6.5.2. Study-Directed Ultrasound Final EDD

During subsequent antenatal visits, the question "Do you have a new and final EDD to report?" appears on the **Antenatal Care CRF**. A Final EDD can only be ascertained after the first study-directed ultrasound results are available, meaning study staff have a completed paper **Ultrasound Results CRF**. If an ultrasound is not available for review, this answer will be marked "no" on the CRF.

The Final EDD is determined by comparing the Working EDD based on LMP or date of conception to the EDD based on the first ultrasound. It would be unlikely that the ultrasound EDD and the Working EDD derived from LMP are exactly the same, though possible. In this instance, the working EDD becomes the final EDD, which is said to be the 'ultrasound is consistent with LMP.'

More likely, the ultrasound EDD will differ from the working EDD. Whether to use the working EDD or the ultrasound EDD depends on how much the two dates differ. The earlier in pregnancy an ultrasound of a viable pregnancy is performed, the more accurate the dating is and the less error range there is around the EDD. If the estimated gestational age by the participant's working EDD differs from the ultrasound estimate by more than the accepted variation for the gestational age range, the ultrasound EDD should be used instead of the participant's working EDD. See table 6-1. In this instance, the Final EDD is said to be based on 'ultrasound not consistent with LMP.' If the gestational age by ultrasound is within the accepted range of the Working EDD, the EDD is said to be based on 'ultrasound consistent with LMP' and the Working EDD becomes the Final EDD.

Table 6-1 outlines the guidelines for redating based on ultrasound. In general, if the Ultrasound EDD is close to the Working EDD, the Working EDD becomes the Final EDD. If the Ultrasound EDD is very discrepant from the Working EDD based on the GA range, the pregnancy is "redated" and the Ultrasound EDD becomes the Final EDD.

Table 6-1. Guidelines for Redating based on Ultrasonography

Gestational Age Range (based on reported LMP, on the date of ultrasound)	Discrepancy between Ultrasound Dating and LMP that Supports **Redating**
≤ 8 6/7 weeks	More than 5 days
9 0/7 weeks to 15 6/7 weeks	More than 7 days
16 0/7 weeks to 21 6/7 weeks	More than 10 days
22 0/7 weeks to 27 6/7 weeks	More than 14 days
28 0/7 weeks and beyond	More than 21 days

Study staff are to use the **Gestational Age (GA) Dating Tool,** which is an Excel document and will apply the rules above to the participant's particular information and determine whether redating is in order. The Tool is available on the MATRIX-007 website.

GA Dating Tool Instructions

1. Open the GA Dating Tool file in Excel (on laptop).
2. Enter the PID and data from the Ultrasound Results CRF into the blue fields in the Excel tool: Ultrasound Date, GA per Ultrasound report (GA on date of the ultrasound), EDD per ultrasounds scan, and LMP.
3. The yellow portion of the Excel will populate, including the number of days discrepant between the GA based on LMP versus the ultrasound. Based on the number of days discrepant, the tool will indicate if the pregnancy should be redated based on the ultrasound. If redating response is:
    a. 'YES' – use 'EDD per ultrasound scan' as the Final EDD
    b. 'NO' - use the 'EDD per LMP' as the Final EDD (this should be the same as the Working EDD)
4. Print the Excel spreadsheet, add study staff initials and date, and file in the participant chart

5. Clear the information in Excel before using for another participant.
6. Open the already completed **EDD CRF** in the participant's REDCap record and update the CRF with the Final EDD and indicate if the date is 'consistent with the LMP' (same as Working EDD) or 'ultrasound, not consistent with LMP' (redated).

Discrepancies between Clinical Care and Research EDD

A copy of the study-directed ultrasound report (paper CRF) with the Final EDD noted by study staff on the bottom of the report should be provided to the participant's clinical care team. Ideally the clinical care team will adjust their pregnancy dating and update ANC records accordingly, but it is possible that they might disregard the information provided. Ideally the participant will bring her ANC card in every visit for review; it may indicate that the EDD used by the clinical team is very different from the study-calculated EDD. Because the EDD can impact clinical decision making, it is recommended that the study staff make an effort to discuss this discrepancy with the clinical care team. Ultimately, if the clinical care team elects to use their own EDD, this should not impact the study pregnancy dating for determining pregnancy outcome (term or preterm delivery, for example).

6.5.3. Non Study-Directed Ultrasound Final EDD

It is expected to be exceptionally rare that a participant will have a clinically indicated ultrasound performed before the study-directed ultrasound and have the report at hand. However, if this were to occur, it is possible that this ultrasound might inform the best estimate of the Final EDD, provided the necessary components are present. Should a participant provide an ultrasound report before the study-directed ultrasound is performed (i.e. prior to enrollment or between enrollment and the appointment for the study-directed ultrasound), fill out the **Ultrasound CRF** in REDCap based on the available report (for enrolled participants) and notify the Safety Sub-committee via an SSC Query Form.

The EDD from an ultrasound report available at enrollment is appropriate to use as the starting point for the perinatology website for eligibility determination (see SSP section 6.5.1 for guidance), but assume this as the working EDD until the SCC has the opportunity to review the components of the non-study directed ultrasound.

It is possible that a non-study directed ultrasound may be sufficient to determine the Final EDD but because some ultrasounds are not high quality, this decision should be left to the SCC. Of note, a study-directed ultrasound should be scheduled for as close to 8 weeks as possible regardless of whether a non-study directed ultrasound has been performed.

Note: All non-study ultrasound reports should be made into a certified copy and stored in the participant chart.

6.6. Maternal Vitals

Maternal vitals are taken per the following study visit schedule and documented in the **Vitals CRF** in REDCap.

- Height: Enrollment
- Weight: Enrollment and Antenatal Visits
- Fetal heart tones: Enrollment and Antenatal Visits
- Blood pressure: Enrollment, Antenatal; if indicated at all other visits.

6.6.1. Weight

Weight should be measured in kilograms and should be rounded to the nearest tenth decimal place, if applicable (e.g., 54.7 kg). Scales must be calibrated at a frequency per the manufacturer's recommendations or any local regulations, whichever is more stringent. It is recommended that scales be calibrated at least annually. At each site, consistent weighing procedures should be followed for all participants. Participants should remain clothed, but each site may choose to weigh participants consistently in terms of outerwear and apparel – i.e., always removing shoes or heavy sweaters/coat, hats, etc.

6.6.2. Height

Height should be measured in centimeters and should be rounded to the nearest whole number, as applicable (e.g., 160 cm). For participants with hairstyles that could affect height measurements, a tongue depressor or other device should be held gently and horizontally to the wall chart/measuring tape at the top of the participant's head (not at the top of her hairstyle) to obtain accurate measurements.

6.6.3. Blood Pressure

Blood pressure devices are expected to be calibrated regularly per manufacturer's directions.

Follow best practices when taking a participant's blood pressure:

- She should empty her bladder before your reading.
- Have her sit in a comfortable chair with her back supported for at least 5 minutes before your reading.
- Have her put both feet flat on the ground and keep her legs uncrossed.
- She should rest her arm with the cuff on a table at chest height.
- Make sure the blood pressure cuff is snug but not too tight. The cuff should be against bare skin, not over clothing.
- Ask her to please avoid speaking while the blood pressure is being measured.

If the participant develops hypertension during study follow-up (systolic ≥ 140 and/or diastolic ≥ 90), it is recommended that study sites repeat the blood pressure after the participant has a few minutes to relax. The lowest of repeat blood pressure readings should be recorded on the Vitals CRF. If the blood pressure remains elevated, the participant should be referred for further treatment and management immediately.

Hypertensive disorders of pregnancy should be reported on the **Medical Event/Conditions CRF** and any medication(s) should be recorded on the **Medications Log.** For further guidance on completing blood pressure entries into REDCap, please see CRF Completion Guidelines.

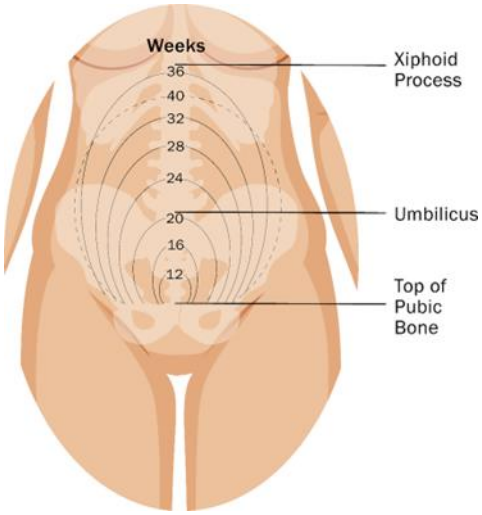
6.6.4. Fetal Heart Tone Assessment

Fetal heart tones are to be assessed as part of the clinical assessment starting at 16 weeks gestation. While a fetoscope is one method of obtaining fetal heart tones, the protocol specifies that a hand-held doppler should be used. The rationale for not checking heart tones prior to 16 weeks is that heart tones can be more difficult to auscultate earlier in gestation, particularly in a heavy participant. Please note that some hand-held dopplers have an earphone jack. Using headphones can be helpful.

The following steps are recommended:

- Know the participant's gestational age.
- Check the fetal heart rate after you have completed an assessment of the abdomen/uterus.
- Make sure the participant is resting comfortably on their back on the exam table.
- Palpate the fetal back.
- Place a small amount of ultrasound gel on the abdomen.
- Press the transducer against the participant's skin in a reasonable location for the gestational age.
- In general, the maternal lower abdomen is a good bet.
- As pregnancy progresses, aim transducer towards where you think the fetal back is lying.
- Move the doppler around until you find fetal heartbeat.
- Sometimes keeping the transducer in the same spot but changing the direction is sufficient to pick up heart tones.
- Check mother's radial pulse to confirm you are NOT hearing the maternal heart rate.
- Listen for approximately 15 seconds.
- Explain what you are doing to the participant and what you are hearing.
- Indicate the presence of fetal heart tones on the **Vitals CRF.** The beats per minute is not recorded on the CRF but can be included in chart notes, especially if the heart rate is abnormal.
- Clean the probe per manufacturer's directions.

Figure 6-4: Fundal Height



While the rate is not recorded in the database, the clinician should take note of the rate. A normal fetal heart rate falls between 110 and 160 beats per minute. There are some clinical scenarios worth considering:

- The clinician is unable to find fetal heart tones. This should be communicated to the participant with the caveat that it is difficult sometimes to hear heart tones because of the baby's position. The study staff should make every effort to schedule an ultrasound for the participant as soon as possible. This would be an example of a clinically indicated study-directed ultrasound (See 6.4.5). This situation may be very distressing to the participant.
- The clinician hears heart tones but they are lower than 110. The most common explanation for this scenario is that the maternal heartbeat is being captured by the doppler. The

clinician can feel the maternal radial pulse and compare to what is auscultated by doppler. If the beats are simultaneous, the clinician should continue to look for fetal heart tones. If in fact the heart tones are low (and not maternal), a prompt referral to the maternity ward is indicated. It would be best if the research staff could accompany the participant to ensure that she takes the referral and to explain to the clinical team what transpired.

- The clinician hears an audible deceleration of the heart rate. Multiple explanations are possible for this including, but not limited to deceleration associated with temporary compression of the umbilical cord or deceleration at the end of a normal acceleration of the fetal heart rate. In cases where a deceleration of unknown etiology occurs, the participant should be referred to the maternity unit for further evaluation including non-stress test or other assessment of fetal well-being as locally available.
- The clinician hears heart tones, but they are higher than 160. The most common reason for this is fetal activity. Particularly if the participant reports significant activity, waiting for the movement to settle down and rechecking in 15-20 minutes is appropriate. If the heart tones are persistently elevated, a prompt referral to the maternity ward is indicated. It would be best if the research staff could accompany the participant to ensure that she takes the referral and to explain to the clinical team what transpired.

6.7. Pregnancy Outcomes

During the first visit following a participant's pregnancy outcome, detailed information about the pregnancy outcome should be obtained. This will typically occur at the pregnancy outcome (PO) visit, which should be completed as soon as possible after the pregnancy outcome, ideally within 5 days. The study visit has a wide window (up to 6 weeks from the time of pregnancy outcome), but the World Health Organization recommends that a surface exam of the infant take place within 5 days of delivery, hence the emphasis on conducting this visit as soon as possible. As described elsewhere, if the local IRB allows, providing extra reimbursement or a birth pack/small gift at this visit may more fairly compensate participants who go to the trouble to complete the visit early. If the PO visit is missed (window has closed), effort should be made to obtain complete pregnancy outcome information as soon as possible (See SSP Section 5 for guidance on scheduling and missed visits for the PO visit). When at all possible, study staff should review medical records (hand-held or health facility records) related to a participant's pregnancy outcome (See SSP section 6.2 above for guidance on medical record abstraction).

Data about the pregnancy outcome will be recorded on the **Pregnancy Outcome CRF**, which focuses on data related to the maternal participant, and the **Infant Outcome CRF**, which focuses on data about the fetus/infant. The Pregnancy Outcome CRF must be completed first. The questions on this CRF ask for specifics about the date and location of the outcome as well as outcomes experienced by the mother. The questions "How many of fetus/infants came from this pregnancy?" will indicate how many Infant Outcomes CRFs need to be completed. In the setting of multiples, a separate Infant Outcome CRF must be completed for each fetus/infant. The **Infant Outcomes CRF** asks questions about whether the infant was born alive, the mode of delivery, gestational age at delivery, complications for the infant, etc.

An important aspect of completing the Infant Outcome CRF is to determine if the infant is enrolled into the study. By virtue of signing consent, CARE PrEP participants consented to enroll their infants at delivery. For this reason, all live infants will be enrolled upon birth, unless in the unusual case that the mother withdrew her consent for the infant before birth. In most circumstances, the live infant will be enrolled into the study at birth and have an infant PID assigned at the Pregnancy Outcome Visit. Regardless of the outcome/enrollment status of the infant, the Infant Outcome CRF

will be completed under the maternal record in REDCap. This will allow the Infant Outcome CRF to pull data from the Pregnancy Outcome CRF completed in the same REDCap record to determine the pregnancy outcome category.

If a pregnancy results in an intrauterine loss (i.e., stillbirth), the Infant Outcome CRF is still completed for this infant but because the infant is not enrolled into the study and will not have a separate PID generated. If the infant is born alive but dies shortly after birth, the infant was technically briefly enrolled and should have a PID assigned. See SSP section 5 for infant enrollment guidance and 7 for PID assignment guidance. In the case of a multifetal gestation, indicate the Fetal ID from the Ultrasound Results CRF on the Infant Outcome CRF.

