9. Clinical Considerations

9.1 Overview of Section 9

This section provides information on the clinical considerations for participants in HPTN 083. The Schedule of Procedures and Evaluations in Appendices IA-ID and II of the protocol indicates when specific clinical, counseling, and questionnaire procedures are required along with relevant laboratory testing. These considerations are presented in Steps 1-3 below.

Safety assessments will be obtained at every visit throughout the study. However, the Investigator of Record or designee should perform any additional symptom-directed examinations at his/her discretion at any time during any visit if s/he determines it to be clinically necessary, particularly if there are any on-going medical or mental health conditions which may require follow-up.

Information pertaining to participant safety monitoring and adverse event reporting procedures are provided in Section 10 of this manual. Information on performing laboratory procedures is described in Section 11 of this manual. Further instructions for the electronic data capture system are provided in Section 13 of this manual.

The HPTN 083 study will begin with the Screening visit, followed by:

- Step 1 – Oral Safety Visits (Week 0/Enrollment, Weeks 2 and 4)
- Step 2 – First injection visit (Week 5), Safety visit (Week 6), Remaining injection visits (Weeks 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 137, 145, 153, 161, 169, 177, 185), All remaining safety visits (Weeks 10, 19, 27, 35, 43, 51, 59, 67, 75, 83, 91, 99, 107, 115, 123, 131, 139, 147, 155, 163, 171, 179, 187)
- Step 3 – Open-label extension (Day 0, Weeks 12, 24, 36, 48)

Any questions regarding the safety assessments and clinical management of participants in HPTN 083 should be directed to the HPTN 083 Clinical Management Committee (083CMC@hptn.org). See Section 9.7 of this SSP for further information about the CMC.

9.2 Participant-Reported Medical History at Baseline (Pre-Existing Conditions) and during Follow up

In order to obtain a complete, accurate, and relevant medical history at screening and enrollment and to assess medical eligibility, it will be necessary to ask the participant about their past medical conditions as well as any conditions the participant is currently experiencing at the time of the Screening and Enrollment visits (i.e., pre-existing conditions).

Information pertaining to the participants' medical history (particularly symptoms, conditions, and diagnoses that affect eligibility or participation in the study) should be obtained. This includes, but is not limited to, a history of hospitalizations, surgeries, allergies, any condition that required prescription or chronic medication (that is, more than 2 weeks in duration), and acute conditions occurring prior to Enrollment (see section 4.7 of the SSP manual for definition of randomization).

The medical history collects a participant's medical information by major body systems, including a participant's drug, tobacco and alcohol use history. The history explores any medical conditions or any medications that are deemed exclusionary for this study. The purpose for obtaining this information during screening/enrollment is to:

- Assess and document participant eligibility to participate in the study.
- Assess and document the participant's baseline medical conditions and symptoms for comparison with signs, symptoms and conditions that may be identified or reported during follow-up.
- Monitor any potential adverse events associated with the use of the study product during the course of the study.

When collecting past medical history from the participant, the clinician should ask probing questions in order to collect the most complete and accurate information possible, especially with regard to severity and frequency. Sites should have a consistent method for documenting this information. In all cases, information obtained at Screening, Enrollment, and all follow-up visits should be documented in the participant's chart and on appropriate e-case report forms.

9.2.1 Pre-existing conditions

Pre-existing Conditions are a subset of a participant's medical history and consist of all ongoing and/or relevant medical conditions, problems, signs, symptoms and abnormal findings that are observed and/or reported prior to enrollment (randomization) into the study. Participants have not yet been exposed to study product at this time, thus, these conditions are not considered AEs. However, new conditions identified during follow-up that were not present at enrollment and pre-existing conditions that increase in severity (grade) or frequency during follow-up, are considered AEs.

NOTE: Any abnormal laboratory value from samples collected at the enrollment visit, but prior to randomization (i.e. baseline sample) are considered pre-existing conditions and should be recorded as such.

All ongoing conditions recorded as pre-existing are to be documented in the source documents and transcribed onto the Pre-existing Conditions e-case report form. This form is to be completed at the Enrollment Visit based on all screening and enrollment source documents. The purpose of recording pre-existing conditions is for comparison with signs, symptoms and conditions that may be identified or reported during follow-up (after initiation of study drug). Therefore, as much information as possible should be recorded about the severity and frequency of any pre-existing condition in source documents as well as in the comments field of the Pre-existing Conditions form to best describe the condition at study entry. This allows for greater objectiveness in noting any grade increase of the pre-existing condition.

All pre-existing conditions noted at screening and on-going at enrollment (prior to the initiation of the oral study product) must be graded even though they are not considered to be adverse events. The purpose of grading a pre-existing condition is because the Pre-

existing Conditions e-case report form serves as the "starting point" from which study clinicians must determine whether abnormal conditions, signs, symptoms, and findings identified during follow-up are adverse events (AEs).

9.2.2 Targeted Medical History for Ascertainment of Eligibility

A participant's medical history must be obtained at screening for ascertainment of eligibility by performing a targeted medical history, based primarily on the inclusion and exclusion criteria listed in the protocol (Sections 3.1 and 3.2 of the protocol). Additional items should be noted during the targeted medical history:

- A bleeding history should be obtained to assess whether the participant will be suitable for the injections given during the study. A bleeding history should include, but is not limited to, assessment of easy bruisability, prolonged or abnormal bleeding of the gums, epistaxis, rectal or upper gastrointestinal bleeding, and genetic predispositions to bleeding. Participants should also be asked about any medications which are used to thin the blood or have anticoagulant properties (including aspirin at doses greater than 325 mg per day). It should be noted that a history of the above or use of regular or low dose ASA is not necessarily exclusionary, but should prompt further evaluation as to the safety/advisability of administering large-volume intramuscular injections. The CMC should be consulted prior to enrollment if any of the above is present. Note that anticoagulant medications may not be administered within 7 days prior to or 7 days after a CAB LA injection, and as such, such medications should not be considered obligatory for the health of a participant.

- Signs and symptoms of acute HIV infection should be assessed. These symptoms may include:

    - Fever
    - Fatigue
    - Headache
    - Myalgia
    - Weight loss
    - Pharyngitis or sore throat
    - Lymphadenopathy,
    - Rash
    - Diarrhea
    - Oral or genital ulcers

  Site staff should assess the possible causes of these symptoms, length of time the participant has been experiencing these symptoms, and severity grade. Participants are required to be HIV RNA negative based on a sample collected 14 days prior to enrollment. If a constellation of symptoms suggestive of acute HIV infection (per the judgment of the IoR or designee) is present at the Enrollment visit (at Enrollment, prior to randomization; and for sites that do split enrollment visits due to physical location constraints, prior to administration of study product), enrollment (or dispensation of study product if applicable) will not be allowed. Participants with symptoms concerning for acute HIV infection may be re-screened

in consultation with the CMC once appropriate testing has ruled out acute HIV infection Consult with the CMC if further guidance is needed.

- Otherwise eligible participants with an exclusionary test result (other than reactive HIV tests and Hepatitis testing (HBsAg and HCVAb)) can be re-tested once during the screening process. If a participant is re-tested and a non-exclusionary result is documented within 45 days of specimen collection, the participant may continue with enrollment. If after re-testing the laboratory test results continues to be exclusionary, participant screen fails. At the discretion of the IoR or designee, an additional screening attempt may be done (see Section 4.6.3 of this manual and Section 5.1 of the Protocol for further information).

- Participants with clinically significant cardiovascular disease (as per Section 3.2 of the protocol) cannot enroll and cannot be re-screened for the study.

- In order to implement the QTc exclusion criteria, sites should use primarily the QTc provided in automated fashion by the ECG machine. If this value is >500 msec using either Bazlett (QTcB) or Federica (QTcF) calculation, the potential participant should be excluded from enrollment. It is acceptable to repeat the ECG once in the context of a single screening cycle. If the QTc is not calculated by the ECG machine, the QTc should be manually calculated (http://www.thecalculator.co/health/QTc-Calculator-385.html). Staff should note that the same formula (QTcB or QTcF) be used for a given participant for all ECGs throughout the study.

9.2.3 Complete Medical History at Enrollment

A complete medical history must be obtained at Enrollment; this may be obtained during Screening at the discretion of the Investigator of Record or their designee (as indicated in Section 5.2 of the protocol). If the complete history is obtained during Screening, then only an update (as appropriate) is needed to complete the history at Enrollment. If new signs/conditions are identified at Enrollment (prior to randomization), these newly identified conditions should be documented on the Pre-existing Conditions e-form as needed.

Guidelines for collecting the complete baseline medical history include:

- Probe for history of conditions by body system.
- Document symptoms, illnesses, allergies, hospitalizations, and surgeries.
- Document both acute and chronic conditions, and both ongoing and resolved conditions.
- Document whether each condition is currently ongoing; conditions ongoing at the time of enrollment/randomization are entered on to the Pre-existing Conditions e-case report form. For ongoing recurrent conditions that are expected to be experienced during follow-up (e.g., headaches), the condition need not be present on the day of enrollment to be considered ongoing at the time of enrollment, and

should be entered on to the Pre-Existing Conditions e-case report form, including the date of resolution of the most recent episode if it resolves prior to enrollment.

- For all ongoing conditions, assess and record the current severity of the condition per the DAIDS Toxicity Table. See Section 10 of this SSP for further clarifications and guidelines regarding severity grading.

9.2.4 Targeted Medical History at Follow-Up Visits

At scheduled follow-up visits, collection of interval medical history should be obtained to:

- determine whether previously reported and/or documented conditions are ongoing or have changed with regard to severity or frequency
- determine whether newly-identified symptoms, illnesses, or condition have occurred since the last medical history was performed

Note: For purposes of this study, "newly-identified" is defined as a condition that:

- was not present at baseline
- was present at baseline (ongoing at enrollment) and has now increased in severity grade or frequency or has resolved after enrollment and prior to the current report;
- has already been reported as an adverse event but it has increased in severity grade/frequency

At the participant's first follow-up visit, retrieve their complete medical history source document and look up the Pre-existing Conditions form for reference. At each subsequent visit, retrieve the participant's most recent follow-up medical history source document for reference.

At each follow-up visit, begin the follow-up medical history by reviewing with the participant and eliciting updates (resolution, outcome date, severity grade, etc.) on those symptoms/conditions that were documented as ongoing since the participant's last visit. Site clinicians should then probe and evaluate for any new onset conditions/symptoms since the participant's last visit. Clinicians should use their clinical experience and judgment to elicit complete and accurate medical history information from participants.

- New onset conditions/symptoms that began since the last visit may require completion of an AE Log e-CRF. This includes any reoccurrences of conditions/symptoms that were previously reported and had resolved at a prior visit, documentation should include the current severity grade.
- Ongoing conditions that have increased in severity grade or frequency should be recorded as new events.
- Ongoing conditions that have not changed in severity or frequency, or have improved but not yet resolved, do not warrant any changes to the AE Log e-CRF.

- Ongoing conditions that have resolved since the last visit should have their entries updated with an "Outcome Date".
- In the case of study staff assessment of psychological distress (defined clinically, or outside of the scope of what study staff is comfortable handling), within or outside of the context of the study-related assessments, sites should refer such participants to locally available support or acute care services. A compendium of such services including but not limited to: Acute and chronic (longitudinal) mental health support, substance abuse treatment, intimate partner violence services, and primary care. The compendium should be available to all study staff who have study participant contact. While study-related assessments are not formally "scored" for the purposes of data collection or CRF reporting, study staff may use the instruments at their discretion to help triage the decision to provide a support or treatment referral. As an example, a CESD-10 score (see Table 9-2 below, also found at: http://www.actonmedical.com/documents/cesd_short.pdf) of 10 or greater might be considered a sufficient, but not a necessary result to initiate a referral to mental health services for a diagnosis of depression. Where clinical standards of care for such referrals exist, such standards should be followed additionally.
- If a participant reports issues swallowing the Truvada/ placebo tablets due to its size, they may split the tablet in half and then swallow immediately. Although a pill cutter is preferred, it's not required for pill-splitting. The Truvada/placebo should not be chewed, ground, or otherwise dissolved.

If during follow-up a condition is identified as being present at baseline and the participant inadvertently did not report it as part of the baseline medical history, the clinician should add the information to the Pre-existing Conditions documentation. A chart note should also be documented to explain why the information is recorded retrospectively.

For all abnormal conditions or symptoms identified during follow-up, the severity grade of the condition or symptom must be documented, as must onset and resolution dates, when applicable.

9.3 Physical Exams

A targeted physical examination is required at Screening and all follow-up visits, starting at Week 2. At the Enrollment (Step 1, Week 0) visit, a complete physical exam is required (and may be performed at screening, see Section 9.3.2. below). A physical exam may be conducted at the discretion of the Investigator of Record or designee during an interim visit in response to clinically indicated and/or reported symptoms.

9.3.1 Targeted Physical Exam for Ascertainment of Eligibility

As with targeted history, a targeted physical exam is performed at screening for ascertainment of eligibility, based primarily on the inclusion and exclusion criteria listed in the protocol (see Sections 3.1 and 3.2 of the HPTN 083 protocol).

9.3.2 Complete Physical Exam at Enrollment (or Screening)

A complete physical exam is required at the Enrollment visit. This exam may be performed at Screening per discretion of the Investigator of Record or designee. A full physical will include the following:

- Height (this is a one-time measurement at Screening or Enrollment)
- Weight (see instructions in Section 9.3.4 below)
- Vital signs (temperature, blood pressure, pulse)

And examination of the following body systems/components:

- HEENT (head, eyes, ears, nose and throat)
- Neck
- Lymph nodes
- Cardiovascular (including performing an ECG)
- Pulmonary
- Abdomen
- External genital exam (if clinically relevant)
- Skin
- Neurological
- Extremities
- Mental status

Any abnormal findings should be documented on the Pre-existing Conditions e-CRF. It is important to grade these pre-existing conditions in the source document so that adverse events (AEs) can be reported if the severity of the conditions increases.

Body mass index (BMI) must be calculated using the weight and height measurements obtained during the complete physical exam at baseline. The reason for this is to determine the appropriate needle size to be used for the injections. A 25, 23 or 21 gauge needle is acceptable; however, other size gauges may be used. A 1.0 or 1.5-inch needle is recommended for BMI $\leq$ 30 and 2-inch needle is recommended for BMI > 30; the choice should be made based on best judgment of the site staff as the needle length required to deliver the injection intramuscularly, as opposed to subcutaneously. Refer to this link for a BMI calculator:
http://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/english_bmi_calculator/bmi_calculator.html

The BMI should be documented in the participant chart.

9.3.3 Targeted Physical Exam at Follow-Up Visits

Targeted physical exams are performed at each follow-up visit (or at Enrollment if a complete physical exam was performed at Screening). These exams are driven by the signs and symptoms that the participant reports since the previous visit (or initially reported at Enrollment). Regardless, at a minimum, the participant must be weighed (see

instructions in Section 9.3.4 below) and vital signs recorded at each visit (temperature, blood pressure, pulse).

As safety is one of the objectives of this study, the goal at each visit is for the clinician to be assured that through the targeted physical exam and any ensuing conversation (history) that the participant is healthy enough to continue in the study and on the study drugs. Minimally, collecting vital signs at the follow-up visits gives the clinician a rudimentary idea of the participant's health state that may be overlooked by conversation (history) alone.

9.3.4 Instructions for Weight Collection

Collecting participants' weight is required as part of all physical exam (complete and targeted physical exams). To ensure consistency and accuracy in weight measurements, any time weight is collected, sites should follow the steps below:

- Measurements should be made at the same time of day each time, *if possible*.
- Participant should remove shoes, sweaters, coats, scarves, etc. prior to weighing.
- Participants should be asked to void (urinate/empty bladder) before weight is measured.
- Whenever possible, weight should not be measured during bouts of severe diarrhea or other obvious disturbances of hydration status.
- Participants should not engage in strenuous exercise for 8 hours preceding the measurements because of its potential effect on hydration status. If the participant reports that he/she did engage in strenuous exercise for 8 or more hours preceding the measurement, weight measurement should be performed anyway and document on participant's record.
- The same scale should be used for all measurements performed for this protocol to the extent possible. The scale should be calibrated at minimum annually.
- Before the participant is weighed, make certain that the scale is in balance if it is a beam-balance scale or reads zero if it is an electronic scale.
- Instruct the participant to stand with both feet centered on the scale with arms at the sides. The participant should not move or hold onto anything during the measurement.
- Allow the scale to stabilize and record the weight in the units shown on the scale (lbs or kg).

Weight data will be entered into an eCRF at:

- Step 1: Enrollment (Day 0), Weeks 2 and 4
- Step 2: All injection visits (Weeks 5, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 137, 145, 153)
- Step 3: All visits (Day 0, Weeks 12, 24, 36, 48)
- Annual Visits

9.3.5 Additional Considerations for Complete and Targeted Medical History and Physical Exams

The following additional assessments will be made throughout the study as part of the complete and targeted medical history and physical exams:

9.3.5.1 Adverse events

All abnormal findings (i.e., Grade 1 and higher) are to be graded and recorded in the participant's source documentation. AE Grade 1 or higher clinical, as well as Grade 2 and higher laboratory AEs, and any AE (clinical or laboratory) that leads to a study product hold (temporary or permanent) will be captured on the electronic Adverse Experience (AE) Log. Please note, if a laboratory result cannot be graded per the DAIDS toxicity table, it will not be reported as an AE. For example, the DAIDS toxicity table does not provide grading for non-fasting lipid profile; thus, these results will not be graded or reported as an AE. Therefore, it is important to counsel participants prior to visits requiring lipid profile testing (Weeks 57 and 105) to come to the visit fasting. Prior to initiation of these visits, confirm with participants when was the last time they had anything to eat or drink. To ensure participant's comfort, prioritize participants who are fasting so testing is done as quickly as possible and if possible provide a snack to the participant after blood is collected (or ask participants to bring something to eat to the visit). If a participant is not fasting when she/he presents to the clinic, do not collect blood for lipid profile, rather, reschedule the participant to return to the clinic as soon as possible to collect the sample.

See Section 10 of the SSP for more details regarding the reporting of AEs, as well as the HPTN 083 protocol Section 6.

9.3.5.2 Electrocardiogram assessment

An electrocardiogram (ECG) will be done at Screening (for eligibility purposes), Weeks 57, 105, and 153. The ECGs must be read by a clinician (not required to be read by a physician or cardiologist). Any abnormal findings for which the clinician is unsure of how to interpret will prompt a query to the CMC, particularly at Screening for additional input on whether the participant meets the eligibility criteria based on the ECG findings.

Of note, Appendix III of the protocol (Toxicity Management) provides guidance for QTc criteria for permanent discontinuation of study product, which instructs the sites in the event of a prolonged QT interval to obtain two more ECGs within one hour, and then use the averaged QTc values of the three ECGs to determine whether the participant should permanently discontinue study product. In such cases, the averaged value of the three QTc values should be recorded on the ECG e-CRF.

9.3.5.3 Neurologic Symptoms

As part of the clinical Review of Systems, specific attention should be paid to assessments of neurologic symptoms in order to monitor any potential central nervous

system side effects. Specific symptoms to be probed include whether the participant has experienced: seizure, trouble sleeping, vivid/strange dreams, dizziness, problems concentrating, feeling lightheaded, tremor, headache, change in vision, weakness, numbness, tingling, fainting, and urine or stool incontinence. Any neurologic symptoms should be documented on site-specific source documents (e.g. chart notes), and on the appropriate AE (or SAE) eCRF as outline in Section 6 of the protocol. Based on clinician's assessment, any symptoms of concern should be notified to the CMC.

9.3.5.4 Injection site reaction (ISR) assessment

ISRs are captured on the Injection Site Reaction Evaluation e-CRF one-week post-injection, at Weeks 6, and 10, and thereafter 2 weeks after each injection (Weeks 19, 27, 35, 43, 51, 59, 67, 75, 83, 91, 99, 107, 115, 123, 131, 139, 147). ISR examinations will include an assessment of pain, tenderness, pruritis, warmth, purulence, rash, erythema, swelling, induration, and nodules (granulomas or cysts). Participants should be instructed that ISR discomfort can be managed symptomatically (e.g., cold/warm compress, acetaminophen, ibuprofen) as necessary. Per the HPTN 083 Protocol, Toxicity Management Appendix III, the CMC must be notified of all Grade 3 and higher ISRs to determine etiology and assess appropriate continued study participation. Any questions regarding assessment of ISRs should be directed to the CMC.