It is expected that the participant will present for the PO visit and then, afterwards, study staff will access medical records at the health facility to capture additional information. Any Pregnancy Outcome or Infant Outcome CRFs started at the PO Visit should be re-opened and updated with any new data based on record abstraction. The 'Enter today's date' and 'what type of visit is this?" should remain the original date on which the CRF was started because this data entry is considered an extension of the PO Visit. Updates made to the CRFs based on record abstraction should be noted in the CRF Notes of the CRF. Below are the main clinical variables collected on each CRF and any special considerations.

The following is guidance on a subset of questions from the Pregnancy Outcome and Infant Outcome CRFs.

Pregnancy Outcome CRF

- Outcome/ delivery location
    - To distinguish between a home birth (or any setting outside of a health facility) or one in a hospital (birth in a facility's emergency transport vehicle is not considered a facility delivery)
- Date of Pregnancy outcome
    - In the event that a participant does not know the exact date, study staff should probe the participant to determine the most accurate date possible. A day, month, and year are required to be recorded in REDCap
- Any pregnancy/outcome-related complications associated with the mother
    - The listed complications are study secondary endpoints and should be specifically considered and marked if present. If present, they should also be recorded on the maternal **Medical Events/Conditions CRF**, as discussed in SSP Section 6.3. Some complications may not be explicitly stated in the medical chart but if your clinical impression is that a complication did occur, mark that the complication occurred and explain the clinical scenario in the open text field. Also, notify the Safety Sub-committee via a SSC Query.
- Any medical records reviewed or new ultrasound reports available
    - If there was a recent pregnancy ultrasound and the report is available, the results should be entered into the **Ultrasound Results CRF**.
- Any new other medical event/conditions and medications
    - Record any medications or medical events/conditions on the maternal **Medications CRF** or **Medical Events/Conditions CRF**.
    - Note: If there is a maternal death, attempt to determine the both the date and time of death and the date and time of the pregnancy outcome; record these times in the Medical Events/Conditions CRF.

Infant Outcome

- Pregnancy outcome (full term live birth (≥37 weeks), premature live birth (<37 weeks) stillbirth/intrauterine fetal demise (≥20 weeks), spontaneous abortion <20 weeks, therapeutic/elective abortion, other) – this is the primary endpoint
    - The CRF will first ask if the outcome was living or not. REDCap will then determine the outcome categorization based on this response and the GA on the day of the outcome that was recorded on the Pregnancy Outcome CRF.
    - An important consideration is that the primary endpoint that is calculated based on study-derived inputs may differ from what is written in the medical chart. If this is the case, answer the question "Is there a medical record that provides a different outcome from the above calculated outcome?" yes, and additional questions will appear to explain the discrepancy. See below for guidance and examples.
- Delivery method
    - If a pregnancy ended with a surgical procedure or early miscarriage (<20 weeks), check "no delivery."
    - If the pregnancy ended in a delivery >20 weeks, indicate the mode of delivery.
- Sex: female, male, intersex (i.e. ambiguous genitalia)
    - Complete this based on medical records.
- Type of "Stillbirth/intrauterine fetal demise," whether fresh or macerated.
- Fetal/infant congenital anomalies (CA) identified prior to the exam is in reference to congenital anomalies identified by the health care team. If present, include on the **Medical Event/Condition CRF**.
    - Any CA indicated should also be assessed during the infant physical exam if performed and reflected in the Infant Physical Exam CRF.
- If any resuscitation efforts or additional special care occurred after delivery, for example antibiotics, neonatal care unit stay, respiratory support.
    - Record any medications or medical events/conditions on the infant's Medications CRF or Medical Events/Conditions CRF.
- Infant metrics at or around time of delivery: Weight, length, head circumference, temperature, pulse, rate of respiration, Apgar scores.
    - The questions will appear for a live birth or stillborn infant. If a home birth occurred and the baby was brought to a health facility afterward, the metrics taken from this timepoint would be acceptable. Data is expected to be missing for some of these metrics if not standard of care to perform and/or record in delivery records.
- Any new other medical event/conditions and medications
    - Record any medications or medical events/conditions on the infant Medications CRF or Medical Events/Conditions CRF.

6.7.1. Discrepancies

Pregnancy outcome data is ideally based on medical records over participant report. However, it is possible that the categorization of the outcome based on the study GA dating differs from what is in a medical record. This could happen if the ANC or the delivery facility considers the participant's EDD to be different than what the study determined as the Final EDD. For example, the medical record considers the outcome to be a full-term live birth with a GA of 38 weeks at delivery, but the study determined the GA at birth to be 36 weeks, making this a pre-term live birth. In this instance, there is an opportunity on the Infant Outcome CRF to explain this discrepancy with the questions: "Is there a medical record that provides a different outcome from the above calculated outcome?"

and "Explain the discrepancy, including what data was provided on the record." Another example: the chart indicates a stillbirth, but one or more Apgar scores recorded in the medical record is greater than zero. Because a positive APGAR score is compatible with life, this outcome should be recorded on the CRF as a live birth and the discrepancy noted.

Please note, the Infant Outcome CRF will automatically calculate the outcome categorization based on 1) the outcome date entered on the Pregnancy Outcome CRF 2) the EDD on the EDD CRF, and 3) if the outcome is living or non-living on the Infant CRF. Study staff should complete these variables based on the best information they have available. An alternative outcomes categorization from a medical record can be entered into REDCap, but staff should rely in the study-derived outcome; the Infant Outcome CRF in REDCap will base skip patterns on the study-derived outcome.

6.8. Edinburgh Postnatal Depression Scale (EPDS)

The Edinburgh Postnatal Depression Scale (EPDS) will be used as a screening tool to help identify depressive symptoms and other mental health issues in maternal participants. Administration of the tool is required at the Pregnancy Outcome visit and Postnatal 3-month Visit; and if indicated at the Postnatal 6-Month Visit. Scores of ≥10 relate to possible depression and ≥13 probable depression, however clinical judgement should always be used to determine need for further evaluation/referrals (or first line support if/when site has capacity to offer).

The EPDS is a 10-item questionnaire that is available in all local languages as a CRF. The questionnaire may be administered by any study staff member who has been trained in questionnaire administration and associated site SOPs as referenced below. Further guidance on administration of the EPDS is as follows:

- Read the introductory statement at the beginning of the questionnaire, highlighting that the questions on this form ask about how the participant has felt over the course of the past seven days.
- Read each statement to the participant word-for-word; after reading each statement, read the response categories for that statement word-for word. Note that the response categories differ for each statement.
- As needed, repeat the numbered statements and/or response categories (repeat probe) to help the participant understand the statements and the response categories she is asked to choose from. Note that the English version is based on American English and some phrases may not be familiar or well understood in some local context. Site teams may develop alternative phrasing that can be explained to the participant after the statement is read from the CRF. If needed, other types of probes may also be used to help the participant choose the response category that best matches how she has felt in the past seven days.
- After all the questions are answered, **REDCap will automatically calculate the total score based on the participant responses.**
- For this study, the EPDS is not intended to be — and should not be — used for diagnostic purposes.
- Scores of 10 or higher indicate *possible* depression, scores of 13 or higher indicate *probable* depression. Both should prompt discussion with participant on reported symptoms and assessment of whether the participant may require additional support, evaluations, and/or treatment for possible depression or other mental health issues. **If the participant expresses suicidal thoughts (last item) or thoughts that she may harm her infant, specifically, a response of "Yes, quite often," "Sometimes", or "Hardly Ever" to the statement "The thought of harming myself has occurred to me,"**

immediate referral and possible hospital evaluation should be pursued. Ideally, this really should be a "warm handoff" where participants are personally escorted by a health personnel to an advanced care facility with a mental health specialist. Sites should maintain a list of resources for referral in this context and include them in site-specific SOPs.

- Do not read the last item on the form (regarding referral) to the participant. Record "yes" or "no" for this item based on whether referrals were subsequently made. "Yes" should be recorded whenever referrals to relevant services or resources available within the study site or external to the study site. All referrals should be documented in participant chart notes.

Although the EPDS is not a diagnostic tool, any score of 10 or higher, or the response to 'The thought of harming myself has occurred to me' is anything other than 'never', document this event on the **Medical Event/Conditions CRF** as 'positive depression screener'. Should a participant return for a later visit after referral for an elevated score and report a diagnosis, that diagnosed condition should be captured on the Medical Events/Conditions CRF.

6.9. Point-of-Care Testing

Study-required testing for this study includes only point-of-care (POC) testing for HIV, syphilis, and urine pregnancy (hCG). Testing is expected to be done 'bedside' by study staff while the participant is completing study visits. No laboratories are expected to be used nor should study sites rely on the study-linked health facility staff to perform tests requested outside of SOC. Only study staff designated on the study site MATRIX-007 DoD may perform POC testing on participants. Study staff intended to perform such testing must provide proficiency credentials or training certificates verified by the Country PI to be current and in accordance with national guidelines and receive approval before staff can be delegated on the DoD for POC testing responsibilities. Country-specific proficiency documentation should be outlined in SOPs.

After testing at study visits is complete, all blood and/or urine samples must be disposed; no samples are to be stored for future use or given to health facility providers for additional testing. Dispose all specimens and medical waste according to the study-linked medical waste management policies and SOPs. Study sites should have biohazard bags and sharps containers available within the study space and for off-site visits, as appliable.

Any study-performed testing must be documented on the respective **Pregnancy Testing Log, HIV Rapid Testing Log,** and **Syphilis/HIV Combo Testing Log.** These are paper-based logs that are kept per site SOPs. Log templates are available on the MATRIX-007 website. Each time a test is performed, study staff must complete an entry on the appliable log. The logs are the source documentation for performance and results of all study-performed POC testing. The top of each page of the log must have the site name, kit lot, kit name, and expiration filled out. Each entry (row) will require: PID, test date, outcome, and staff initials. If there is a change in kit brand/type or lot, a new page log should be started. The previous log should be closed out by lining through any blank rows per GCP (with staff initials and date) and adding the final page count to the bottom of each page.

6.9.1. Pregnancy Testing

Pregnancy testing is required at enrollment unless the potential participant has had either a positive pregnancy test performed at a health care facility or an ultrasound demonstrating an intrauterine

pregnancy with a heartbeat within the 5 preceding days. Documented results required for verification and should be copied per GCP and stored as a source document in the participant's chart.

Pregnancy tests performed by the study are expected to be qualitative rapids with binary outcomes (positive/negative). If a quantitative test is performed or adequate documentation of one is available through other service care, a concentration of 20 miU/mL of hCG is the minimum cut-off to be considered "positive."

Sites will procure urine pregnancy test kits locally and submit the package insert to the MATRIX-007 management team. If there is a stock or quality issue identified with kits (such as stock outs or trend in false negatives or positives), notify the Safety Sub-committee for guidance on continued pregnancy testing. Sites should also have collection cups and a toilet available for participants to provide a urine sample. Only study staff may perform the test; the test should not be given to the participant to perform. Perform the test according to site SOPs and the package insert. If the urine pregnancy test cannot adequately be interpreted because of interfering factors, for example excess blood or extreme cloudiness due to amorphous material, another urine sample should be attempted for collection.

Results of the pregnancy test must be documented on the **Pregnancy Testing Log** (paper) and in the participant's **Eligibility CRF** for Enrollment and **Testing Results CRF** at follow-up visits in REDCap.

Pregnancy tests can be performed as indicated in the postnatal follow up period. Participants who are diagnosed with a new pregnancy in the postpartum period may be enrolled into CARE-PrEP a second time, provided all eligibility criteria are met. The participant would continue with their follow-up visits from the index pregnancy while initiating study visits for the second pregnancy. See SSP Section 5 Study Procedures for details on how to handle documentation of two pregnancy episodes for the same person in the context of CARE PrEP.

6.9.2. HIV Testing

HIV rapid testing is required at all study visits for maternal participants unless there is documentation of an HIV test performed in the 5 days the visit or documentation of ART use (see SSP section 5 for more guidance). Documentation should be made into a certified copy per GDP/GCP and stored as a source document in the participant's chart. If both syphilis and HIV testing is required at visit, the syphilis/HIV combo rapid test should be performed (See SSP Section 6.9.3 below).

Only the first screening rapid in the national HIV testing algorithm is to be performed in CARE PrEP; participants needing additional testing will be referred for testing through the national health system. Study sites are to use a test kit brand approved by the MoH; preferably the same kit type used in CATALYST. Ideally, study teams should procure a stock of kits for the study that is not dependent on the national supply chain (to avoid stock outs) or depletes stock meant for health facility SOC testing. Consumables needed for blood sample collection and test processing should also be well stocked for study use only.

Sites are required to develop and follow SOPs for HIV counseling and testing, which should include details about pre- and post-test counseling. All HIV pre- and post-test counseling should be provided in accordance with local counseling standards and study staff who provide HIV counseling should be trained to do so per local practice standards. Counseling staff should also be trained on

study-specific HIV testing methods and interpretation of test results. Client-centered approaches should be used to assess participant knowledge of relevant information, dispel misconceptions, ensure participant readiness for HIV testing, and confirm participant understanding of test results. Information should be provided in a manner that is respectful and interactive. Referrals should be provided when indicated. Refer to the **HIV Testing and Counseling Guide,** available on the MARIX-007 study website.

Counseling messages following rapid HIV test results are provided in Table 6-2 below.

Table 6-2: Counseling Messages Following HIV Rapid Test Results

Test Result	Counseling Message
Negative Rapid test	Test result indicates **no HIV infection**.
Positive Rapid test	1. Test results indicate **possible HIV infection.** **At enrollment visit:** 1. Potential participant is not eligible for MATRIX-007. 2. Additional testing is needed. Potential participant can be referred today for confirmation testing at the health facility linked with the study site. Offer to escort them to the testing services. They can also choose to receive confirmation testing at another health facility of their choosing, but it is important to follow-up on testing immediately. 3. If confirmatory testing determines the participant to not be infected with HIV, the participant may rescreen for the study. **Follow-up visits:** 1. Additional testing is needed. Potential participant can be referred today for confirmation testing at the health facility linked with the study site. Offer to escort them to the testing services. They can also choose to receive confirmation testing at another health facility of their choosing, but it is important to follow-up on testing immediately. 2. The participant can continue in the study as planned, regardless of the confirmation testing outcome. Further HIV rapid testing at study visits can be omitted for participants confirmed to be living with HIV. 3. Remind participant to notify study staff of the testing results or make a plan to follow-up with them or the HTS provider.