It is important to distinguish between signs and symptoms from the injection process itself versus an ISR. Although these definitions are somewhat arbitrary, for protocol consistency, sites should follow the following definitions: An ISR typically begins 24-48 hours after an injection. However, if for example a participant experiences pain or discomfort from the actual procedure of giving an injection, e.g., the insertion of the needle beginning at time of, during or immediately after the procedure, this is, for purposes of reporting, considered associated with the injection procedure and is <u>not</u> considered an ISR. If a participant reports that on the day after the injection or later, he/she experience symptoms (e.g., pain, redness, swelling, etc.) at the injection site, this would be an ISR. If an ISR is reported, use the Injection Site Reaction eCRF, using the "Site Reactions to Injections and Infusions" category for grading as found in the DAIDS Table for Grading the Severity of Adult and Pediatric Events, Corrected Version 2.1. If a participant experiences immediate pain or discomfort or other immediate signs and symptoms as a result of the procedure of giving an injection, it may be reported as an AE on the AE log eCRF using the category "Estimating Severity Grade for Parameters Not Identified in the Grading Table" for grading. Participants should be instructed to contact the site regarding any injection site reactions of concern to either the participant or the site staff (and they may take a picture if they wish, and email it to the site). See the last bullet in Section 9.5 of the SSP (below) for instructions to the participant upon leaving the clinic following an injection.

Sites should document all interventions that have been attempted to mitigate injection site reactions, which should include at a minimum:

- Pre-treatment (prior to injection administration) warm compresses
- Topical or oral pre-treatment with NSAID preparations, unless contraindicated

- Immediate post-injection massage to injection location
- Post-treatment warm or cold compresses
- Post-treatment NSAID or other analgesic preparations, topically or orally

Such interventions and their outcome should be documented in the source documents and the CMC consulted prior to discontinuation of Step 2 follow-up. A proactive and comprehensive approach to mitigating ISRs should be undertaken, with premature transition from Step 2 to Step 3 being reserved for refractory cases in extreme circumstances.

Note: Participants who wish to prematurely discontinue injections in Step 2 due to an injection site reaction AE must follow the procedures detailed above and in Appendix III, Guidance for Injection Site Reactions (ISRs) prior to discontinuation of Step 2 procedures.

9.3.5.5 Exercise assessment

Obtain information related to physical activity or exercise preceding the safety CPK evaluation to better assess test results. Exercise-related questions will be captured on the Post-Injection Exercise CRF at visits with required chemistry panels. This information is intended to be a particular area of emphasis to be captured during the targeted medical history and exam.

9.4 Concomitant medications

Sites should document in the participant chart all medications/preparations (prescription and non-prescription) including alternative/complementary medications/preparations (e.g., herbs, vitamins), and any hormones (e.g., cross-sex hormone therapy) taken by study participants within 30 days prior to enrollment and anytime thereafter during study participation.

Per Section 4.5 of the HPTN 083 protocol, alcohol and recreational and street drug use reported by a participant during the study will by recorded in the participant's study chart only (and not captured on the concomitant medication e-log). Tobacco use and medical marijuana use also should be included in the participant's study chart only. Charts notes for these items should include the specific substances used and dates and frequency of use.

It is helpful to ascertain the baseline medication information in the context of the baseline medical history. Participants should be asked open-ended questions to elicit participant report of current medications, and use the information obtained in the medical history to probe for additional medications that the participant may otherwise forget to report. For example, if the participant reports headaches as part of their medical history, but does not spontaneously list any medications taken for headaches, ask what medications they take for headaches. Similarly, if a participant reports taking a medication for a condition that they inadvertently did not report when providing medical history information, add the condition to the baseline medical history source document.

At each follow-up clinic visit, retrieve the participant's previously completed Concomitant Medications Log form, record any new medications provided to the participant by study staff, and actively ask the participant whether they are still taking all previously-recorded medications, at the same dose and frequency. Also, actively ask whether the participant has taken any new medications since the last medical history was taken. To further probe for updates, if the participant reports any intercurrent illnesses, symptoms, etc. since their last medical history, ask whether they took any medications for those. Add all new information to the Concomitant Medications e-Log. If a participant reports taking a new medication for a condition that they inadvertently did not report when providing follow-up medical history information, add the condition to their follow-up medical history source document. To help ensure accurate reporting of concomitant medications information, participants should be encouraged to bring all medications to all study visits.

Note: It is preferable to list the generic name of a concomitant medication on the Concomitant Medications e-Log; however, listing the trade/brand name is acceptable.

9.4.1 Precautionary and Prohibited Medications

In order to avoid adverse events caused by drug interactions, whenever a concomitant medication is taken, site staff should review the concomitant medication's and study product's most recent package insert (PI - for Truvada®) and investigator's brochure (IB - for cabotegravir) to obtain the most current information on drug interactions and contraindications. Concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study.

After Enrollment, for any drug listed in the Truvada PI or cabotegravir IB, it is required that the HPTN 083 CMC be notified for recommendations for continuing or stopping (or holding) study product.

Experimental agents not otherwise specified in the SSP Manual may not be administered. Precautionary and prohibited medications include:

<u>Cabotegravir:</u>

- Not to be administered concurrently:
  - Cytotoxic chemotherapy or radiation therapy
  - Systemically administered immunomodulators
    - NOTE: Stable physiologic glucocorticoid doses (defined as prednisone ≤15 mg/day or equivalent as a stable or tapering dose) are not prohibited. Use of corticosteroids for an acute condition such as asthma exacerbation, or receiving a short course (defined as ≤2 weeks of pharmacologic glucocorticoid therapy) is also not prohibited
  - barbiturates
  - carbamazepine
  - oxcarbazepine
  - phenytoin

- pheonobarbital
- rifabutin
- rifampin
- rifapentine
- St. John's wort

- Prohibited within 7 days before and 7 days after an injection
  - high dose aspirin (>325 mg per day)
  - anagrelide
  - apixaban
  - argatroban
  - bivalirudin
  - clopidogrel
  - dabigatran
  - dalteparin
  - enoxaparin
  - fondaparinux
  - heparin
  - lepirudin
  - prasugrel
  - rivaroxaban
  - ticagrelor
  - ticlopidine
  - warfarin
- Oral formulation precautions
  - Antacid products containing divalent cations (e.g., aluminum, calcium, and magnesium) must be taken at least 2 hours before or at least 4-6 hours after the oral CAB administration

Truvada:

- Medications containing the following ingredients should not be administered concurrently:
  - emtricitabine or tenofovir disoproxil fumarate (e.g. ATRIPLA®, COMPLERA®, EMTRIVA, GENVOYA®, ODEFSEY®, STRIBILD®, or VIREAD, Descovy).
  - lamivudine (e.g. Combivir, Dutrebis, Epivir, Epivir-HBV, Epivir A/F, Epzicom, Triumeq, or Trizivir)
  - adefovir (e.g. HEPSERA®)
  - tenofovir alafenamide (e.g. Vemlidy)
  - didanosine (e.g. Videx EC)
  - atazanavir (e.g. Reyataz, Evotaz (atazanari/cobicistat))
  - ledipasvir/sofosbuvir (e.g. HARVONI®)

- darunavir (e.g. Prezista)
- lopinavir/ritonavir (e.g. Kaletra)
- orlistat (e.g. Alli, Xenical)

Please note the following general notes related to precautionary and prohibited medications:

- Medications containing these ingredients and brand names may vary per county. Always verify ingredients of concomitant medications to avoid use of prohibited medications.
- It is acknowledged that the listing of prohibited and precautionary medications for Truvada® can be confusing since there is no distinction between prohibited and precautionary medications; however, this listing is consistent with the Truvada® package insert and should not be altered.

Intralipid 20% fat emulsion: There are no precautionary/prohibited medications in the current package insert for Intralipid 20% fat emulsion.

Additional information regarding recommended, prohibited, and precautionary concomitant medications can be found in the cabotegravir IB and the Truvada® PI.

9.4.2 Considerations for Co-administration of Precautionary and Prohibited Medications

- Co-administration of precautionary and prohibited medications should be clinically monitored by site clinician, as per considerations below:
  - Drugs that are eliminated by active tubular secretion (e.g. acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose (please refer to Table 9-1 below) or multiple NSAIDS), as these may increase concentrations of emtricitabine, tenofovir, and/or the co-administered drug.
    - Please report to the CMC if a participant takes a total daily dose of NSAIDS that meets or exceeds high dose, as designated in the Table 9-1 below, for MORE than 72 consecutive hours.
    - Acyclovir and valacyclovir may be used when indicated. If needed for treatment – sites do NOT need CMC permission for the use of these products, but sites should counsel the participant to increase hydration to avoid additive nephrotoxicity; no additional laboratory monitoring is required per protocol.
  - Drugs that decrease renal function (e.g., cause nephrotoxicity) as these may increase concentrations of emtricitabine and/or tenofovir.

Table 9-1: Comparable NSAID Dose Levels*

Nonselective NSAIDs	Low Dose	Medium Dose	High or Max Dose
Diclofenac potassium	50mg bid	50mg tid	50mg qid (in OA/RA only)
Diclofenac sodium	50mg bid	75mg bid	50mg qid or 100mg SR bid (in RA only)
Fenoprofen	200-300mg qid	600mg tid-qid	800mg qid
Flurbiprofen	50mg bid	50mg tid-qid	100mg tid
Ibuprofen	400mg tid	600mg tid-qid	800mg qid
Ketoprofen	25–50mg tid	75mg tid	IR =300mg/day (divide), SR =200mg/day
Naproxen	250mg tid	500mg bid	1250mg/day (divided)
Naproxen sodium	275mg tid	550mg bid	1375mg/day (divided)
Oxaprozin	600mg qd	1,200mg qd	1,200mg qd
Sulindac	150mg bid	200mg bid	200g bid
Piroxicam	10mg qd	20mg qd	40mg per day (not indicated for OA or RA)
Partially-selective NSAIDs	**Low Dose**	**Medium Dose**	**High or Max Dose**
Etodolac	200mg tid	400mg bid	1,200mg max (IR or SR divided doses)
Meloxicam/Mobic	7.5mg qd	7.5mg qd	15mg qd
Nabumetone	1,000mg qd	1,000mg bid	2,000mg/day (qd or divided bid)
Cox-2 inhibitors	**Low Dose**	**Medium Dose**	**High or Max Dose**
Celecoxib/Celebrex	200mg qd	200mg bid	200mg bid

COX = cyclo-oxygenase; IR = immediate release; NSAID = nonsteroidal antiinflammatory drug; OA = osteoarthritis; RA = rheumatoid arthritis; SR = sustained release
*This table does not represent exact or equivalent dosing conversions. It is based on U.S. Food and Drug Administration approved dosing ranges and comparative doses from clinical trials.
Source: www.ashp.org/emplibrary/NSAIDsConversiontools.pdf

- Consult the CMC for instructions when a participant or provider decides it is in the participant's best interest to initiate PEP.
- Non-study provided TDF/FTC or TAF/FTC for PrEP is not permitted during any portion of HPTN 083. Exceptions to this include use of non-study provided PrEP per primary care physician discretion during annual follow-up (when participants are off study-provided product per protocol) and during Step 3 *in circumstances in which a participant is not on study-provided open label TDF/FTC per protocol* (e.g., in the case of an AE).
- If use of a prohibited medication is needed for treatment of a condition (including but not limited to TB or LTBI), blinded study products should be held. During the blinded study product hold, participants will be offered study-provided open label TDF/FTC. The participant may return to blinded study product once use of prohibited medication is no longer needed. Visit schedule depends on which step the participant is in when blinded study product hold is required due to prohibited medication use:
    - Step 1: Consult the CMC for the follow-up visit schedule and considerations for returning to blinded study product.
    - Step 2: Follow the protocol-required Schedule of Evaluations and Procedures and visit schedule **with the exception of provision of blinded study product**. At the discretion of the Investigator of Record, the "safety" visit following what would typically be the "injection" visit may be skipped in

these circumstances until resumption of blinded study product occurs, at which point safety visits should resume per the Schedule of Evaluations and Procedures. The SDMC will provide instructions for coding of these visits.

NOTE: These requirements also apply to any participant who stopped blinded study product prior to all relevant national and local approvals of Version 3.0 of the protocol.

Sites should contact the CMC for clinical guidance on implementation of this blinded study product hold, concurrence on the appropriateness of planned resumption of blinded study products upon prohibited medication completion, and resumption of blinded study products when/if appropriate.

9.5 Injection Instructions

As outlined in the SSP Section 8 – Study Product Considerations, injections must be administered within **two hours of study product preparation by the site pharmacy**. Therefore, coordination with the site pharmacy is important when scheduling and setting up the flow of these visits.

The following links provide instructional videos for administering IM injections in the gluteal muscle.

Links with instructions for the ventrogluteal location can be found at the HPTN 083 webpage: https://www.hptn.org/research/studies/hptn083. To access the videos, please use the password HPTN.

This link provides instructions for the dorsogluteal location: https://www.youtube.com/watch?v=yM5BVjh8THU. These videos are provided as examples only. Sites should use their clinical judgement and be guided by participant preference regarding which approach to use for injections.

Specific instructions for the injections are as follows:

- Participants should be instructed not to take their oral study product on the day of their Week 5 study visit. However, if a participant takes study product on the day of Week 5 visit, DO NOT defer injection and document on participant's file.
- Prior to administering the injection, and as part of the targeted physical exam, assess if participant has had a buttock implant or fillers since previous visit. If implant/filler is present, do not administer injection. Inform the CMC and follow guidance in Section 5.3.1 of this manual for follow-up schedule.
- Ensure appropriate supplies are on hand: alcohol wipes, gloves, and a filled syringe with the appropriate gauge and inch needle.
- An appropriate needle size (per BMI, as outlined above) should be used for each intramuscular (IM) injection. The needle should be long enough to reach the muscle mass and ensure an IM injection, but not so long as to involve underlying nerves, blood vessels, or bones. Longer needle lengths may be necessary for participants

with higher body mass indexes (BMI > 30), to ensure that injections are administered intramuscularly as opposed to subcutaneously. The clinical staff should consult with the pharmacy staff regarding each participant and the appropriate needle length that should be used.

NOTE: BMI may be recalculated during follow-up, at clinician's discretion, if participant experience substantial weight change that could impact needle size.

- Wash hands.
- Use alcohol to clean the area of the body to be injected.
- Use discretion as to where in the gluteus muscle each injection is given according to individual participant circumstance. If possible, injections should be spaced approximately 2 cm from one another, from the site of any previous injection or any injection site reaction.
- Hold the muscle of the injection site firmly between your thumb and fingers of one hand.
- With the other hand, hold the needle and syringe like a pencil. Using a quick dart-like motion, insert the needle at a 90-degree angle through the skin and into the muscle.
- Release your hold on the skin and muscle.
- Pull back slightly on the plunger to see if blood is present. If there is blood, remove the needle and syringe and start over with a new needle and syringe. If a new needle and syringe is needed, please discard the contaminated needle and syringe and request new participant's study product from pharmacy. If there is no blood, inject the medicine.

  NOTE: In the rare case the needle malfunctions, such that the full amount of the study product is not administered, remove the needle from the end of the syringe, place a new needle, and continue the injection with the same study product.
- Push the plunger slowly down to inject the medicine into the muscle.
- Take the needle out.
- Apply pressure at the injection site and gently rub the site.
- Apply a bandage if needed.
- Discard the used needle and syringe properly.
- Check for any immediate injection site or other adverse reactions. There is no need to keep a participant in the clinic under observation after an injection.
- Instruct participants regarding how to manage any ISR at home, including:
  - If possible and if disclosure about participating in this study is not an issue, have someone look at the injection site if they cannot see/access it.
  - Note color, tenderness, any drainage. A picture should be taken if possible.
  - For pain, Tylenol, Ibuprofen/other NSAIDS, hot packs should be administered.

- For swelling, Ibuprofen/other NSAIDS should be administered.
- If any drainage, fever, chills, fatigue, weakness, the site should be contacted immediately.
- Do not attempt to squeeze or drain any fluid from injection site
- Cover with a sterile bandage and contact clinic immediately if drainage occurs.

Questions regarding the injection instructions should be directed to the CMC.

9.6 Specimen Collection

Blood, urine, and rectal swabs will be collected throughout the study. The protocol outlines the clinical procedures and corresponding testing to be performed on the specimens in the HPTN 083 in Section 5.0. Sections 6 and 11(checklists and lab) of the SSP also should be consulted for further specifications. The following additional considerations should be noted:

- At Enrollment/Week 0, GC/CT testing will be performed using urine and rectal swab. Results from the enrollment visit are not required prior to enrollment. (See Section 11 of this manual for further information).

- At Enrollment, and Visits 57 and 105, a fasting lipid profile is obtained. Participants should be fasting for at least 8 (preferably 12) hours before sample collection. Prior to initiation of these visits, confirm with participants when was the last time they had anything to eat or drink. If a participant is not fasting when she/he presents to the clinic, do not collect blood for lipid profile, rather, reschedule the participant to return to the clinic as soon as possible to collect the sample. Study drug should not be held if a fasting sample was not obtained. If the fasting lipid profile cannot be collected at the Enrollment visit, schedule the participant to return to the clinic for sample collection within 72 of the visit (that is, within 72 of study product initiation). If a sample cannot be obtained within this timeframe, contact the CMC for guidance on an acceptable timeframe to collect the sample.

- Since plasma samples for drug levels will be collected throughout the study, blood sample must be collected at injection visits PRIOR to the injections.

- Calculated creatinine clearance must be performed at every visit where chemistry testing is being performed, using the Cockcroft-Gault formula. The formula for males is:

  eCcr (male) in mL/min = [(140 - age in years) x (actual body weight in kg)] / (72 x serum creatinine in mg/dL).

  This formula also appears in Section 11.3.3.1 of the SSP (Laboratory and Specimen Management Procedures Section).

  Notes related to the creatinine clearance:

- *Creatinine clearance calculation for TGW is based on sex at birth.*
- *"Age in years" refers to participant's current age. It should not be rounded up, even if next birthday is in the near future. For example, a 26 year old participant presents to the clinic on 11 February, but he is turning 27 the following day, 12 February. The age to be used for calculation is 26 and not 27. Age should not include decimal places (i.e. 26.5 or 26.75)*
- *Adverse events related to creatinine clearance should be based on examination of BOTH the absolute creatinine clearance AND the change in creatinine clearance from baseline (Enrollment/ Visit 2.0). When gradable, only the higher grade of these two assessments should be entered on the Adverse Event e-CRF. Clinical Management of Grade 3 and Grade 4 changes in creatinine clearance should **ONLY** follow the "Toxicity Management General Guidance" found in Appendix III of the HPTN 083 protocol when the absolute creatinine clearance is < 90 mL/min. That is, changes in creatinine clearance of >30% from baseline that **DO NOT** result in an absolute creatinine clearance < 90 mL/min do **NOT** need to be reported to the CMC or more frequent clinical monitoring.*

9.7 Clinical Management Committee

As outlined in the HPTN Manual of Operations (MOP), a CMC is constituted for each HPTN study with a biomedical intervention. The HPTN 083 CMC will provide consultation and decision-making regarding management of toxicities and study product administration, interpretation of clinical or laboratory eligibility criteria, and other questions related to general clinical management of participants. The CMC is comprised of physicians from a subset of the sites, and also includes the Protocol Chair and Co-Chair, pharmaceutical sponsor investigators, DAIDS Medical Officer, DAIDS Protocol Pharmacist, Medical Safety Physician, and representatives from the HPTN LOC, HPTN LC, and the HPTN SDMC. The CMC primary responder, the Medical Safety Physician, will be responsible for soliciting input and responding to a site queries within a 24-hour time period.

Sites should be mindful that throughout the HPTN 083 protocol and associated protocol appendices, as well as the SSP manual, are examples of situations and adverse events that require consultation with the CMC.

Queries from sites are submitted to the following email alias list: 083CMC@hptn.org.

Queries must be formatted to include the information outlined below.