Results of the HIV rapid tests must be documented on the **HIV Testing Log** (paper) and in participant's **Eligibility CRF** for Enrollment and **Testing Results CRF** at follow-up visits REDCap.

Participants who have an invalid test may have the rapid repeated on a new blood sample collected.

In the case of a positive rapid, the participant should be referred for confirmation testing immediately following the visit. Ideally, study staff can escort the participant to HIV testing services at the CARE PrEP-linked health facility. HIV testing services (HTS) providers should have been sensitized to the CARE PrEP study and understand the testing requirements of the study and that participant's will be referred for confirmation testing. Participant may also choose to have confirmation testing performed at a different facility. If a direct referral cannot be made by study staff, encourage participants to immediately seek confirmation testing. For enrolled participants, study staff should have a plan to obtain confirmation testing results, such as following up with the participant and/or checking in with the HTS provider.

In addition to providing confirmatory testing, the health clinic can provide instruction to the participant about whether PrEP should be stopped temporarily or not, and they can facilitate establishing appropriate ANC care. Acute HIV seroconversion is an important risk factor for perinatal transmission; ensuring pregnant women who acquire HIV are placed on ART expeditiously is a priority.

A positive result of a study-performed rapid test during study eligibility assessment makes the participant ineligible to enroll (results in a screen fail), regardless of the confirmatory testing outcome. However, the participant may rescreen once for the study – the participant would need to have another study-performed rapid test or provide documentation of negative HIV testing within the prior 5 days of the rescreen (could be documentation of the confirmatory testing).

During study follow-up, if confirmatory testing demonstrates that the participant is not infected with HIV, study participation can continue per usual. Study staff can make a note of the outcome in the participant's chart notes. HIV rapid testing would be repeated at the next visit as scheduled. For confirmatory testing that indicates a seroconversion, study staff should document the results on a new Testing Results CRF, which can be done at an interim visit when results are received or the next scheduled study visit depending on when results are received. Additionally, a **Medical Events/Conditions CF** should be completed to document the 'seroconversion' and any antiretroviral (ART) drugs initiated should be documented on the **Medications CRF**. Study staff should also check that the participant has received PMTCT counseling and the participant's clinical care providers are aware of the seroconversion. Further HIV rapid testing at study visits can be omitted for participants confirmed to be living with HIV.

Study staff must also notify the Safety Sub-Committee of a confirmed seroconversion using an SSC Query Form. See SSP section 6.15 below for query guidance.

6.9.3. Syphilis testing

Awareness of a syphilis infection is critical in pregnancy because the infection can be transferred to the fetus and lead to poor outcomes for both mothers and infants. All maternal participants should receive syphilis testing at least once during a pregnancy; testing requirements may differ by national guidelines

In MATRIX-007, syphilis testing is required at enrollment unless there is documentation of a MATRIX-007 approved test (as defined in Country SOPs) done during the pregnancy and within the preceding 3 months or the participant has documentation of undergoing current treatment. If the previous test was positive but it is unclear if the participant received treatment, test at this visit to confirm the current syphilis status. A certified copy per GDP/GCP of the test result or treatment

records should be made and stored as a source document in the participant's chart. Please refer to the syphilis testing algorithm in Figure 6-5 at the end of this section for determining when testing is needed or can be omitted at the Enrollment Visit. Testing can also be performed if indicated at all other visits.

Following is the hierarchy of preferred study-performed testing options that should be used based on availability and congruence with local SOC testing.

1. Standard Q HIV/syphilis Combo (*preferred*)
2. First Response HIV/syphilis Combo (*if the Standard Q test is not available and if approved locally for use and with the approval of the MATRIX-007 LOG*)
3. Local Standard of Care RPR with TPHA/TPPA or other treponemal specific confirmatory test (*if the Standard Q test is not available, with the approval of the MATRIX-007 LOG).*

Each country must develop an SOP, in consultation with the LOG, that describes the current SOC testing within country, which test types may be accepted to omit study-performed testing, and what test types will be used for study-performed testing

The LOG must be aware of the brand of kit planned for use prior to implementation (at study start and for a change during the study).

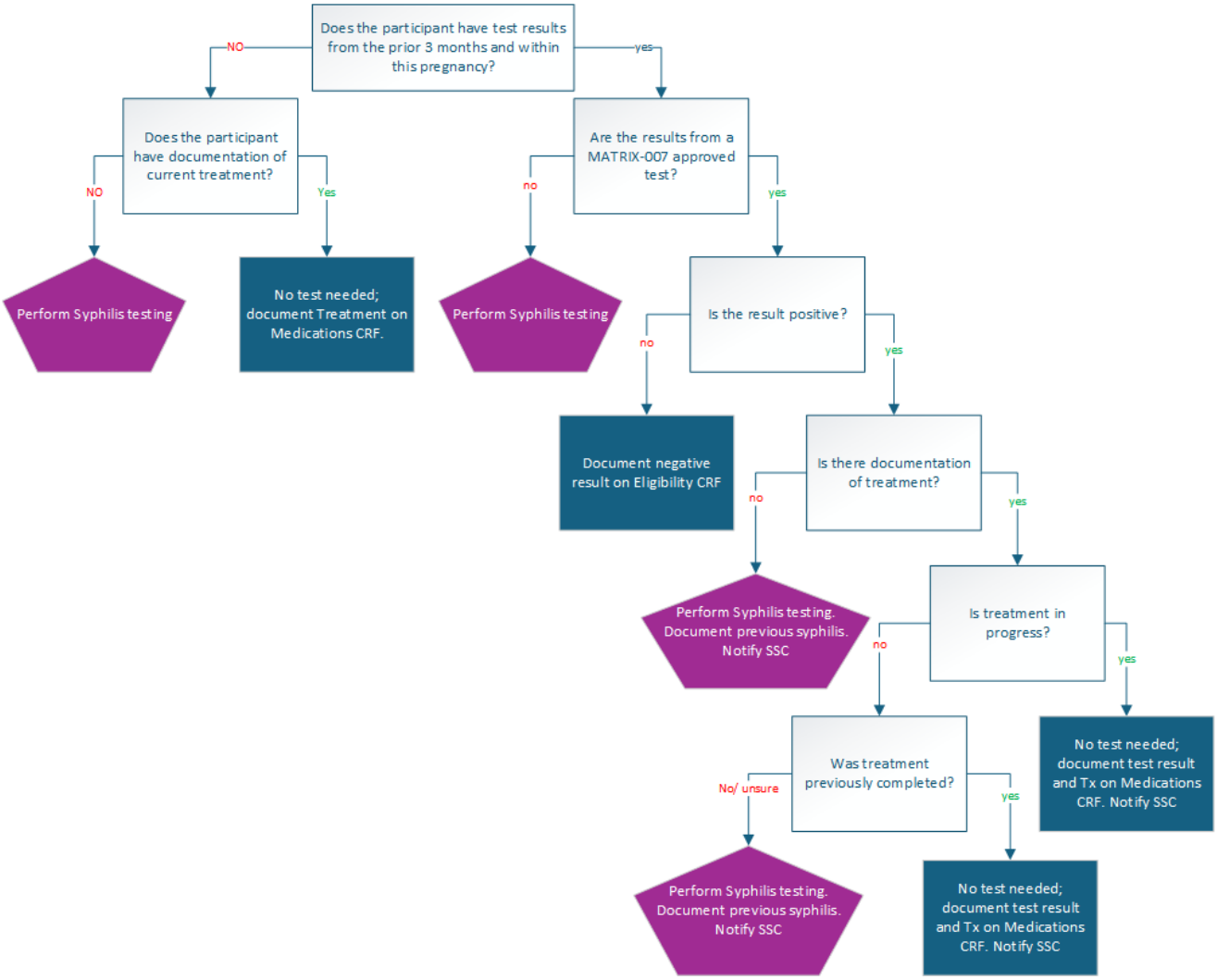
Ideally, study teams should procure a stock of kits for the study that is not dependent on the national supply chain (to avoid stock outs) or depletes stock meant for health facility clients. Consumables needed for blood sample collection and test processing should also be well stocked for study use only.

There is no syphilis only testing option within the study. Therefore, even if an HIV test is not needed at a visit but syphilis testing is needed, HIV testing will be included with the syphilis test. Results of the syphilis/HIV combo tests must be documented on the **Syphilis Testing Log** (paper) and in the participant's **Eligibility CRF** for Enrollment and **Testing Results CRF** at follow-up visits in REDCap. Study staff may also document the test outcome in the participant's hand-held ANC records if this is an acceptable practice within the local healthcare context.

Per protocol, syphilis testing can be done as indicated during follow-up visits. For example, national guidelines may recommend repeat syphilis testing in the third trimester and site staff might recognize that the participant has not had a repeat syphilis test despite being 34 weeks pregnant. It would be acceptable and encouraged to offer syphilis testing to that participant. Another example might involve a participant who reports that she was evaluated for a painless vulvar ulcer the month before her CARE PrEP visit. Knowing that this symptom (painless vulvar ulcer) can be associated with syphilis, the site staff might elect to do a rapid syphilis test. (Note: the rapid syphilis test depends on antibody formation for detection so the test may not pick up active syphilis in the first few weeks of the infection.)

In cases of a participant with a positive syphilis test or diagnosis, study staff must notify the Safety Sub-committee (SSC) via a SSC Query Form, providing all clinical details about the possible or diagnosed syphilis case. See SSP section 6.15 below for SSC query guidance. Participants with positive results from a study-provided rapid should be referred for clinical care and treatment, and additional testing, if required per local SOC. A syphilis diagnosis should also be recorded on the **Medical Events/Conditions CRF** as 'syphilis.' For a positive study-directed rapid without a diagnosis confirmation, record 'positive syphilis screening' on the CRF.

Figure 6-5: Syphilis testing Algorithm at Enrollment



6.10. Enrolled Infants Medication and Medications Assessment

If the pregnancy results in a live-born infant, and consent has not been withdrawn for the infant to enroll in MATRIX-007, then a clinical history of the infant should take place at the PO visit (scheduled as soon as possible after the outcome and ideally within 5 days of delivery). This should include review of delivery/well baby medical records as it relates to infant conditions, as well as review of any medication taken or being administered. Study staff should seek out primary medical records whenever possible, however, if these cannot be obtained, maternal reports of any conditions/medications are acceptable.

During follow-up, sites should review any previously reported medical conditions for updates and assess for any new conditions or symptoms that have developed since that last visit. The **Medical and Medications Guide** provides some sample questions. Ultimately, study staff are encouraged to use their clinical skills to elicit pertinent health updates.

Relevant significant conditions identified through medical history review and infant physical exams should be reported on the **Medical Events/Conditions CRF** in the infant record in REDCap. This CRF is used the same as described in the maternal medical assessment SSP section 6.3 above. In

general, include congenital anomalies, abnormal growth, chronic medical conditions, developmental delays; hospitalizations and surgeries, any diagnoses made by a medical provider, abnormal lab results. Exclude common benign neonatal/infant findings such as milia, erythema toxicum, benign pustular melanosis, seborrhea ("cradle cap"), upper respiratory infection (common cold).

Any relevant medications administered to the infant from the time of birth should be documented on the **Medications CRF** in the infant record. Please note the start and stop dates of these medications as well as the indication, frequency, dose, route, and indication. This CRF is used the same as described in the maternal medical assessment SSP section 6.3 above. See the Medical and Medication Guide for specific instructions on reportable medical events and conditions.

Assessment of the infant at all visits should also include review of the infant's physical health, anthropometry (growth), and feeding history. The following sections will provide guidance on these assessments.

6.11. Infant Care

Globally, most common immediate causes for early childhood mortality include infectious conditions, e.g., diarrhea, respiratory infections, malaria, and measles. Per the WHO ETAT guidelines, the following emergency signs in infants should prompt immediate action:

- Obstructed or absent breathing
- Severe respiratory distress
- Central cyanosis
- Signs of shock (cold extremities with capillary refill time >3 seconds and a weak, fast pulse)
- Coma (or seriously reduced level of consciousness)
- Seizures
- Signs of severe dehydration in a child with diarrhea with any two of these signs: lethargy or unconscious, sunken eyes, very slow return after pinching the skin

There are a number of conditions that are common within the first year of an infant's life which are summarized in this section. Close attention and appropriate referrals should be made

- **Rash**: Many newborn rashes are benign and do not require treatment or referral. Please refer to training slides for examples, photos, and management guidance.
- **Thrush (oral candida infection):** Thrush may develop as early as 7 to 10 days of age and appears often within the first year of life. In the healthy newborn, thrush is a self-limited infection, but it usually should be treated to avoid feeding problems. Infants with recurrent or persistent thrush should be tested for HIV.
- **Undernutrition, stunting, and wasting:** Because of rapid growth and increased vulnerability to infection, children <2 years of age are most at risk groups for undernutrition. Severe acute malnutrition (SAM) is diagnosed by using the weight-for-length graph.
- **Infant vomiting:** Can be hard to tell if infant is spitting up or vomiting because some infants reflux forcefully or in large amounts. In infants <3 months old, forceful vomiting always requires further evaluation. Potential causes in these infants include narrowing of stomach (pyloric stenosis) or blockage of intestines (intestinal obstruction). Infants can also vomit because of infections

- **Serious bacterial infection:** Pneumonia is one of the leading causes of childhood deaths. Clinical diagnosis and treatment of pneumonia a challenge, especially in neonates and young infants <2 months of age. Fast breathing (≥60 breaths/min.) in infants up to 59 days a sign of pneumonia (small proportion of healthy young infants breathe faster than 60 breaths per minute).
- **Lower Respiratory Tract Infection:** Characterized in infants by poor feeding, irritability and lethargy, grunting/cyanosis, fever, cough/wheeze, chest in drawing.

Treating these illnesses is outside of the clinic site's capacity, but the site staff should facilitate prompt referral to an appropriate health care facility.

6.11.1. Infant Feeding Assessment

Infant feeding assessment is completed at the Pregnancy Outcome Visit and Post-natal Visits for enrolled infants. The **Infant Assessment Feeding CRF** should be completed based on self-report from the maternal participant. A sample **Breastfeeding Support factsheet** is available on the MATRIX-007 website as a resource for mothers. The factsheet can be adapted to local context and translated into local languages. Study staff should also have referral resources available for any maternal participant needing additional support related to breastfeeding. Conditions necessitating site staff to facilitate prompt referral include, but are not limited to, signs of infant dehydration; blue coloration around the infant mouth during feeding; discharge of milk through the nose while feeding; and sudden decrease in infant appetite. Such conditions warrant referral to a pediatric health provider.