- Include "083 CMC: [Insert PTID] – [One-line summary of query – for example – "Elevated ALT" in the subject line of the email message.
- Include all of the following in the body of the email message:

  1. **Site name and number**
  2. **Name of person submitting query**
  3. **Participant Identification number (PTID) and Week on Study (Use "Screen" if pre-enrollment)**

4. **Query submission type *(choose one of the following)***
- **Initial submission**
- **Follow-up submission (this pertains to the PTID, i.e., a follow-up query to the initial submission**
5. **Reason for query and case narrative**

An example of the suggested e-mail is provided here:

Subject line of email: 083 CMC: Participant 103-000011 – Elevated ALT

Body of email:

Site name and number: Site 103 – University Prevention Clinic

Person submitting query: Hedda Lettuce, Study Coordinator

PTID and Week on Study: 103-000011, Week 2

Query Type: Initial submission

Reason for query: 32-year-old participant week 2 on blinded oral study medication found to have Grade 4 CK elevation after cross-fit competition with Grade 3 ALT elevation. Per protocol, participant will be unable to progress to injection phase. Please advise on further work-up and follow-up schedule (unless CMC can envision a way to continue participant on-study products).

Con meds: Tylenol, Ibuprofen, Naprosyn, Isoniazid, PZA, Ethambutol

Denies Alcohol, other recreational drug use

Pertinent laboratory values with chronology, values, and DAIDS toxicity table grade:

	Reference Ranges*	**4/6/17 W2**	**3/23/17 EntryW0**	**3/19/17 screen**
AST	10-40 U/L	812 (G4 25xULN)	15	16
ALT	9-46 U/L	225 (G3 7xULN)	15	15
CK	21-215 U/L	7100 (G4 20x ULN)	43	49
creatinine	0.60-1.35 mg/dL	0.97	0.97	1.04

**NOTE: Reference Ranges included on this table are for example purposes only; it does not represent ranges to be used in the study.*

Sites that submit queries will print and file the full CMC correspondence regarding the query and place in the relevant participant regulatory binder/participant study file.

9.8 Toxicity Management

Sites should regularly consult the HPTN 083 protocol Appendix III – Toxicity Management as well as the Toxicity Management Diagrams at the end of this section, for guidance related to toxicities. It should be noted that Appendix III of the Protocol refers to several instances where the CMC must be contacted in the case of AE management

and grading. AEs that require CMC consultation, the CMC should be notified as soon as possible after site awareness, ideally within 72 hours.

All toxicity management must be fully documented in participant study records. When the CMC is consulted in relation to toxicity management, all communication should be filed in participant study records.

9.9 Suspected or Confirmed HIV Infection

Section 5.13 and Appendix II in the HPTN 083 protocol and Section 11 of the SSP should be followed for any participant regarding suspected or confirmed HIV infection.

- HIV testing will be done at **all** study visits. Please reference HIV testing algorithms found in Appendices IE-1G in the HPTN 083 protocol and Section 11 of the SSP manual.
- An HIV Confirmation Visit must be scheduled for all participants who become infected at any time during the study for confirmation of HIV infection.
- For participants with confirmed HIV infection during Step 1, permanently discontinue the oral study product. These participants will be transitioned to local HIV-related care services.
- For participants with confirmed HIV infection during Step 2, permanently discontinue study product. After the HIV Confirmation Visit, these participants will have procedures done at Week 12, 24, 36, and 48 per Appendix II and the toxicity management guidelines in Appendix III of the protocol. These participants will also be referred to immediate suppressive HIV treatment and care per the study-required SOP for seroconversion (see below).
- For participants with confirmed HIV infection during Step 3, permanently discontinue study product and follow them at least for the duration of Step 3, and refer to local HIV-related care services.

IMPORTANT: In order to maintain the blind to the primary endpoint of the study, do NOT contact the CMC regarding questions about HIV seroconversions and management of participants with HIV infection. Email 083HIV@hptn.org for any questions related to the requirements for suspected or confirmed HIV infection or clinical management of HIV infection. The persons included on this email alias are independent of the study. Sites should follow the template below when sending email to the 083HIV email alias:

The subject line of the email: 083/084 HIV: Participant 103-000011 – Reactive ELISA

Body of email:

Site name and number:

The person submitting a query:

PTID and Week on Study:

Query Type:

Reason for query:

Example:

Site name and number:	XXX CRS	0001
The person submitting the query:	Janet Smith	
PTID and Week on Study:		24
Query Type:	Initial Query	
Reason for query:	Reactive ELISA	
A 32-year-old participant's ELISA test for week 24 was reactive. She had flu-like symptoms 3 weeks ago and has missed taking her pills on two occasions. She denies having unprotected sex in the past months. We have called the participant to stop taking the study medication, and to come next week for confirmatory lab work. Please advise if our plan is in order.		

PTID:		Person Submitting the results		
HIV Test	Index visit -Visit 9.0 (22 June19)	Confirmatory Visit (24 June19)	Post Product-Hold Visit (22 July 19)	Comments
HIV Rapid Test				
HIV ELISA 4th Gen				
HIV Discriminatory Test (Geenius)				
HIV RNA Test				
HIV DNA Test				
CD4				
DBS				
Plasma storage				
HIV resistance testing				

For participants with discordant or discrepant HIV test results, please follow guidance in in Appendix V of the SSP.

As outlined in Section 5.13.2 of the protocol, sites must have in place an SOP that outlines the plan for the facilitation of a participant with confirmed HIV infection into immediate suppressive ART. Sites are not responsible for the provision of ART in these cases, but are responsible for the facilitation in to HIV treatment and care.

9.9.1 Assessment of Acute HIV Infection

During follow-up, prior to study product administration, assess for signs and symptoms of acute HIV infection. Acute HIV infection is defined as the period of rapid viral replication that immediately follows the initial establishment of infection with HIV. Symptoms of acute HIV infection may be indistinguishable from a typical viral syndrome. Symptoms of acute HIV infections are listed above (Section 9.2.2).

Clinicians should assess the possible causes of these symptoms, length of time the participant has been experiencing these symptoms, and severity grade. Symptoms should be managed clinically per standard of care. If a participant has signs or symptoms consistent with acute HIV infection, or expresses a concern about recent HIV acquisition, testing will be performed per protocol.

9.10 Sexually Transmitted Infections (STIs)

Section 5.14 of the HPTN 083 protocol and Section 11 of the SSP should be followed for procedures regarding testing for GC/CT and syphilis. As noted in the HPTN 083 protocol, treatment for STIs will be provided per local guidelines (and may include referral for treatment).

Any positive/reactive laboratory test results for syphilis from the time of study enrollment and any positive/reactive test during the study must be referred to the CMC for adjudication accompanied by any prior testing and treatment results. The communication with the CMC should occur prior to the subsequent study visit at which the positive/reactive testing is resulted. Cases of syphilis discovered prior to study participation should be included as a pre-existing condition.

Symptomatic screening for STIs beyond what is required by the protocol will be performed at a site's discretion and costs associated may come out of each site's respective per participant study reimbursements.

When reporting sexually transmitted infections, sites need to report infections diagnosed as part of protocol-required testing for GC/CT and syphilis on the STI eCRF as well as the AE Log eCRF. All other STIs diagnosed as part of standard of care will be reported on the AE Log eCRF only. If sites only reported STIs in one place, is not required to report retroactively.

9.10.1. Hepatitis B and Hepatitis C

Section 5.15 of the HPTN 083 protocol and Section 11 of the SSP should be followed for procedures regarding Hepatitis B and Hepatitis C testing.

Of note, persons with any result other than "negative" or "not detected" for the HBsAg test and/or any result other than "negative" for the HCV antibody testing will be excluded from the study. If the HBsAg test is not "negative" (or its equivalent) then the hepatitis B virus may present at low levels. This means that the participant may have either acute or chronic hepatitis B infection. Participants who do not have evidence of

immunity to HBV will be referred for HBV vaccination. Although HBV immunity is not required for enrollment, non-immune participants should be monitored for signs of HBV infection throughout the study.

The case of isolated HBcAb positivity (HBcAb+, HBsAb -, HBsAg -) may represent a false positive, a cross reaction to HCV (which would be exclusionary in the setting of a positive HCV Ab), or a very low positive chronic HBV antigenemia below the level of detection of laboratory assays for HBsAg. HBV DNA testing will not be provided by the study; for the purposes of HPTN 083, absence of detectable HBsAg at screening will be considered sufficient for study enrollment **unless prior knowledge of detectable HBV DNA exists (by self-report or medical record).** All participants without detectable HBsAb should be referred for vaccination against HBV as per local guidelines and availability.

9.11 Tuberculosis

As noted above in Section 9.4.1, rifampin, rifapentine, and rifabutin are contraindicated for concurrent use with cabotegravir. If any rifamycin medication is planned to be used, blinded study product should be held. Follow guidance outlined in Section 9.4.2 for visit schedule.

Sites should contact the CMC for clinical guidance on implementation of this blinded study product hold, concurrence on the appropriateness of planned resumption of blinded study products upon prohibited medication completion, and resumption of blinded study products when/if appropriate.

9.12 BMD (DXA) Subset

Sites participating in the BMD subset should refer to Appendix 1 of this manual – the DXA Manual of Operations for HPTN 083 Study.

The DXA subset will consist of 350 participants, 175 in each arm, and will be enrolled along with the main study. As sites are activated to the study and begin enrolling, participants will be asked if they are willing to participate in this subset. Enrollment into the subset will be based on when sites are activated to the study and pace of enrollment at each site, i.e., slots are not distributed to sites – rather, the subset will be filled on a rolling basis until the 350 slots are filled. Late activating sites may not have the opportunity to participate in the subset if enrollment is full (e.g., slots will not be saved for late-activating sites).

The HPTN SDMC will track enrollment into the subset. Sites will be informed of the number of available slots until the subset is closed.

The subset procedures will include DXA scan, and dietary calcium and Vitamin D assessment. Please note that the Vitamin and Calcium assessment is simply querying the participant about their dietary intake of both – it is not a formal interviewer administered assessment. The Vitamin D and Calcium Assessment eCRF will be completed with the information provided by participants. For participants in the subset, the following procedures and testing are required:

- At the Enrollment visit: DXA scan, 25-OH-Vit D blood test, and the dietary calcium and Vitamin D assessment. The target visit window at enrollment is -30 days/+7 days of enrollment.
- During study follow-up (at Weeks 57 and 105): DXA scan, and dietary calcium and Vitamin D assessment. The target visit window during follow-up is -/+ 8 weeks of each visit.