6.12. Infant Physical Exam

Each time an infant presents for a scheduled visit (Pregnancy Outcomes Visit and Post-natal Visits), a physical exam will be conducted. This will include taking growth measurements of weight, length, and head circumference (HC) and performing a surface exam to assess for congenital anomalies. Only trained clinical study staff delegated to perform infant exams on the country Delegation od Duties (DoD) Log are permitted to perform these procedures.

6.12.1. Growth Measurements

For enrolled infants, study staff will review growth measurements for length, weight, and head circumference (HC) at birth (recorded in delivery/birth records) and obtain measurements at each infant study visit (Pregnancy Outcome Visit and Post-natal 3-- and 6 month visits).

Pregnancy outcome visit

Pregnancy outcome visits should occur, ideally, within the first 5 days of life. When a mother and infant present for the pregnancy outcome visit, study staff should review the birth records and the infant's weight, length, and HC in the **Infant Outcome CRF**. Then, study staff should take measurements (weight, length, HC) during the visit and record them in the **Infant Physical Exam CRF.** *If the pregnancy outcome visit occurs within the first 2 weeks of life*, use the rules below to ensure that the baby's weight change from the birthweight is appropriate.

- It is normal for term and preterm infants to lose up to 10% of their birthweight during the first 2 weeks of life. Loss greater than 10% should be immediately referred or managed by the study staff (only if comfortable) with close follow-up.

- Some weight gain, however, can also be normal during the first 2 weeks of life.
- While small increases in length and head circumference are expected in the first 2 weeks of life (up to 1cm per week for length; up to 0.5 cm for HC), measurement error in birth records is common. Thus, study staff should at least ensure no loss of HC has occurred. If it appears a loss of HC has occurred, use the infant growth Tables 6-3.1 to 6-3.12 below to ensure the HC is at least within the normal range for age. If it is not, refer the infant.
- *Note when using Tables 6-3 below for preterm infants, **postmenstrual age** should be used, not their chronological age.*
    - Postmenstrual age=gestational age (in weeks) + chronological age (in weeks)
    - For example, if a baby was born at 36 weeks gestation and they are 1 week old at the pregnancy outcome visit today: postmenstrual age=36+1=**37 weeks**.
    - You should look at all measurements corresponding to 37 weeks, keeping in mind that the range for normal is between the 3rd and 97th percentiles.

Postnatal Visits

For the 3-month and 6-month post-natal visits (or any pregnancy outcome visits that occur after 2 weeks of life), study staff should take measurements (weight, length, HC) and record them in the **Infant Physical Exam CRF**. Use the rules and Tables 6-3 below to ensure weight, length, and HC and their respective trajectories are appropriate. Be sure to note whether the infant was born full-term or preterm when applying the rules and table values.

- The range for normal for all measurements should be considered as between the 3rd and 97th percentiles. For example, the normal weight range for a 1-month old term girl would be 3.2-5.4 kg.
- If any of the infant's measurements fall outside the normal range, referral should be considered, particularly for head circumferences that fall outside of the normal range.
- If the infant falls within the normal range of measurements, study staff should ensure that the infant's growth trajectory is roughly appropriate. Any of the following information below may be helpful to do so:
    - Use the infant growth Tables 6-3.1 to 6.3.12 below to approximate the percentiles for weight, length, and HC across visits. In general, most infants will track along a similar percentile through infancy for each measure. (For example, a baby in the 20th percentile for length at the 3-month visit will typically be around the 20th percentile for length at the 6-month visit. Some deviation is normal, but if an infant cuts across 2 percentile categories, referral should be considered.
    - Study staff may check any health passports, growth charts, or documentation that the caregiver has brought along to help determine if growth is proceeding as expected
    - Full-term infants should gain approximately 20-30 grams per day for the first 3-4 months of life (excluding the first 2 weeks of life, when weight loss can be normal)
    - Full-term infants typically double their birthweight by 6 months of age
    - Preterm infants typically gain 15g/kg/day for the first few months (excludes the first 2 weeks, when weight loss can be normal)
    - *Note when using the tables below for preterm infants, **postmenstrual age** should be used, not their chronological age.*
        - Postmenstrual age=gestational age (in weeks) + chronological age (in weeks)
        - For example, if a baby was born at 36 weeks gestation and they are 3 months old at the visit today: postmenstrual age=36+12=**48 weeks**.

- If the infant's measurements fall outside of the normal range or you are concerned that any of their growth trajectories (weight, length, HC) might not be appropriate, then consider the following questions:
    - Are there health issues or factors from the additional information gathered during the medical history that may be impacting growth, e.g., illness and/or decreased appetite?
    - How does the infant appear on physical exam? How is his/her strength/color/alertness/, etc.? Are there any unusual features that could suggest a syndrome or genetic abnormality?
    - If you suspect any abnormalities or health conditions, document in the **Medical Events/Condition CRF**, with diagnosis, if known, and refer.

Finally, if growth measurements are available from medical records when measurements cannot be taken by study staff, the abstracted measurements can still be recorded in an **Infant Physical Exam CRF**. A CRF Note should describe the scenario and date of the measurements.

Tables 6.3 1-11: Measurement-for-age Percentiles

Table 6-3.1: Weight-for-age percentiles, TERM Girls (kg)

Months	3rd	15th	Median	85th	97th
0	2.4	2.8	3.2	3.7	4.2
1	3.2	3.6	4.2	4.8	5.4
2	4.0	4.5	5.1	5.9	6.5
3	4.6	5.1	5.8	6.7	7.4
4	5.1	5.6	6.4	7.3	8.1
5	5.5	6.1	6.9	7.8	8.7
6	5.8	6.4	7.3	8.3	9.2

Table 6-3.2: Length-for age percentiles, TERM Girls (cm)

Months	3rd	15th	Median	85th	97th
0	45.6	47.2	49.1	51.1	52.7
1	50.0	51.7	53.7	55.7	57.4
2	53.2	55.0	57.1	59.2	60.9
3	55.8	57.6	59.8	62.0	63.8
4	58.0	59.8	62.1	64.3	66.2
5	59.9	61.7	64.0	66.3	68.2
6	61.5	63.4	65.7	68.1	70.0

Table 6-3.3: HC-for-age percentiles, TERM Girls (cm)

Months	3rd	15th	Median	85th	97th
0	31.7	32.7	33.9	35.1	36.1
1	34.3	35.3	36.5	37.8	38.8
2	36.0	37.0	38.3	39.5	40.5
3	37.2	38.2	39.5	40.8	41.9
4	38.2	39.3	40.6	41.9	43.0
5	39.0	40.1	41.5	42.8	43.9
6	39.7	40.8	42.2	43.5	44.6

Table 6-3.4: Weight-for-age percentiles, TERM Boys (kg)

Months	3rd	15th	Median	85th	97th
0	2.5	2.9	3.3	3.9	4.3
1	3.4	3.9	4.5	5.1	5.7
2	4.4	4.9	5.6	6.3	7.0
3	5.1	5.6	6.4	7.2	7.9
4	5.6	6.2	7.0	7.9	8.6
5	6.1	6.7	7.5	8.4	9.2
6	6.4	7.1	7.9	8.9	9.7

Table 6-3.5: Length-for-age percentiles, TERM Boys (cm)

Months	3rd	15th	Median	85th	97th
0	46.3	47.9	49.9	51.8	53.4
1	51.1	52.7	54.7	56.7	58.4
2	54.7	56.4	58.4	60.5	62.2
3	57.6	59.3	61.4	63.5	65.3
4	60.0	61.7	63.9	66.0	67.8
5	61.9	63.7	65.9	68.1	69.9
6	63.6	65.4	67.6	69.8	71.6

Table 6-3.6: HC-for-age percentiles, TERM Boys (cm)

Months	3rd	15th	Median	85th	97th
0	32.1	33.1	34.5	35.8	36.9
1	35.1	36.1	37.3	38.5	39.5
2	36.9	37.9	39.1	40.3	41.3
3	38.3	39.3	40.5	41.7	42.7
4	39.4	40.4	41.6	42.9	43.9
5	40.3	41.3	42.6	43.8	44.8
6	41.0	42.1	43.3	44.6	45.6

Table 6-3.7: Weight-for-age percentiles, PRETERM Girls (kg)

Postmenstrual age (exact weeks)	Centiles						
	3rd	5th	10th	50th	90th	95th	97th
27	0.41	0.44	0.47	0.61	0.80	0.86	0.91
28	0.52	0.55	0.59	0.76	0.97	1.05	1.10
29	0.64	0.67	0.72	0.91	1.16	1.25	1.30
30	0.77	0.81	0.86	1.09	1.37	1.46	1.52
31	0.91	0.95	1.01	1.27	1.58	1.68	1.75
32	1.06	1.11	1.18	1.46	1.80	1.92	1.99
33	1.22	1.27	1.34	1.65	2.03	2.16	2.24
34	1.38	1.43	1.52	1.86	2.27	2.41	2.50
35	1.55	1.60	1.70	2.07	2.51	2.66	2.76
36	1.72	1.78	1.88	2.28	2.76	2.92	3.02
37	1.89	1.96	2.06	2.49	3.01	3.17	3.29
38	2.06	2.13	2.25	2.71	3.26	3.43	3.55
39	2.23	2.31	2.43	2.92	3.50	3.69	3.82
40	2.41	2.49	2.62	3.13	3.75	3.95	4.08
41	2.58	2.66	2.80	3.35	3.99	4.20	4.34
42	2.75	2.84	2.98	3.55	4.24	4.45	4.60
43	2.91	3.01	3.16	3.76	4.48	4.70	4.85
44	3.08	3.18	3.34	3.96	4.71	4.95	5.11
45	3.24	3.34	3.51	4.16	4.94	5.19	5.35
46	3.40	3.50	3.68	4.36	5.17	5.42	5.60
47	3.55	3.66	3.84	4.55	5.39	5.65	5.83
48	3.70	3.82	4.01	4.74	5.61	5.88	6.06
49	3.85	3.97	4.16	4.92	5.82	6.10	6.29
50	3.99	4.12	4.32	5.10	6.02	6.32	6.51
51	4.13	4.26	4.46	5.27	6.22	6.53	6.73
52	4.26	4.40	4.61	5.44	6.42	6.73	6.94
53	4.40	4.53	4.75	5.60	6.61	6.93	7.14
54	4.52	4.66	4.89	5.76	6.80	7.12	7.34
55	4.64	4.79	5.02	5.92	6.98	7.31	7.54
56	4.76	4.91	5.15	6.07	7.15	7.50	7.73
57	4.88	5.03	5.27	6.21	7.32	7.67	7.91
58	4.99	5.14	5.39	6.35	7.49	7.85	8.09
59	5.10	5.25	5.51	6.49	7.65	8.01	8.26
60	5.20	5.36	5.62	6.62	7.80	8.18	8.43
61	5.30	5.47	5.73	6.75	7.95	8.33	8.59
62	5.40	5.57	5.83	6.87	8.10	8.49	8.75
63	5.49	5.66	5.93	6.99	8.24	8.64	8.90
64	5.58	5.76	6.03	7.11	8.38	8.78	9.05

Table 6-3.8: Length-for age percentiles, PRETERM Girls (cm)

Postmenstrual age (exact weeks)	Centiles						
	3rd	5th	10th	50th	90th	95th	97th
27	27.8	28.3	29.0	31.7	34.6	35.5	36.1
28	29.7	30.2	30.9	33.5	36.3	37.2	37.8
29	31.5	32.0	32.7	35.2	38.0	38.8	39.3
30	33.2	33.7	34.3	36.8	39.5	40.3	40.9
31	34.8	35.3	35.9	38.4	41.0	41.8	42.3
32	36.4	36.8	37.5	39.9	42.4	43.2	43.7
33	37.8	38.2	38.9	41.3	43.8	44.5	45.0
34	39.2	39.6	40.3	42.6	45.1	45.8	46.3
35	40.5	40.9	41.5	43.9	46.3	47.0	47.5
36	41.7	42.1	42.8	45.1	47.5	48.2	48.7
37	42.9	43.3	43.9	46.2	48.6	49.3	49.8
38	44.0	44.4	45.0	47.3	49.7	50.4	50.9
39	45.0	45.4	46.1	48.3	50.7	51.4	51.9
40	46.0	46.4	47.1	49.3	51.7	52.4	52.9
41	47.0	47.4	48.0	50.3	52.7	53.4	53.8
42	47.9	48.3	48.9	51.2	53.6	54.3	54.7
43	48.7	49.1	49.8	52.1	54.5	55.2	55.6
44	49.6	50.0	50.6	52.9	55.3	56.0	56.5
45	50.3	50.7	51.4	53.7	56.1	56.8	57.3
46	51.1	51.5	52.1	54.5	56.9	57.6	58.1
47	51.8	52.2	52.9	55.2	57.7	58.4	58.9
48	52.5	52.9	53.6	55.9	58.4	59.1	59.6
49	53.1	53.6	54.2	56.6	59.1	59.8	60.3
50	53.8	54.2	54.9	57.3	59.8	60.5	61.0
51	54.4	54.8	55.5	57.9	60.5	61.2	61.7
52	54.9	55.4	56.1	58.5	61.1	61.9	62.4
53	55.5	55.9	56.6	59.1	61.7	62.5	63.0
54	56.0	56.5	57.2	59.7	62.3	63.1	63.6
55	56.6	57.0	57.7	60.3	62.9	63.7	64.2
56	57.1	57.5	58.2	60.8	63.5	64.3	64.8
57	57.6	58.0	58.7	61.3	64.1	64.9	65.4
58	58.0	58.5	59.2	61.9	64.6	65.4	66.0
59	58.5	59.0	59.7	62.4	65.2	66.0	66.5
60	58.9	59.4	60.2	62.9	65.7	66.5	67.0
61	59.4	59.8	60.6	63.3	66.2	67.0	67.6
62	59.8	60.3	61.0	63.8	66.7	67.5	68.1
63	60.2	60.7	61.5	64.2	67.2	68.0	68.6
64	60.6	61.1	61.9	64.7	67.6	68.5	69.1

Table 6-3.9: HC-for-age percentiles, PRETERM Girls (cm)