If a participant in the subset prematurely transitions out of Step 2 to Step 3 or annual visits, and the transition occurs close to the Week 57 or Week 105 DXA timepoints, the CMC may authorize that a DXA be performed.

Table 9-2: CESD-10 Score

Center for Epidemiologic Studies Short Depression Scale (CES-D 10)

Below is a list of some of the ways you may have felt or behaved. Please indicate how often you have felt this way during the past week by checking the appropriate box for each question.

Items:	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	All of the time (5-7 days)
1. I was bothered by things that usually don't bother me.				
2. I had trouble keeping my mind on what I was doing				
3. I felt depressed.				
4. I felt that everything I did was an effort.				
5. I felt hopeful about the future.				
6. I felt fearful.				
7. My sleep was restless.				
8. I was happy.				
9. I felt lonely.				
10. I could not "get going."				

Scoring

	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of the time (3-4 days)	All of the time (5-7 days)
Items 5 & 8	3	2	1	0
All other items	0	1	2	3

Score is the sum of the points for all 10 items. If more than 2 items are missing, do not score. A score of 10 or greater is considered depressed.

This quiz is intended for educational purposes only and should not be understood to constitute any type of diagnosis or healthcare recommendation.

Please call your PCP or AMA Social Worker to report your score or any concerns. If you are having thoughts of hurting yourself or others, please call AMA immediately and tell the operator it is an emergency, or go to your local emergency room.

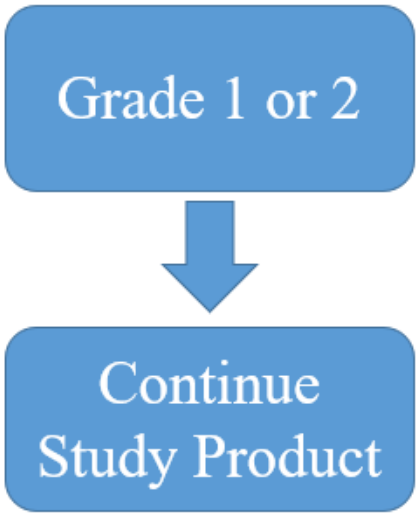
Allison Galbraith, LICSW
Acton Medical Associates
(978) 263-1131 ext. 310
321 Main Street
Acton, MA 01720

Additional Information

This is the short version of the 20-item CES-D. The CES-D was developed in the 1970s by Lenore Radloff while she was a researcher at the National Institute of Mental Health.

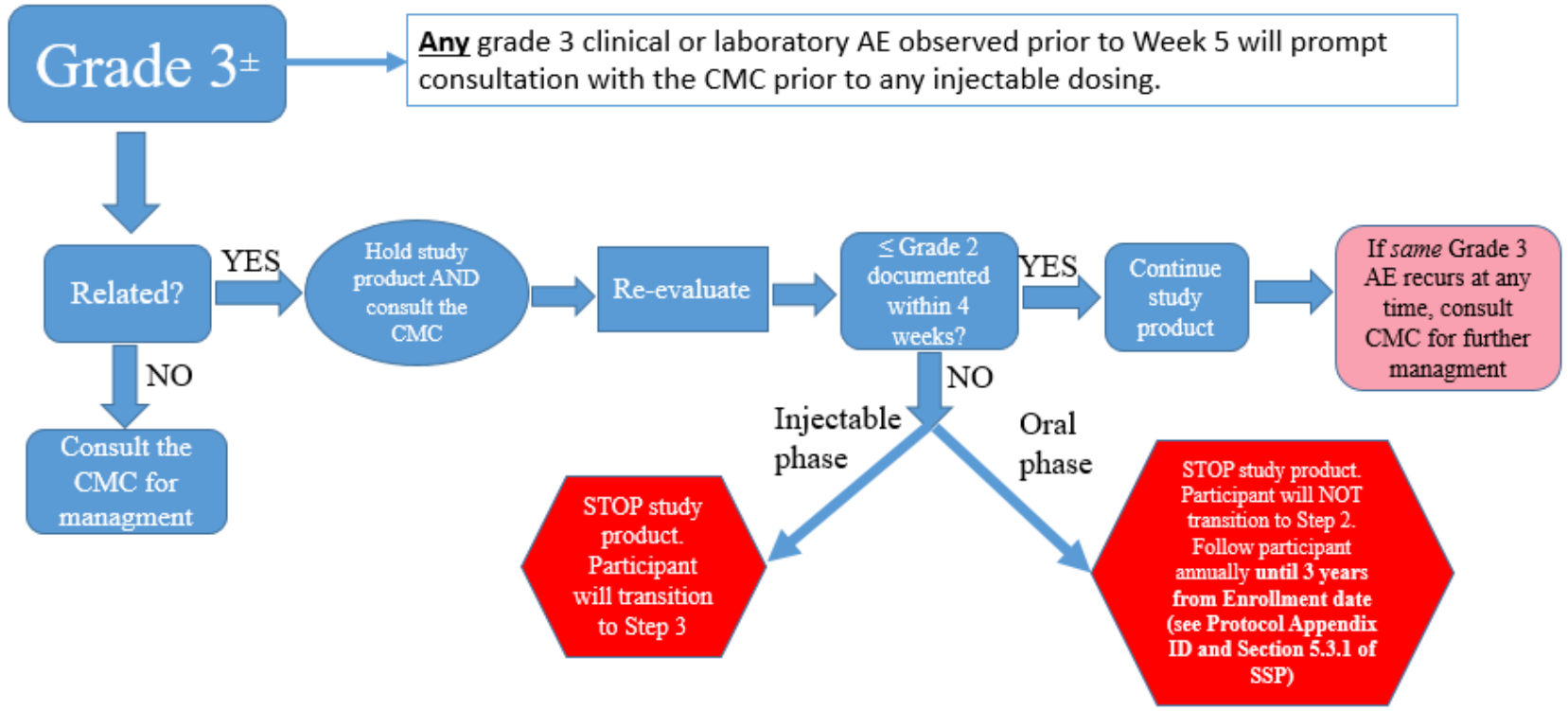
Protocol Version 3.0 31 October 2019 Diagram Version 3.1 12 February 2020

General Guidance*



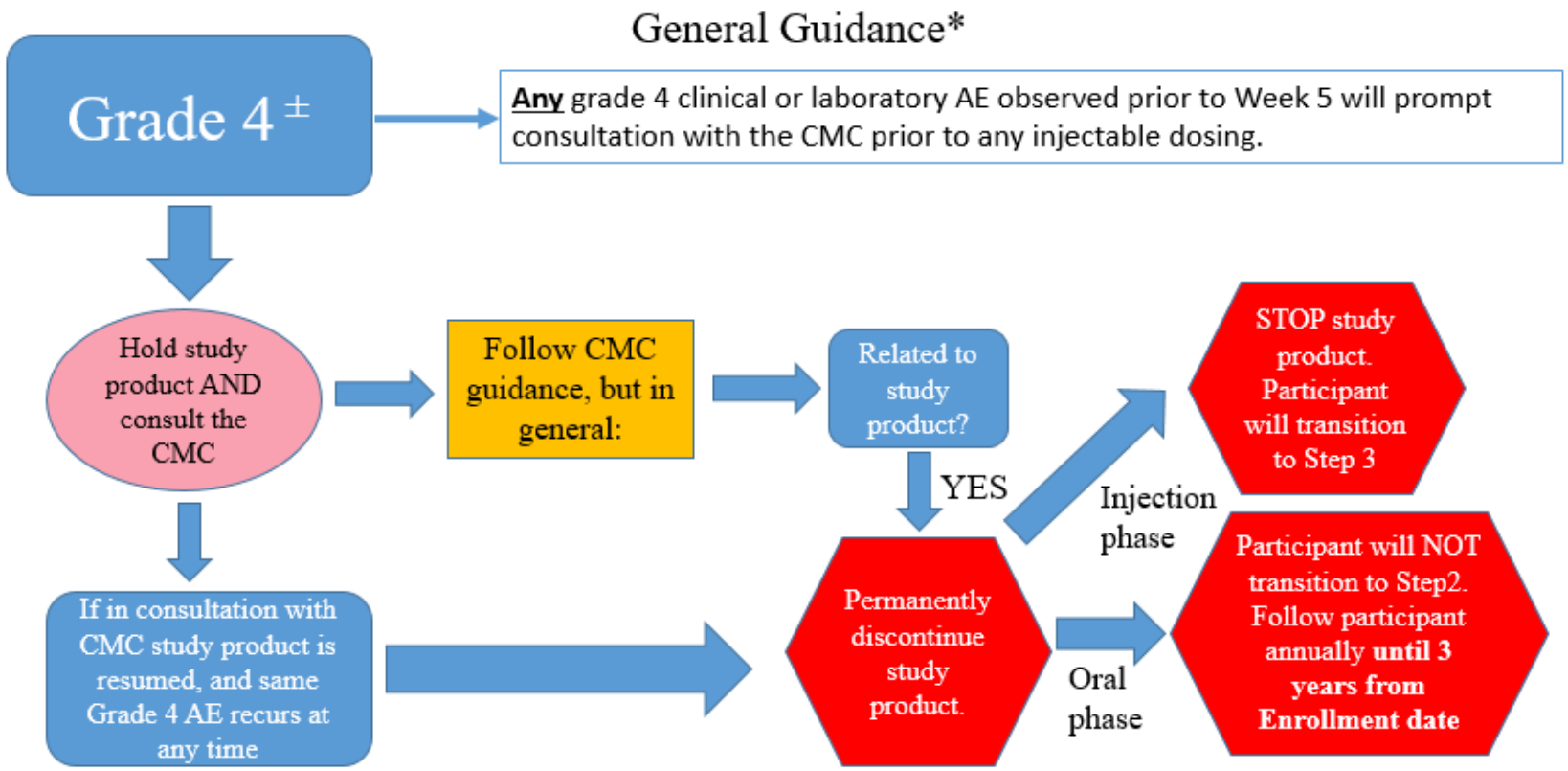
*If condition is addressed on Appendix III tables, follow specific guidance. This general guidance only applies to abnormalities without specific guidance in the Toxicity Management Section of the protocol.

General Guidance*



*If condition is addressed on Appendix III tables, follow specific guidance. This general guidance only applies to abnormalities without specific guidance in the Toxicity Management Section of the protocol.

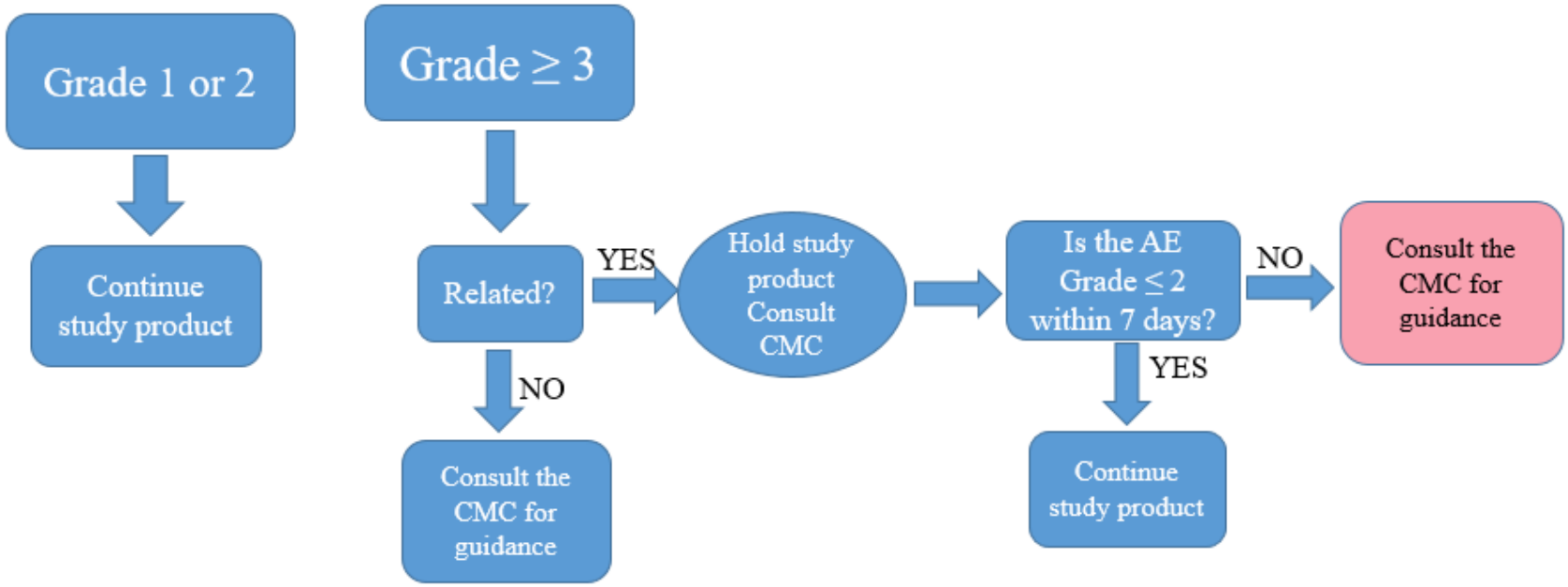
± At Week 0 (study enrollment), consult the CMC for guidance regarding follow up and ongoing study product administration



*If condition is addressed on Appendix III tables, follow specific guidance
± At Week 0 (study enrollment), consult the CMC for guidance regarding follow up and ongoing study product administration

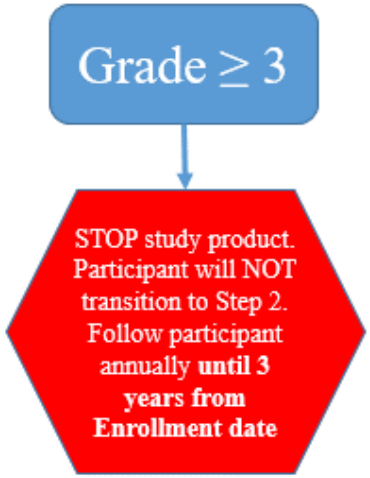
Specified Toxicities

Nausea, Vomiting, and Diarrhea*



*For all grade levels, treat symptomatically

Specified Toxicities
ALT
Oral Phase (Step 1)

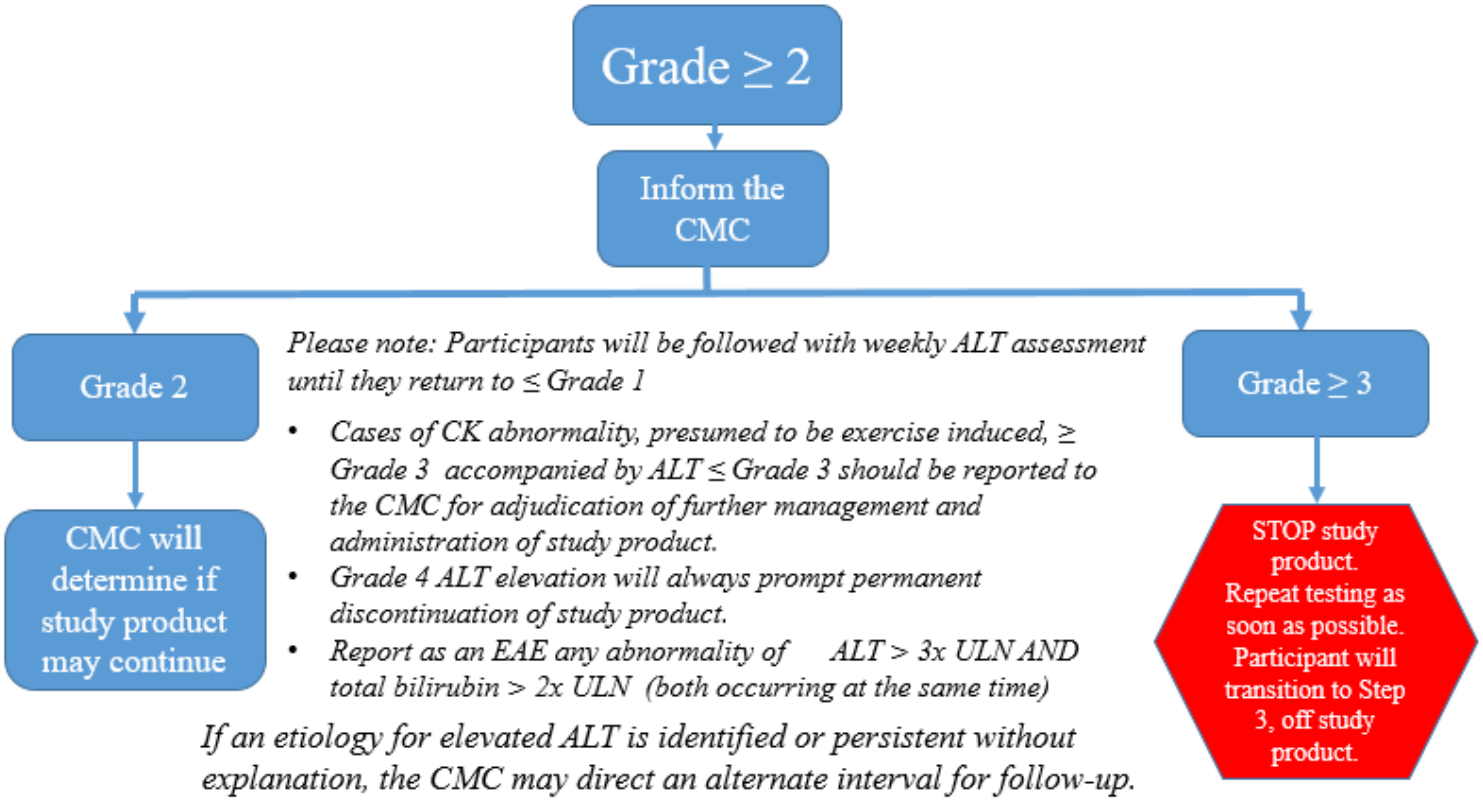


Please note: All cases should be reported to the CMC. Participants will be followed with weekly ALT assessment until they return to ≤ Grade 1

If an etiology for elevated ALT is identified or persistent without explanation, the CMC may direct an alternate interval for follow-up.

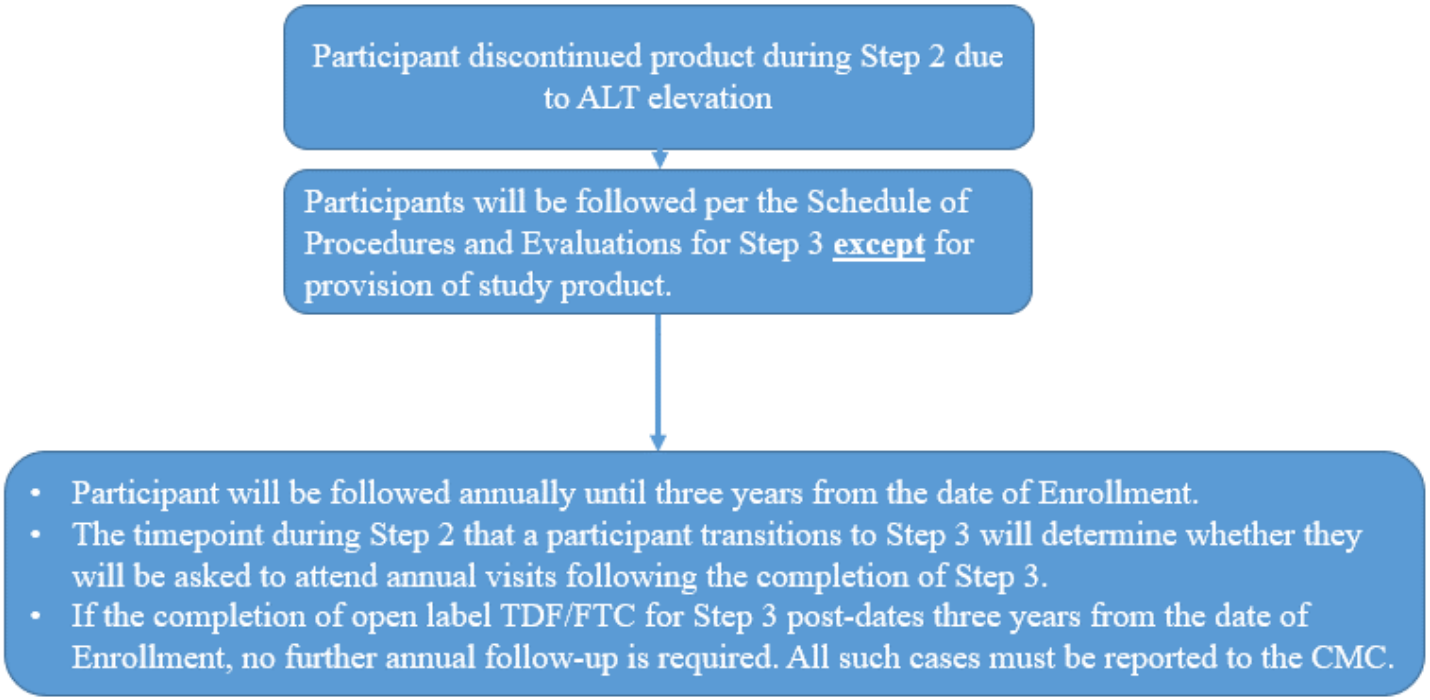
- *Cases of CK abnormality, presumed to be exercise induced, ≥ Grade 3 accompanied by ALT ≤ Grade 3 should be reported to the CMC for adjudication of further management and administration of study product.*
- *Grade 4 ALT elevation will always prompt permanent discontinuation of study product.*
- *Report as an EAE any abnormality of ALT > 3x ULN AND total bilirubin > 2x ULN (both occurring at the same time)*

Specified Toxicities
ALT
Injection Phase (Step 2)



If an etiology for elevated ALT is identified or persistent without explanation, the CMC may direct an alternate interval for follow-up.