Postmenstrual age (exact weeks)	Centiles						
	3rd	5th	10th	50th	90th	95th	97th
27	20.7	21.1	21.8	24.0	26.2	26.8	27.2
28	22.1	22.5	23.1	25.1	27.2	27.7	28.1
29	23.4	23.7	24.3	26.2	28.1	28.6	28.9
30	24.5	24.9	25.4	27.1	28.9	29.4	29.7
31	25.6	25.9	26.4	28.1	29.7	30.2	30.5
32	26.6	26.9	27.3	28.9	30.5	30.9	31.2
33	27.5	27.8	28.2	29.7	31.2	31.7	31.9
34	28.4	28.6	29.0	30.5	31.9	32.3	32.6
35	29.1	29.4	29.8	31.2	32.6	33.0	33.2
36	29.9	30.1	30.5	31.9	33.2	33.6	33.9
37	30.6	30.8	31.2	32.5	33.8	34.2	34.5
38	31.2	31.4	31.8	33.1	34.4	34.8	35.0
39	31.8	32.0	32.4	33.7	35.0	35.3	35.6
40	32.4	32.6	33.0	34.2	35.5	35.9	36.1
41	32.9	33.1	33.5	34.8	36.0	36.4	36.6
42	33.4	33.6	34.0	35.3	36.5	36.9	37.1
43	33.9	34.1	34.5	35.7	37.0	37.3	37.6
44	34.3	34.6	34.9	36.2	37.4	37.8	38.0
45	34.8	35.0	35.4	36.6	37.9	38.2	38.4
46	35.2	35.4	35.8	37.0	38.3	38.6	38.9
47	35.6	35.8	36.1	37.4	38.7	39.0	39.3
48	35.9	36.2	36.5	37.8	39.1	39.4	39.7
49	36.3	36.5	36.9	38.1	39.4	39.8	40.0
50	36.6	36.8	37.2	38.5	39.8	40.2	40.4
51	36.9	37.2	37.5	38.8	40.1	40.5	40.7
52	37.2	37.5	37.8	39.2	40.5	40.8	41.1
53	37.5	37.7	38.1	39.5	40.8	41.2	41.4
54	37.8	38.0	38.4	39.8	41.1	41.5	41.7
55	38.0	38.3	38.7	40.0	41.4	41.8	42.1
56	38.3	38.5	38.9	40.3	41.7	42.1	42.4
57	38.5	38.8	39.2	40.6	42.0	42.4	42.6
58	38.8	39.0	39.4	40.8	42.3	42.7	42.9
59	39.0	39.3	39.7	41.1	42.5	42.9	43.2
60	39.2	39.5	39.9	41.3	42.8	43.2	43.5
61	39.4	39.7	40.1	41.6	43.0	43.5	43.7
62	39.6	39.9	40.3	41.8	43.3	43.7	44.0
63	39.8	40.1	40.5	42.0	43.5	43.9	44.2
64	40.0	40.3	40.7	42.2	43.7	44.2	44.5

Table 6-3.10: Weight-for-age percentiles, PRETERM Boys (kg)

Postmenstrual age (exact weeks)	Centiles						
	3rd	5th	10th	50th	90th	95th	97th
27	0.45	0.48	0.51	0.67	0.88	0.95	0.99
28	0.57	0.60	0.64	0.83	1.07	1.15	1.20
29	0.70	0.74	0.79	1.00	1.27	1.37	1.43
30	0.85	0.88	0.94	1.19	1.50	1.60	1.67
31	1.00	1.04	1.11	1.39	1.73	1.84	1.92
32	1.17	1.21	1.29	1.60	1.98	2.10	2.18
33	1.34	1.39	1.47	1.81	2.23	2.36	2.46
34	1.51	1.57	1.66	2.04	2.49	2.64	2.74
35	1.70	1.76	1.86	2.26	2.75	2.91	3.02
36	1.88	1.95	2.06	2.50	3.02	3.19	3.31
37	2.07	2.14	2.26	2.73	3.29	3.48	3.60
38	2.26	2.34	2.46	2.96	3.57	3.76	3.89
39	2.45	2.53	2.67	3.20	3.84	4.04	4.18
40	2.64	2.73	2.87	3.43	4.11	4.32	4.47
41	2.82	2.92	3.07	3.66	4.38	4.60	4.76
42	3.01	3.11	3.27	3.89	4.64	4.88	5.04
43	3.19	3.30	3.46	4.12	4.90	5.15	5.32
44	3.37	3.48	3.66	4.34	5.16	5.42	5.59
45	3.55	3.66	3.84	4.56	5.41	5.68	5.86
46	3.72	3.84	4.03	4.78	5.66	5.94	6.13
47	3.89	4.01	4.21	4.99	5.90	6.19	6.39
48	4.06	4.18	4.39	5.19	6.14	6.44	6.64
49	4.22	4.35	4.56	5.39	6.37	6.68	6.89
50	4.37	4.51	4.73	5.59	6.60	6.92	7.13
51	4.52	4.66	4.89	5.77	6.82	7.15	7.37
52	4.67	4.82	5.05	5.96	7.03	7.37	7.60
53	4.81	4.96	5.20	6.14	7.24	7.59	7.83
54	4.95	5.11	5.35	6.31	7.45	7.80	8.04
55	5.09	5.24	5.50	6.48	7.64	8.01	8.26
56	5.22	5.38	5.64	6.65	7.83	8.21	8.46
57	5.34	5.51	5.77	6.80	8.02	8.41	8.66
58	5.47	5.63	5.90	6.96	8.20	8.59	8.86
59	5.58	5.76	6.03	7.11	8.38	8.78	9.05
60	5.70	5.87	6.15	7.25	8.55	8.96	9.23
61	5.81	5.99	6.27	7.39	8.71	9.13	9.41
62	5.92	6.10	6.39	7.53	8.87	9.30	9.58
63	6.02	6.20	6.50	7.66	9.03	9.46	9.75
64	6.12	6.31	6.61	7.79	9.18	9.62	9.91

Table 6-3.11: Length-for-age, PRETERM Boys (cm)

Postmenstrual age (exact weeks)	Centiles						
	3rd	5th	10th	50th	90th	95th	97th
27	28.7	29.2	29.9	32.7	35.7	36.7	37.3
28	30.7	31.1	31.9	34.6	37.5	38.4	39.0
29	32.5	33.0	33.7	36.3	39.2	40.0	40.6
30	34.3	34.7	35.4	38.0	40.8	41.6	42.2
31	36.0	36.4	37.1	39.6	42.3	43.1	43.7
32	37.5	38.0	38.7	41.1	43.8	44.6	45.1
33	39.0	39.5	40.1	42.6	45.2	46.0	46.5
34	40.5	40.9	41.5	44.0	46.5	47.3	47.8
35	41.8	42.2	42.9	45.3	47.8	48.5	49.0
36	43.1	43.5	44.1	46.5	49.0	49.7	50.2
37	44.3	44.7	45.3	47.7	50.2	50.9	51.4
38	45.4	45.8	46.5	48.8	51.3	52.0	52.5
39	46.5	46.9	47.5	49.9	52.4	53.1	53.6
40	47.5	47.9	48.6	50.9	53.4	54.1	54.6
41	48.5	48.9	49.6	51.9	54.4	55.1	55.6
42	49.4	49.8	50.5	52.8	55.3	56.0	56.5
43	50.3	50.7	51.4	53.7	56.2	56.9	57.4
44	51.1	51.6	52.2	54.6	57.1	57.8	58.3
45	51.9	52.4	53.0	55.4	57.9	58.7	59.1
46	52.7	53.1	53.8	56.2	58.7	59.5	60.0
47	53.4	53.9	54.6	57.0	59.5	60.3	60.7
48	54.2	54.6	55.3	57.7	60.3	61.0	61.5
49	54.8	55.3	56.0	58.4	61.0	61.8	62.3
50	55.5	55.9	56.6	59.1	61.7	62.5	63.0
51	56.1	56.5	57.2	59.8	62.4	63.2	63.7
52	56.7	57.1	57.9	60.4	63.1	63.8	64.4
53	57.3	57.7	58.4	61.0	63.7	64.5	65.0
54	57.8	58.3	59.0	61.6	64.3	65.1	65.7
55	58.4	58.8	59.6	62.2	64.9	65.8	66.3
56	58.9	59.4	60.1	62.8	65.5	66.4	66.9
57	59.4	59.9	60.6	63.3	66.1	66.9	67.5
58	59.9	60.4	61.1	63.8	66.7	67.5	68.1
59	60.4	60.8	61.6	64.4	67.2	68.1	68.6
60	60.8	61.3	62.1	64.9	67.8	68.6	69.2
61	61.3	61.8	62.5	65.4	68.3	69.2	69.7
62	61.7	62.2	63.0	65.8	68.8	69.7	70.2
63	62.1	62.6	63.4	66.3	69.3	70.2	70.8
64	62.5	63.0	63.8	66.8	69.8	70.7	71.3

Table 6-3.12: HC-for-age, PRETERM Boys (cm)

Postmenstrual age (exact weeks)	Centiles						
	3rd	5th	10th	50th	90th	95th	97th
27	21.5	21.9	22.6	24.8	27.0	27.6	28.0
28	22.9	23.3	23.9	25.9	28.0	28.5	28.9
29	24.2	24.5	25.1	27.0	28.9	29.4	29.7
30	25.3	25.7	26.2	27.9	29.7	30.2	30.5
31	26.4	26.7	27.2	28.9	30.5	31.0	31.3
32	27.4	27.7	28.1	29.7	31.3	31.7	32.0
33	28.3	28.6	29.0	30.5	32.0	32.5	32.7
34	29.2	29.4	29.8	31.3	32.7	33.1	33.4
35	29.9	30.2	30.6	32.0	33.4	33.8	34.0
36	30.7	30.9	31.3	32.7	34.0	34.4	34.7
37	31.4	31.6	32.0	33.3	34.6	35.0	35.3
38	32.0	32.2	32.6	33.9	35.2	35.6	35.8
39	32.6	32.8	33.2	34.5	35.8	36.1	36.4
40	33.2	33.4	33.8	35.0	36.3	36.7	36.9
41	33.7	33.9	34.3	35.6	36.8	37.2	37.4
42	34.2	34.4	34.8	36.1	37.3	37.7	37.9
43	34.7	34.9	35.3	36.5	37.8	38.1	38.4
44	35.1	35.4	35.7	37.0	38.2	38.6	38.8
45	35.6	35.8	36.2	37.4	38.7	39.0	39.2
46	36.0	36.2	36.6	37.8	39.1	39.4	39.7
47	36.4	36.6	36.9	38.2	39.5	39.8	40.1
48	36.7	37.0	37.3	38.6	39.9	40.2	40.5
49	37.1	37.3	37.7	38.9	40.2	40.6	40.8
50	37.4	37.6	38.0	39.3	40.6	41.0	41.2
51	37.7	38.0	38.3	39.6	40.9	41.3	41.6
52	38.0	38.3	38.6	40.0	41.3	41.6	41.9
53	38.3	38.5	38.9	40.3	41.6	42.0	42.2
54	38.6	38.8	39.2	40.6	41.9	42.3	42.5
55	38.8	39.1	39.5	40.8	42.2	42.6	42.9
56	39.1	39.3	39.7	41.1	42.5	42.9	43.2
57	39.3	39.6	40.0	41.4	42.8	43.2	43.4
58	39.6	39.8	40.2	41.6	43.1	43.5	43.7
59	39.8	40.1	40.5	41.9	43.3	43.7	44.0
60	40.0	40.3	40.7	42.1	43.6	44.0	44.3
61	40.2	40.5	40.9	42.4	43.8	44.3	44.5
62	40.4	40.7	41.1	42.6	44.1	44.5	44.8
63	40.6	40.9	41.3	42.8	44.3	44.7	45.0
64	40.8	41.1	41.5	43.0	44.5	45.0	45.3

6.12.2. Surface Exam with Integrated Infant Measurements

A complete surface examination of the infant is one of the most important aspects of MATRIX-007. No studies to date have shown a connection between any type of PrEP and congenital anomalies. However, data for some methods, particularly injectable cabotegravir, are limited. Regulators are particularly interested in the type of safety evidence that can be generated by a detailed examination of infants.

Infant exams are required for any enrolled infant at the Pregnancy Outcome Visit and Post-natal 3- and 6-Month Visits. Therefore, it is important that infants attend these visits. Off-site visits can be considered if the infant is unable to present to the study site for a scheduled study visit. See SSP section 5 for off-site visits procedures.

Infant physical exams are documented on the **Infant Physical Exam CRF**.

Here are some general tips for the infant surface examination:

- Wear clean professional clothing.
- Gather necessary supplies for the examination.
- Ensure the examination room is warm and well-lit.
- Ensure adequate space for the mother or guardian.
- Conduct examination on a comfortable, soft, easily cleanable surface.
- Wash your hands with soap and water or disinfectant if available – don't forget to dry your hands!
- Explain your actions to the mother or guardian and what you find in your examination.

It is important to keep the baby's comfort and safety in mind.

- Keep baby warm or covered as much as possible.
- If possible, ensure the baby is calm before starting.
- Pacify baby by swaddling or gently rocking.
- Attend immediately to signs of distress at any stage of the examination.
- NEVER leave baby unattended on a surface that is not completely enclosed.

When conducting the examination, use a systematic approach. Examine the baby from head down and follow the same routine each time. Start and finish one part of the body before moving to the next. Remove all clothing from the baby and gently lay the baby on its back. Look at the baby and ask yourself:

- Does this baby appear too small or too big?
- Does any body part look too big or too small?
- Do any parts of body or face appear asymmetrical, too big or small, or otherwise abnormal?

Take note of any findings that are abnormal or worthy of further examination.

Weigh the baby using your calibrated infant scale. First, cover the scale with a blanket or cloth. Ensure the scale is at zero before placing the naked baby on the scale. This "tare" function is important to ensure an accurate weight. Record the weight of the baby in grams. Do not leave the baby unattended while being weighed or while you are recording the weight.

Please note that the GBD App video describes using a tape to measure the baby, but in MATRIX-007 we will use a measurement board. To measure baby's length, ensure baby is in an outstretched position. Place child on their back on a clean, flat, firm surface so that baby is lying straight. The

baby's eyes should be looking straight up. The baby's shoulders and buttocks should be flat against the measuring surface and both legs should be fully extended. Make sure that the toes are pointing upward with the feet flat against the foot piece of the measuring board. Correctly positioning baby for length measurement generally cannot be done without two measurers.

Measurer 1 (the mother can do this role if needed)

- Hold baby's head gently with baby looking vertically upward.
- Gently cup baby's ears while holding head.
- Make sure baby's chin is not tucked in to chest or extended back.

Measurer 2

- Align baby's body and legs, extend both legs, and bring foot-piece firmly against baby's heels.
- Place one hand on baby's knees to keep full extension of legs.
- Infant's toes should be pointing upward.

Both legs must be fully extended for an accurate length measurement. If only one of baby's legs is extended, the measurement may be inaccurate. The correct measurement is from the top of the head to heel of the foot. Round the measurement up to the nearest centimeter. Parents can help by staying near baby, e.g., standing between the two measurers and/or holding a toy to distract baby. Parents should not touch baby during weighing, but can be a helper during length measurement.

Examining the skin

Examine the color and texture of the skin all over the baby's body. Please note that some discolorations are normal and/or transient. For example, congenital dermal melanocytosis or slate gray nevus may be present (see images from the training slides). Bruises or skin abrasions noted soon after the time of birth may be related to the birth process. Clinical judgment should be used while assessing the skin and recording findings. Take note of rashes, scars, skin tags, unusual red areas, swelling, hardness, large bullae, marks, and any unusual color. Yellowish skin may indicate jaundice. Blue lips, mouth, or tongue may indicate respiratory or cardiac problems. Both jaundice and perioral blue coloring need immediate attention, with referral to the health facility. Describe significant rashes (flat, raised, red, or pustular) and remember that some rashes may need treatment (see training slides and use your judgment). Look for open tissue on the head, abdomen, and back (rare but urgent). If you see this, cover the area with a sterile dressing and sterile fluid before referring baby for special treatment. Mild increased hairiness at the base of the spine does not need to be recorded; however, record any other isolated unusual areas of hair on the baby's body.

Assessing the head

Observe the shape of the head. This is best done while the baby is in a seated position, supported by the examiner. Check for asymmetry and areas of flatness, especially on the back and sides of the head. Sometime babies born via vaginal birth can have a slightly cone-shaped head, which

typically resolves within a few days after birth and does not need to be noted. Gently palpate the scalp and feel for any fluid, swelling, or bogginess, noting where on the head it occurs. Swelling may be very mild and diffuse throughout most of the scalp, or more pronounced and localized. Feel for the anterior fontanelle and note if it is open or closed. It should be soft and flat. If you feel a very firm, bulging fontanelle or deeply sunken fontanelle, this baby needs emergent referral. The anterior fontanelle typically closes by 1 year of age, but some infant's fontanelles will close as early as 6 months. If a baby is less than 6 months old and the anterior fontanelle is closed, this should be noted and referred. Check for numerous or irregularly placed hair whorls (see photos in training slides). Hair whorls should typically be found at the crown of the head.

Next, measure the circumference of the baby's head. Measure around widest part of the head, with the insertion tape positioned above the ears and around the forehead. Measure and record that circumference in centimeters (round measurement up to nearest centimeter).

Assessing the face, ears, eyes, mouth

Check for a small chin, narrow forehead, abnormal position of the eyes, or other unusual appearance. Check that both nostrils are open by compressing one side at a time and confirming baby can inhale through the opposite side nostril. Examine the shape and size of the ears. Look for small or missing ear parts, skin tags, and pits Check for cataracts, notches, swelling, pus, or other unusual findings in the eyes. Do not force the eyes open. Examine the baby's lips, mouth, and upper and lower gums. Check whether the mouth, lips, and tongue are pink; a blue color is **not** normal. A band of tissue may connect the tongue to the floor of mouth. While this does not need to be recorded, please check to see if the mother is having any challenges with breastfeeding. If so, the finding may need to be referred for further treatment. Examine the baby's upper lip and surrounding area, as well as the palate. In the case of cleft palate, the baby may discharge milk through the nose while breastfeeding. Do not assess for a cleft palate by inserting your finger into the baby's mouth.

Assessing the neck and chest

Gently lift the chin to observe for skin tags or sinus tracts on neck. Slight redness on the back of the neck near the time of birth is a normal variation and need not be recorded. On the chest, check for deformity or as symmetry and any extra nipples. Respirations should be regular, unlabored, and without retractions. You should not see flaring of the nostrils while the baby is breathing.

Assessing the abdomen

Inspect the baby's abdomen (no palpation is needed). Observe the shape and record bulging or distention, visible masses, openings, and any visible defects. Any organ visible outside the abdomen is a medical emergency. You may see diastasis recti, protrusion of the skin along the baby's midline when crying. This does not need to be recorded. Check the umbilicus for redness, pus, blood, and swelling. If present, record this and seek immediate medical assistance. Umbilical hernia is common in infants under 6 months old and typically resolves spontaneously in a few months or years. In umbilical hernia, you will see a small bulge near the belly button. This spot becomes larger and harder when the baby cries, coughs, or strains. Typically, an umbilical hernia is not painful to the touch. Note that a large hernia may need treatment. Umbilical hernias measuring greater than 1.5 cm are unlikely to spontaneously close and should be referred. To measure an umbilical hernia, gently insert your first finger(s) into the umbilical ring. If you are able to insert more than your first finger, the hernia is unlikely to close spontaneously and should be referred. All umbilical hernias should be recorded in the CRF.

Assessing the anus, hips, and genitalia.

Gently clasp both legs and raise them to examine the anus for correct position and opening. If the baby has passed stool, this is a sign that the anus is open. In rare cases, it may not be open (requires surgery). This is known as imperforate anus. Do not insert any instruments or finger to inspect the anus. For examination of the hips and genitals, extend the legs to check if the length of the legs is the same (you do not need to measure this). Check to see if baby's thighs and skin creases are symmetrical. Asymmetrical creases may indicate problems with the baby's hips. Record if asymmetry is noted.

For male genitalia, check the urethral opening. If the urethra is not at the tip of the glans and is on the underside of the tip or glans, this is hypospadias, which should be recorded and referred. Observe the scrotum and palpate gently to confirm that both testes have descended into scrotal sac. Sometimes, the scrotal sac may have a collection of fluid (hydrocele). This should also be recorded and referred.

For female genitalia, check the outer and inner labia and the vaginal orifice. Check to see that the labia are not fused. Do not insert anything into the vaginal opening. For newborns, note whether child has passed urine (indicates that urethra is open).

In rare cases, the genitalia may be ambiguous, i.e., not clearly as expected for a female or male baby. While this is a rare occurrence, site staff should be prepared to regard such a finding with sensitivity and should be urgently referred to a pediatric provider.

Assessing the arms and legs

Observe the shape, length, and symmetry of legs and arms. Check for stiff joints, a finding that tends to be one-sided. Check foot positioning. If the feet appear bent or abnormally positioned, try to gently stretch them into a normal position. If you are not able to do so, this may be clubfoot and should be noted and referred. If you are able to stretch them gently into normal position and the baby is less than 2 months old, then this does not need to be noted.

Examining the baby's fingers

Extend the baby's curled fingers around your own finger. Count digits on each hand and look for fingernails. Check if fingers are unusually short. You should see creases on palms of hands (may be absent in premature babies). Sometimes only one crease is present across the palm, which is known as a transverse palmar crease (1% of newborns). This finding is often harmless but should be noted. Check for fingers that may be fused together or extra fingers.

Examining the baby's toes

Count digits on each foot and look for toenails. Check if toes are of unusual size. Placing your thumb on the soles of the baby's feet makes the exam easier. Look for fused toes Note any webbing, also known as syndactyly. Check for skin creases on the soles of the feet.

Spine

Gently lift the baby up, supporting one hand under its chest and turn it over. Observe the back and spine by holding it gently but firmly with your hands supporting the abdomen and chest. Ensure the baby is positioned safely to allow for observation. Run your finger along the spine to check that it is straight (check for lumps, puffiness). Check for any sinuses/dimples in the sacral area. If you see a sinus/dimple, measure the size of the sinus and the distance from the sacrum. and note if you can see the base of the sinus. All sinuses should be noted in the CRF. If a sinus is more than 5mm in

diameter or >2.5 cm from the anus, refer to a pediatric provider. Some fine hair at the sacrum is normal and does not need to be recorded. A thick tuft of hair, however, should be noted and referred.

Concluding your examination

Wrap the baby in their own clothes or blanket and hand them carefully back to the mother or guardian. Explain your findings to the mother or guardian. Consult a local pediatrician if needed and arrange for referral of any unclear or abnormal findings. Any consultation should be documented, as well as any counseling provided to the mother or guardian. Record all your findings in the Infant Physical Exam CRF. For any abnormal findings or congenital anomalies, record in the infant's Medical Events/Conditions CRF as well. See section 6.13.3.1 below for more guidance on documenting congenital anomalies. If locally permissible, you may also record findings in the baby's patient record.

6.13. Infant Congenital Anomalies

Infant congenital anomalies (CAs) may be identified through healthcare providers at the time of delivery or prior to the infant presenting for a study visit or by study staff during the infant surface exam. All diagnosed and suspected CAs should be documented in relevant CRFs in REDCap and photos/videos uploaded to the Global Birth Defects Description and Coding App (GBD App), if applicable, and if consent for infant photography/video has been provided. See SSP section 6.13.1 below about the GBD App.

During pregnancy outcome review, the **Infant Outcome CRF** will ask if any congenital anomalies were identified at the time of birth by healthcare providers. Any identified CAs should be reassessed during the surface exam if the infant is present and documented on the **Infant Physical Exam CRF.** CAs should also be entered on the **Medical Event/Conditions CRF** under the infant record if the infant is enrolled or under the maternal record if the CA was identified in a fetal loss or non-enrolled infant. Additionally, notify the Safety Sub-committee for any suspected or confirmed congenital anomaly (See SSP section XX below for CA review guidance).

All congenital anomalies whether minor or major must be reported. Multiple minor congenital anomalies may present in a cluster as part of a larger congenital syndrome in some cases. Refer to the training slides (link) for additional information on identification of CAs.

6.13.1. Use of Global Birth Defects App

Major malformations (those with surgical, medical, or cosmetic importance, ascertained up to 6 months of age) are a primary endpoint in MATRIX-007. MATRIX-007 will use the Global Birth Defects Description and Coding App (GBD App) to standardize the approach to ascertaining congenital anomalies.

The GBD App was developed for use in areas where local expertise in congenital anomaly diagnosis is scarce. The purpose of the App is to improve the description and coding of major externally visible congenital anomalies for surveillance and research.

A full description of how the app was designed can be found at Global birth defects app: An innovative tool for describing and coding congenital anomalies at birth in low resource settings - Dolk - 2021 - Birth Defects Research - Wiley Online Library.

The app will assist with the description and coding of externally visible birth defects during the neonatal period. The app contains images of major externally visible birth defects, with definitions and international classification of disease (ICD) version 10 codes with British Pediatric Association (Royal College of Pediatrics and Child Health, RCPCH) one-digit extension for CAs. The app also contains existing video material on the newborn examination (provided by WHO- TDR, Special Programme for Research and Training in Tropical Diseases). As the user taps the screen, the app takes him/her through a series of body regions and images of major externally visible birth defects, to identify the most likely correct description and ICD-10 code. CARE PrEP will use the surveillance version of the app, which allows recording of data (including text, photos, and video) that is uploaded to the app's surveillance system data center. Each study staff responsible to perform infant surface exams or review congenital anomalies should create an account for the app linked to the study project. See SSP Section 7 for guidance on app setup.

For any diagnosed or suspected congenital anomaly in an infant undergoing an exam whose mother has provided consent for photos/videos, study staff should upload photos or video to the GBD App that can be accessible for the MATRIX-007 Congenital Anomaly Review. See SSP section 6.13.2 below for guidance on taking photos and facilitation of the review.

6.13.2. Consent and Counseling About Taking Photos/Videos

All maternal participants should have had the opportunity to consent for photos/video to be taken of their infants when completing the study ICF at the Enrollment Visit. Before any photos or video are taken, study staff must confirm that the mother provided written consent (this can be viewed on the Eligibility CRF or the signed ICF) and reaffirm this consent verbally prior to taking the photos/video.

It is critical that care be taken to provide supportive counseling to the mother regarding the purpose of the photos and to allay any anxiety she may have about her child's condition. As such, suggested counseling messages are provided below for staff to utilize as needed.

Suggested Counseling Messages:

- Provide as much information as possible about the diagnosed or suspected condition—*for example, whether the condition is considered minor or inconsequential to the infant's health, or if more serious, what the options might be for treatment. Reassure the parent(s) that referrals for further counseling and ongoing management of the condition will be provided.*
- Because this is a research study, we may ask to take pictures of conditions even if they are considered minor. The photos are voluntary.
- The photos will help the doctors working on the study to evaluate the condition and decide if it is important to your baby's health.
- There is no current evidence to suggest that exposure to PrEP caused your baby's condition.
- What questions or concerns do you have?

A participant may change her mind about having photographs taken of her infant. If the participant had previously agreed to the photos but now refuses, the source documentation must be clear that she is no longer willing to have the photos taken. If she had previously declined but now agrees, she must be re-consented. Making a note in the source records is not adequate documentation in that case. Finally, if a woman has granted permission on the informed consent but is not keen to have all views taken, please obtain whatever images are allowed and document the participant's restrictions in the Infant Physical Exam CRF, CRF Notes field and chart notes. Should consent not be given to take photos/videos, study staff must provide as detailed a description as possible of the

anomaly in the Infant Physical Exam CRF.

Take photos/video of the congenital anomaly per instructions in the App and SSP Section 6.13.3 below. All photos/videos MUST be taken on study-designated devices. No personal devices of study staff should be used. Assign the photos/video with the infant PID. Any photos/video taken via the app will automatically be deleted form the device, with the only copy stored on the App's secure cloud storage platform.

6.13.3. GBD App Use

The app, for mobile phones and tablet devices, will function in both Android and iPhone operating systems and is available for download in the Android Play Store and Apple App Store. Internet access is needed for downloading and registration of the user, but not operation of the app.

All staff conducting infant surface exams need to be registered users of the app. Study staff may only use the GBD App for recording photos and study data (surveillance version) on a study-designated, institutionally managed device. No personal devices may be used.

Study staff should responsible to document or review congenital anomaly cases should register for an account. The registration code for the study will be provided by the Study Data Manager. Create an account using your institutional email address. Create your own 4-digit PIN; this will be your passcode to log-in to your account.

6.13.3.1. Documentation of the Anomaly

The anomaly will first be documented in the GBD App if the mother is willing to have photos/video taken.

From the home screen of the app, tap the button called BIRTH DEFECTS (Figure 6-6.1). You will be taken to an illustration of a baby (Figure 6-6.2).

Figure 6-6.1

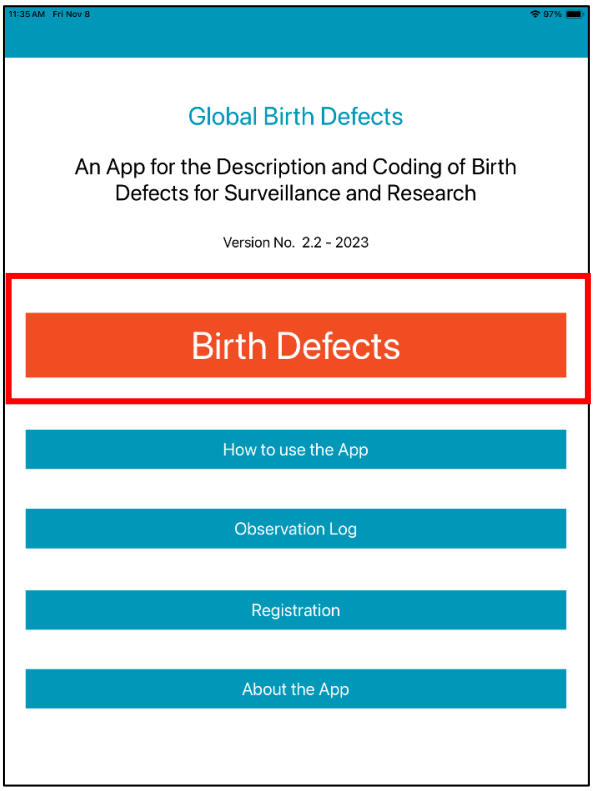


Figure 6-6.2

On this screen, tap the first area of the body with a defect (Figure 6-6.2). Review the images of possible birth defects for that area of the body. When you have identified the image that most closely resembles your finding on the infant surface exam, tap the SELECT button to select that image (Figure 6-6.3). You will be taken to a new page with additional information and resources regarding that finding. You may need to scroll down or across to see all images. The app will prompt you with blue links to additional images so that you can consider alternative diagnoses. You should click on each of these links so that you can review all possible images of alternative diagnoses.

Once you have decided which image most closely resembles your finding, click RECORD BIRTH DEFECT (you may be prompted for additional clinical measurement or descriptive data on that page, which should also be filled in if known) (Figure 6-6.4).

Figure 6-6.3

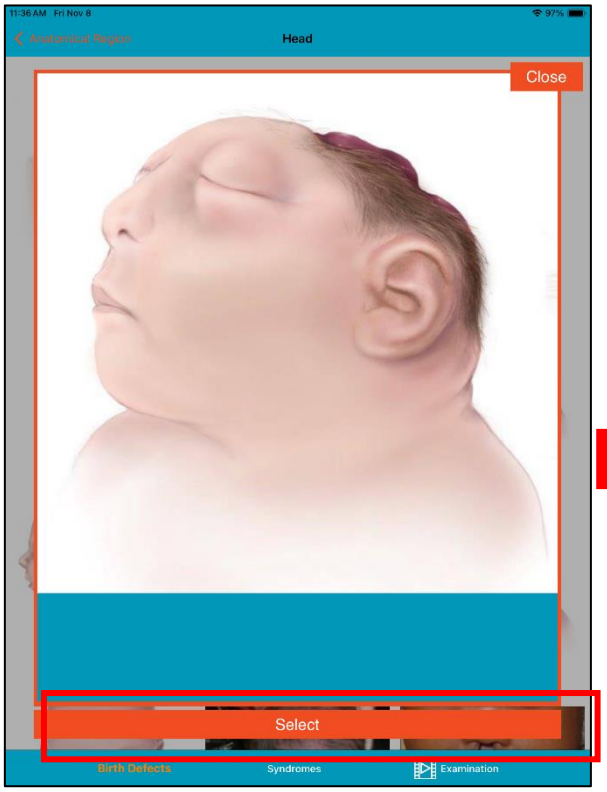
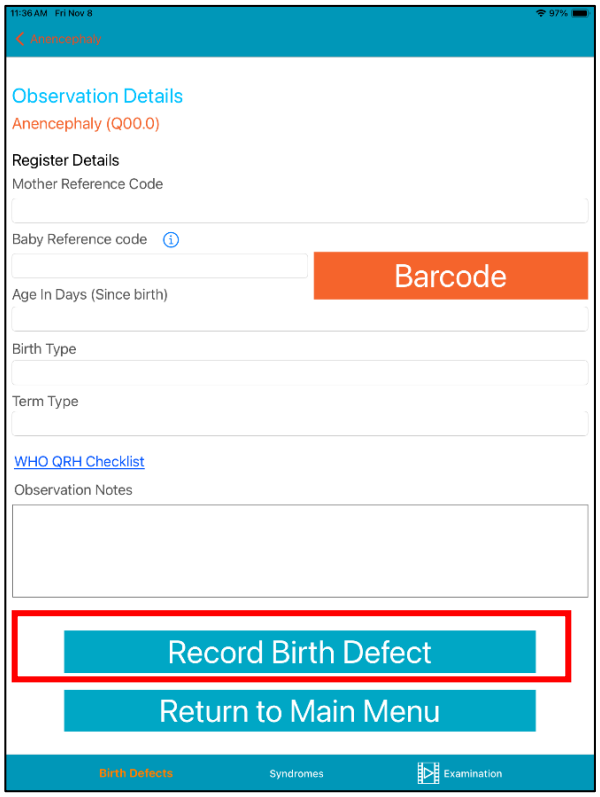


Figure 6-6.4



On the next screen, you will be prompted to input more data regarding the infant (Figure 6-6.5). First, enter the study maternal PID for the Mother reference Code and the study infant PID for the Infant Reference Code. You will be prompted to enter the age in days, the type of birth (livebirth or stillbirth), and whether the infant is preterm or term/post-term. You will also have the option to enter descriptive notes in a Notes section. When done, select RECORD BIRTH DEFECT. Then your observation will be saved and buttons to TAKE PHOTO and TAKE VIDEO will appear. When selecting either button, a prompt will appear to ask if you have appropriate consent to take the photo or video (Figure 6-6.6). Once confirmed, the app will access the device camera for you to take a photo/video through the app.

Figure 6-6.5

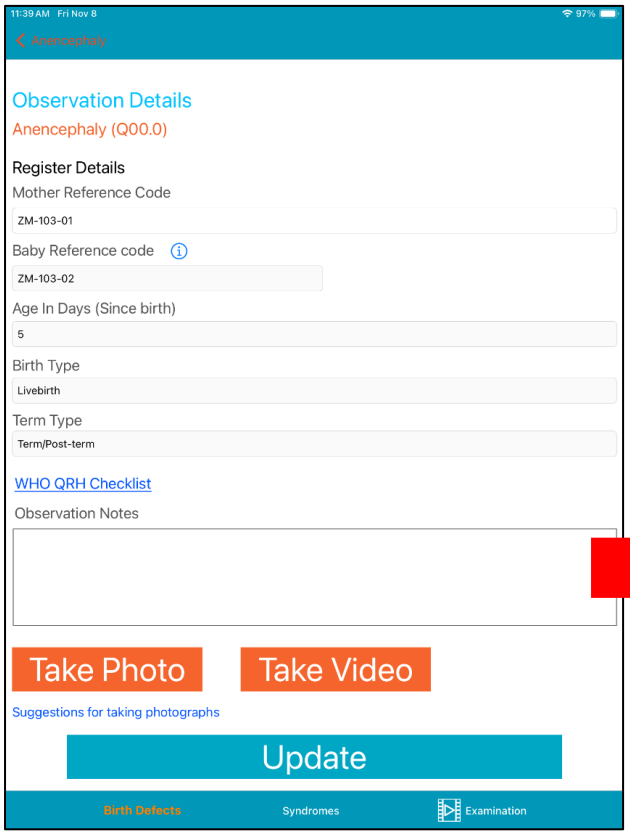
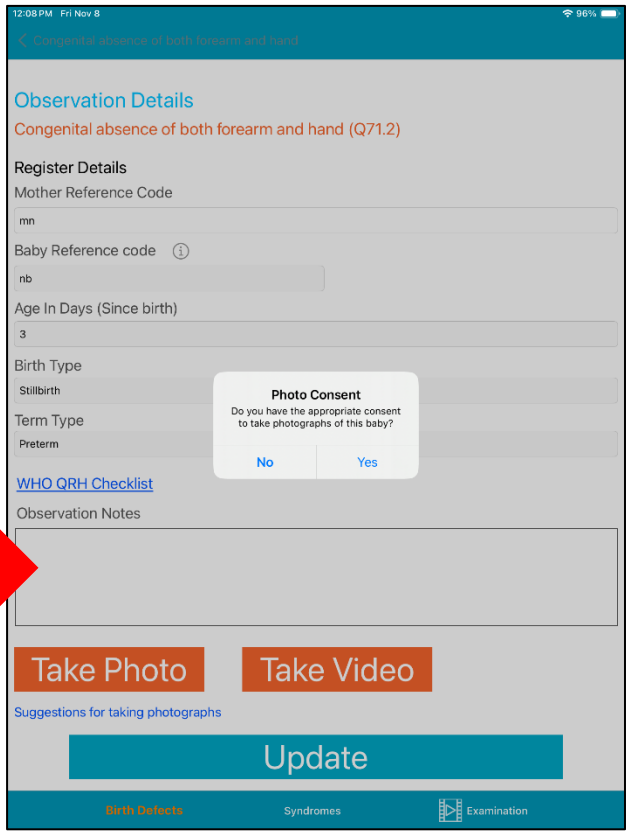


Figure 6-6.6



Repeat this process for each anomaly identified in your examination by tapping RECORD ANOTHER OBSERVATION. This will automatically record the other observations under the same Infant reference Code (PID). If you are instead entering an OBSERVATION for a different infant, select RETURN To MAIN MENU and start the process over.

To view all observations (cases) recorded and upload cases to the server, select the OBSERVATION Log from the home screen (Figure 6-6.7). The cases will be listed by infant reference number, which will be by the Infant PID (Figure 6-6.8). You are able to go into any record from here and update the observation if needed. <u>You must manually upload the recorded observations to the server in order for the SSC to access for the CA Review. To do this push SELECT CASES TO UPLOAD.</u>

Figure 6-6.7

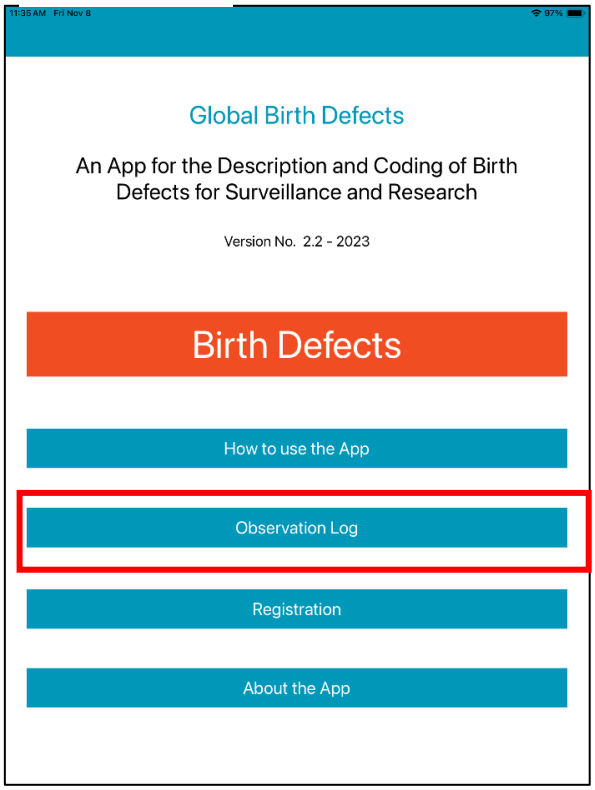
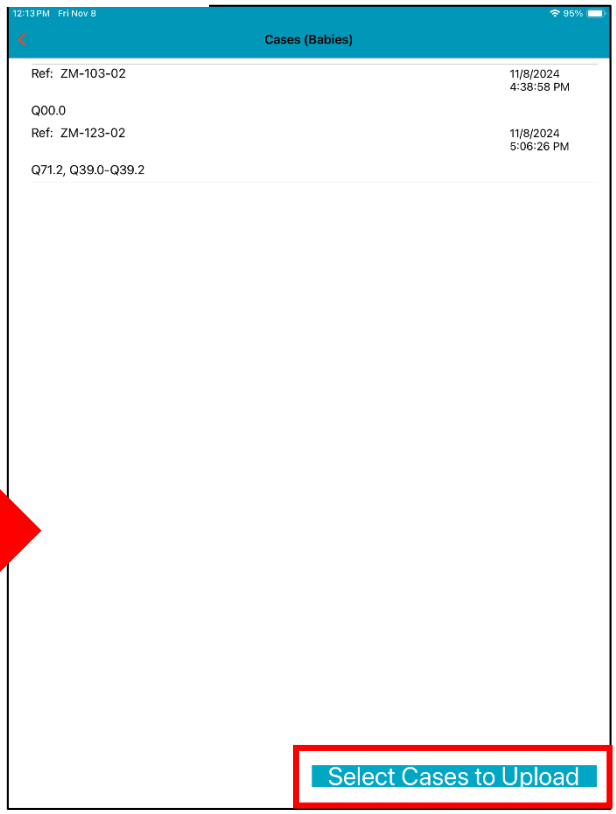


Figure 6-6.~~8~~



If the congenital anomaly is noted during an infant surface exam conducted by study staff, it will also be documented on the **Infant Physical Exam CRF** in addition to the GBD App. Select the body region in the CRF where the CA is located and provide a description in the open text field. Near the end of the CRF, prompts will request if a diagnosis was determined, how certain the diagnosis is and the ICD 10 code. The data recorded in the GBD App and the CRF should match.

Any congenital anomaly identified at birth through a medical record or during a physical exam must be documented on a **Medical Events/Conditions CRF** for the infant. The name of the anomaly per the ICD 10 code should be the brief description of the event. The start date should be the date the congenital anomaly was first identified (either by clinicians or mother noticed since birth or study staff during a study visit). The condition would be ongoing unless there was a medical intervention that resolved the congenital anomaly, in which case the date of the intervention would be the end date.

Lastly, once all the above documentation is completed to the extent possible, study staff should notify the Safety Sub-committee of the congenital anomaly case to initiate the review. See SSP section 6.15 below for guidance.

6.13.3.2. Follow-up and referrals

For participant mothers who have had facility deliveries with a skilled birth attendant, it is anticipated that many infants with congenital anomalies will have had these identified in the delivery room. Referral to specialist care may have already occurred. Confirm with the mother or guardian the following information:

- What she has been told about the baby's diagnosis
- The dates and locations where care has been and is anticipated to be received

- The dates and nature of treatment (if any) that has been and is anticipated to be received

If she has hand carried infant records of specialist care, including results of any imaging, relevant information should be transcribed from those records in the Medical Events/Conditions CRF and chart notes.

In rare cases, the finding may be a new finding. This may be more common among women who did not have a facility birth with a skilled birth attendant and/or among those who have not accessed routine infant care.

If you are uncertain about a finding, document your examination findings in detail and consult the SSC. You should not feel badly about any uncertainty or hesitate to send a query to the SSC. Even expert pediatricians and geneticists sometimes disagree on categorization of a physical examination finding.

Having an infant with a birth defect can be associated with significant stress and stigma for the mother and family. Be prepared to refer the family to psychosocial support if needed, in addition to pediatric specialist care.

6.13.4. Congenital Anomaly Review

Any diagnosed or suspected congenital anomalies identified during the physical exam and/or from medical records will undergo a study-facilitated MATRIX-007 Congenital Anomaly Review. The review is coordinated by the MATRIX-007 Safety Sub-committee and will engage geneticist. The objective of the review is to confirm a suspected congenital anomaly and classify it per the ICD-10, including if it is a major or minor anomaly.

Study staff are responsible to document the congenital anomaly to the extent possible including indicating the type, description of the anomaly, and ICD-10 code (if known) within the Infant Physical Exam CRF and/or Medical Events/Conditions CRF in REDCap, and taking photos/video of the congenital anomaly using the GBD App, if consent was provided.

Upon completing documentation of a congenital anomaly, study staff should alert the Safety Sub-committee (SSC) via a SSC Query Form. See SSP section 6.15 below for information about the SSC.

After email notification is sent, the Study Data Manager will run a report from REDCap with all the relevant data about the case and pull any images uploaded to the GBD App for the case and post a full case report on the CARE PrEP Data SharePoint.

6.13.4.1. Review Process

After the CA case report is available on the CARE PrEP Data SharePoint, the SSC will conduct a preliminary review of the report to assess if the description meets the definition of a possible CA and if the data is complete and clear. This should occur within 2 business days of notification. If the SSC determines the case does not meet CA criteria, study staff will be notified with instructions to correct the condition documentation in REDCap and follow-up with the maternal participant to explain the misclassification. The SSC may also query site staff to seek clarity or additional information before the case undergoes formal review.

Once the SCC determines the case report is ready, the SSC Administrator will initiate the formal Congenital Anomaly Review with the study geneticist, via the case uploaded to the CARE PrEP Data SharePoint. The geneticist will complete a **MATRIX-007 CA Review Form**, where they will

indicate the following: congenital anomaly type/name, ICD10 code, whether major or minor, and certainty of diagnosis. Reviewers will have access to the GBD App for reference. The geneticist will post their completed review to SharePoint within 5 business days of receiving the review request. The SSC will review to confirm agreement with the geneticist's review. If there is disagreement, an ad hoc meeting will be convened to discuss the case and come to consensus. The final Review Form will be shared back to the Country PI, SC and site staff via SharePoint. Site staff are then responsible to transcribe the final report information into the **CA Review CRF** in the infant's record in REDCap.

At subsequent follow-up visits for an infant where a physical exam is done, study staff should continue to indicate the congenital anomaly in the Infant Physical Exam CRF if still present. The CRF Notes can specify that the case has already been reviewed. New photos and notification to the SSC for review is not necessary unless there are new findings. However, any congenital anomaly noted in a participant which was not previously identified at a prior visit should be documented and reported as a new congenital anomaly.

6.14. Clinical Referrals

Study staff are designated to perform study related procedures, not to provide clinical care for participants. However, through the course reviewing records and performing clinical procedures, medical and or psychosocial conditions or events may be suspected or identified that require referral for care and/or support. Study staff should compile plans and lists of referral sources for anticipated concerns that arise that can be immediately actioned during study visits. These details should be include in site SOPs. Site teams are encouraged to socialize referral resources to the CARE PrEP study to build rapport and awareness that will support effective referrals.

Whenever possible, especially for more urgent concerns, study staff should provide warm referrals to care providers or support services. With participant consent, study staff may share clinical findings with care providers to help inform follow-up care.

Examples of clinical situations which mandate urgent, warm referrals include, but are not limited to, maternal severe range blood pressures (>160/110), bradycardic fetal heart tones (<90 bpm), findings of respiratory distress or jaundice in an infant, or signs of dehydration. Generally speaking, site staff should rely on their clinical instincts. If a participant (maternal or infant) appears unwell, referrals should be instituted. Any referrals made should be documented in the study chart. Sites should institute a mechanism whereby they might follow up with the participants to ensure that the referral was taken up. Any attempts to reach the participant in this situation (to check on referral) should be documented in the clinical chart.

6.15. Safety Sub-committee

The MATRIX-007 Safety Sub-committee (SSC) will monitor and advise on safety and clinical aspects of participant management. The SSC has the following responsibilities:

- Review serious adverse events (SAE) and social harms (SH) reported in the study for completeness of documentation and to confirm or provide guidance on the study team's response to the participant. The SSC Administrator is responsible for reporting the event to the FHI 360 PHSC. Country Principal Investigators (PIs) are responsible for reporting to local IRBs/ECs.

- Respond to queries regarding the safety and clinical management of study participants, including questions related to safety events (SAEs and SHs), pregnancy complications, medical conditions and referrals.
- Review routine pregnancy data to identify and assist in addressing any data quality issues or other clinical trends.
- Coordinate Congenital Anomaly Review of suspected congenital anomalies
- Meet routinely (likely monthly) and ad hoc as needed to review summary reports or to address specific safety-related topics/trends.

The SSC is composed of the following members:

- Study Co-Chairs
- CRM and Data Research Associate
- Pregnancy and Breastfeeding (PBF) Technical Lead
- Pediatric Technical Lead

The MATRIX CRM will serve in the role of SSC Administrator to manage SSC operations and be the primary liaison between the SSC, study teams, and FHI PHSC. The SSC will use the email address (matrix007SSC@lists.matrix4prevention.org).

Participant events that require immediate notification to the SSC by study staff include:

- New/updates to SAEs and Social Harms events
- Positive rapid syphilis test or new syphilis diagnosis
- Seroconversion of a study participant during follow-up
- Inferred diagnosis of a pregnancy complication based on a medical record or participant self-report when the diagnosis is not explicitly stated
- Availability of a non-study directed ultrasound report (from ANC services)
- Scheduling of a clinically indicated ultrasound for a suspected pregnancy complication
- Identification of a congenital anomaly in an infant participant

All notifications should be done using an SSC Query Form with email alert of the posted Form to SharePoint ideally within 24 hrs of awareness. See next section for specific guidance. The SCC is also available as a resource for teams to seek input on safety-related questions, as described throughout this SSP.

The SSC will store reports for safety events, pregnancy data, and SSC queries along with any relevant corresponding emails or documentation of key decisions on the CARE PrEP Data SharePoint. Each country will have a designated folder in this section, and access to that folder will be restricted to SCC members and country team staff designated on the DoD Log. More details on coordination and use of the SharePoint folders are included in the SSP section 7.

Quorum for SCC review of a SAE, SH, or SSC query is either one co-Chair, and either the PBF Technical lead or Pediatric Technical Lead, depending on the case. If none of these members are available to review within the required timeframe, then the SCC Administrator may review on their behalf (this should be avoided when possible).

6.15.1. Safety Sub-committee Query

The SSC is available as a resource for answering safety-related questions throughout the duration of the study. For example, teams may have questions about study eligibility, pregnancy complications, syphilis cases, infant medical conditions or reporting/management of SAEs or social

harms. These questions are called SSC queries and should be submitted by using the **Care PrEP SSC Query Form,** available on the MATRIX-007 website. A query form should also be submitted to notify the SSC any of the events noted in section 6.15 above.

Completed SSC query forms should be posted by site/country staff with access to the designated SSC query folder on the CARE PrEP Data SharePoint site, and the SSC should be notified of the query via email. The email notification to the SSC should contain the following:

- **To:** matrix007SSC@lists.matrix4prevention.org
- **Subject:** SSC query for *<brief description of topic such as seroconversion, syphilis diagnosis, or pregnancy complication>* PID XX-XXX, <date of query>
- **CC:** *Include the country PI and SC in the copy line for simultaneous awareness of the event.*
- **Email Narrative** (copy and paste this listing into the body of the email to help ensure that all the required information is included):

  This email is to notify the SSC of a new query posted to the SharePoint site:

  - *Date of query:*
  - *Country:*
  - *Site name:*
  - *PID: [if applicable, list all that apply]*
  - *Brief description of topic (1-3 words)*
  - *Link to form: [link to query form on SharePoint]*

If a response is needed beyond acknowledgment of the notification, the SSC will prepare a consensus response to the query within the original query form on SharePoint and will email the country/site team to notify them of the response once finalized. Intermediary correspondence to assist in preparing the SSC response may occur over email as long as no participant identifying information is included in the emails (reference SSP section 8 regarding definitions of identifying information). All members of the SSC are encouraged to review the information provided by the site in the query and to contribute to the response; however, final determination rests with the protocol chair(s) and/or Technical Leads. This process is expected to occur within three business days. If there is follow-up to an existing SSC query with new information or additional questions for the SSC, a research staff member should update the existing SSC query form, noting the information that is new/updated within the form and the date when the information was added. Notification of updates to SSC queries can be done by "replying all" to the original SSC query notification email.

6.16. Safety reporting

6.16.1. Serious Adverse Events (SAEs)

As CARE PrEP is not a clinical trial, general adverse events will not be captured. Rather, clinically significant medical events will be captured on the **Medical Event/Conditions CRF**. For the purposes of this protocol, a serious adverse event (SAE) is defined by the following two criteria:

1. Adverse medical event that meets at least one of the following seriousness categorizations
   - Results in death
   - Is life-threatening
   - Requires in-patient hospitalization or prolongs an existing hospitalization

- Results in persistent or significant disability/incapacity
- Is Important medical event that may not be immediately life-threatening or result in death or
  hospitalization but may jeopardize the participant or may require intervention to prevent one of the
  outcomes listed above.

2. This adverse event is related or possibly to their CARE PrEP study participation. Note that an adverse event related to PrEP use, a pregnancy complication/outcome or congenital anomaly in an infant participant is NOT a reportable SAEs for this study.

SAE are expected to be extremely rare for this study. An example of an SAE within CARE PrEP might be a participant who becomes lightheaded seeing blood during the HIV test, falls and hits her head and sustains an injury that requires hospitalization, or a participant whose partner becomes physically violent with the participant to the point of hospitalized after finding out about her study participation.

SAEs are documented on a Medical Event/Conditions CRF in the participant's REDCap record with as much data as possible at the time of recognition. Most importantly the CRF must clearly describe the seriousness criteria of the event (see definitions above) and relation to study participation, as well as include event onset date and status at time of reporting (resolution date or ongoing). The question of '*Is the event due to study participation and meets SAE criteria?* marked is '*Yes.*' **The SCC should be notified immediately after the new SAE is reported (entered into REDCap), within 24 hrs of site awareness.** Submit an SSC Query Form per guidance in SSP section 6.15 above. Should new information become available over time, the CRF can be updated but early notification to the SCC and the study team (via CRF completion) is of utmost importance. Site staff are responsible for notifying their individual IRBs.

After email notification is sent, the FHI 360 HQ Data Manager will run the report from REDCap and add a link to the SAE report posted on the CARE PrEP Data SharePoint.

6.16.2. Social Harms

Participants in CARE PrEP may experience social harms (SHs) — non-medical adverse consequences — as a result of their participation in the CARE PrEP study. For example, participants could experience difficulties in their personal relationships with partners, family members, and friends by participating in a research study whether through purposeful or inadvertent disclosure of study participation. SHs related to PrEP use are NOT reportable under CARE PrEP. They could experience stigma or discrimination from family members and members of their community, or retaliation from employers if study visits impact work commitments. While social harms are not explicitly elicited from participants, it is possible that in the course of interacting with the participant, the site staff learn of a social harm. In this instance, study staff should fully document the issues or problems on the **Social Harm CRF** and make every effort to facilitate its resolution. In addition, if local guidance requires, the social harm should be reported to the local IRB. Ongoing social harms should be followed up on until they have resolved, it has been determined that they will not be resolved, or the participant's study participation has ended.

Prior to study initiation, each study site should develop plans for reviewing and recommending responses to SHs in SOPs. Site teams should discuss as a group, and with community representatives as available, what issues and problems are most likely to be encountered by participants at their site and should agree upon how these issues and problems should be handled

logistically. During study implementation, staff teams at each site should continue to discuss actual participant experiences, successful and unsuccessful response strategies, and other lessons learned among themselves and the larger CARE PrEP team. Based on these discussions and lessons learned, procedures for responding to issues and problems should be reassessed and updated as needed throughout the study.

Social harms are documented on a **Social Harms CRF** in the participant's REDCap record with as much data as possible at the time of recognition. Most importantly the CRF must clearly describe the event and relation to CARE PrEP study participation, as well as include event onset date and status at time of reporting (resolution date or ongoing). **The SCC should be notified immediately after the new SH is reported (entered into REDCap), within 24 hrs of site awareness.** Submit an SSC Query Form per guidance in SSP section 6.15 above. Should new information become available over time, the CRF can be updated but early notification to the SCC and the study team (via CRF completion) is of utmost importance. Site staff are responsible for notifying their individual IRBs per policy. All SHs will be reported to FHI PHSC via the MATRIX CRM within 5 days of stie awareness.

After email notification is sent, the FHI 360 HQ Data Manager will run the report from REDCap and add a link to the SH report posted on the CARE PrEP Data SharePoint.

6.16.3. Safeguarding

Safeguarding means preventing harm to people—especially children, youth, and vulnerable adults—during the delivery of humanitarian programs and research studies. This harm includes sexual exploitation and abuse, child abuse, and activities related to human trafficking. CARE PrEP implementing partner institutions are encouraged to have safeguarding policies or plans in place designed to protect study participants, study-associated personnel (e.g., employed at a site facility), and volunteers from any type of harm committed by implementing partner staff or volunteers. Safeguarding also includes protecting study staff from harassment and violence, including sexual harassment and assault. CARE PrEP staff should be trained to identify, report, and support victims per implementing partner policy. Safeguarding policies or plans should be outlined in site SOPs.