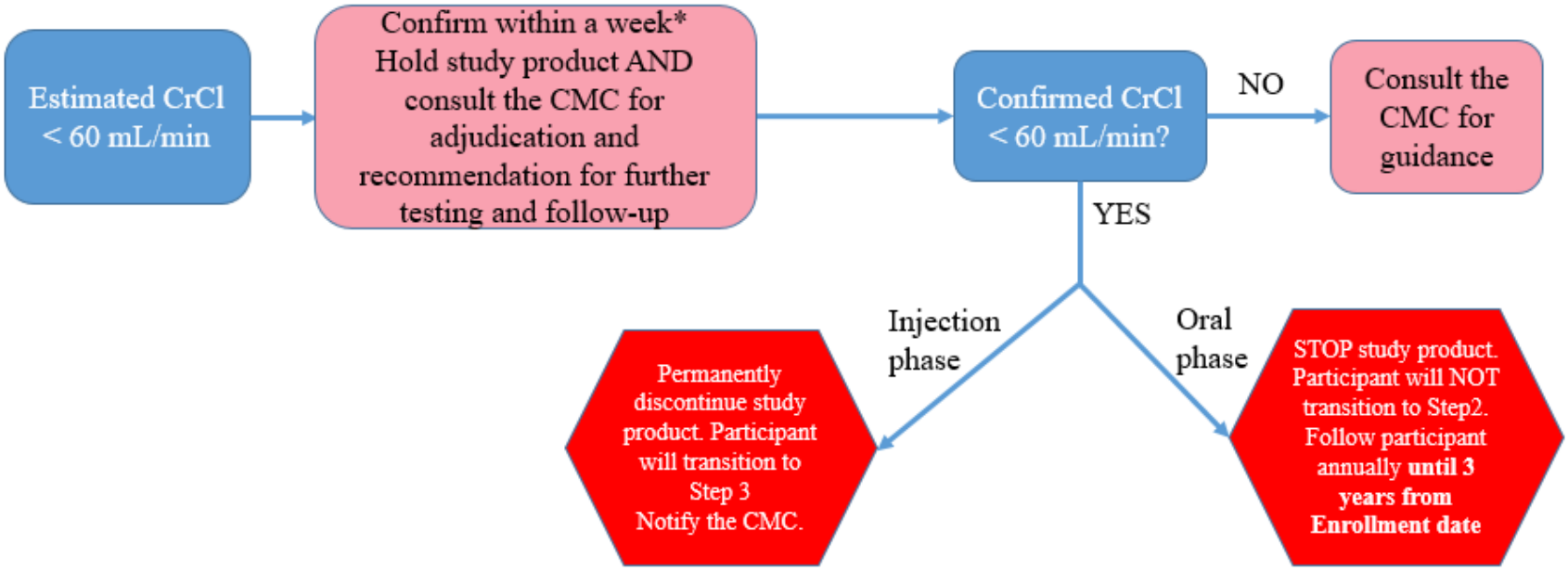
Specified Toxicities
ALT
Open-label Phase (Step 3)



Specified Toxicities
ALT
Considerations

- Grade 1 elevations – study product will continue
- Pre-existing HBV infection is not likely to be a cause of AST/ALT elevations.
  - Participants will be HBsAg negative at enrollment and those without evidence of immunity to HBV will be referred for HBV vaccination.
  - Incident HBV infection acquired while on-study will mandate permanent discontinuation of blinded study products; please ensure non-immune participants are vaccinated to the best of the site's ability
- Careful assessments should be done to rule out the use of alcohol, lactic acidosis syndrome, non-study medication-related product toxicity, herbal medications/supplements, or viral hepatitis as the cause of elevation in AST or ALT of any grade.
- The participant must be assessed for any symptoms or signs of hepatotoxicity, including fatigue, malaise, anorexia and nausea, jaundice, acholic stools, right upper quadrant pain, or hepatomegaly.
- If the AST/ALT elevation is considered most likely to be due to concomitant illness or medication, standard management, including discontinuation of the likely causative agent, if possible, should be undertaken.
- If symptoms or signs of clinical hepatitis are present, study product must be held or discontinued
- All participants with elevated values should be considered for testing for Hepatitis A, B, and C infection.
- In areas where Hepatitis A outbreaks are ongoing or likely to occur, vaccination of all participants, or non-immune participants, should be considered. Please contact the CMC for any questions.

Specified Toxicities
Creatinine Clearance



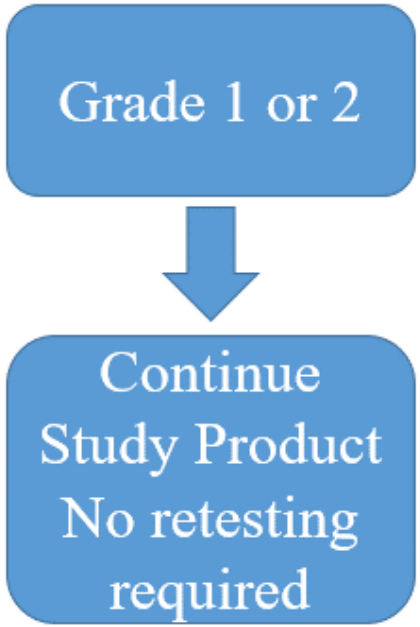
*Participants that fail to have confirmation within 2 weeks, product will be discontinued until CMC adjudication and recommendations
NOTE 1: For gradable changes in creatinine clearance per the DAIDS Toxicity Table, please refer to the "General Guidance" management schema, even if the estimated absolute value of the Cr Cl is >= 60 mL/min.
NOTE 2: Calculated creatinine clearance must be performed at every visit where chemistry testing is being performed, using the Cockcroft-Gault formula.

Specified Toxicities
Creatinine Clearance

- Adverse events related to creatinine clearance should be based on examination of BOTH the absolute creatinine clearance AND the change in creatinine clearance from baseline (Enrollment/ Visit 2.0).
- When gradable, only the higher grade of these two assessments should be entered on the Adverse Event e-CRF.
- Clinical Management of Grade 3 and Grade 4 changes in creatinine clearance should follow the "Toxicity Management General Guidance" ONLY when the absolute creatinine clearance is < 90 mL/min. That is, changes in creatinine clearance of >30% from baseline that DO NOT result in an absolute creatinine clearance < 90 mL/min Do NOT need to be reported to the CMC or more frequent clinical monitoring.
- Changes in creatinine clearance of > 30% that are accompanied by a serum creatinine that remains within normal limits Do NOT need to be reported to the CMC and Do Not require more frequent clinical monitoring.

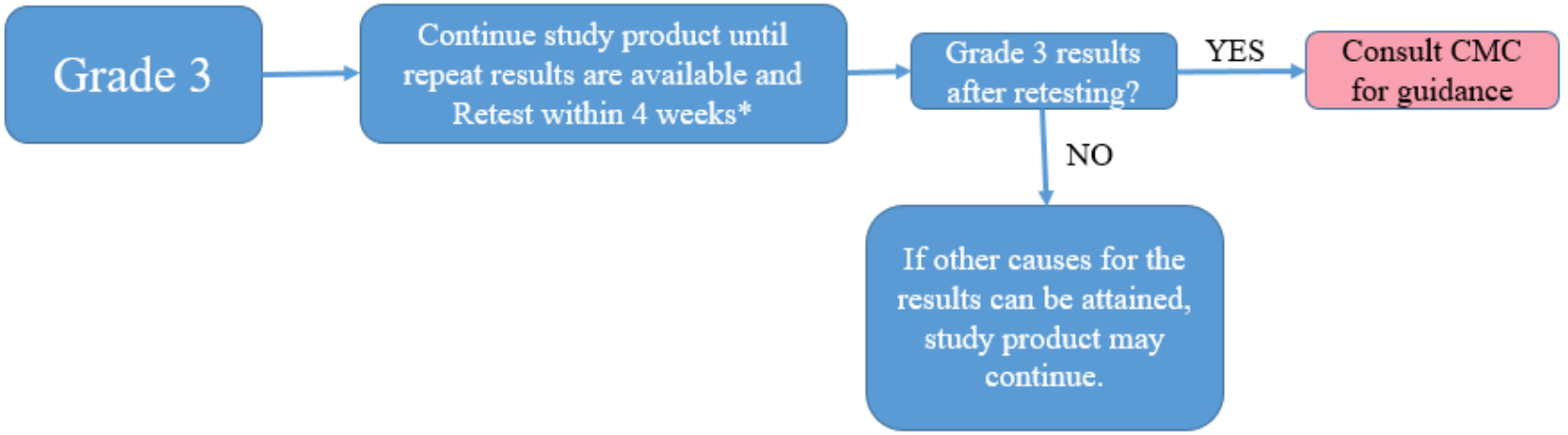
Specified Toxicities

Creatinine Phosphokinase (CK or CPK)



Specified Toxicities

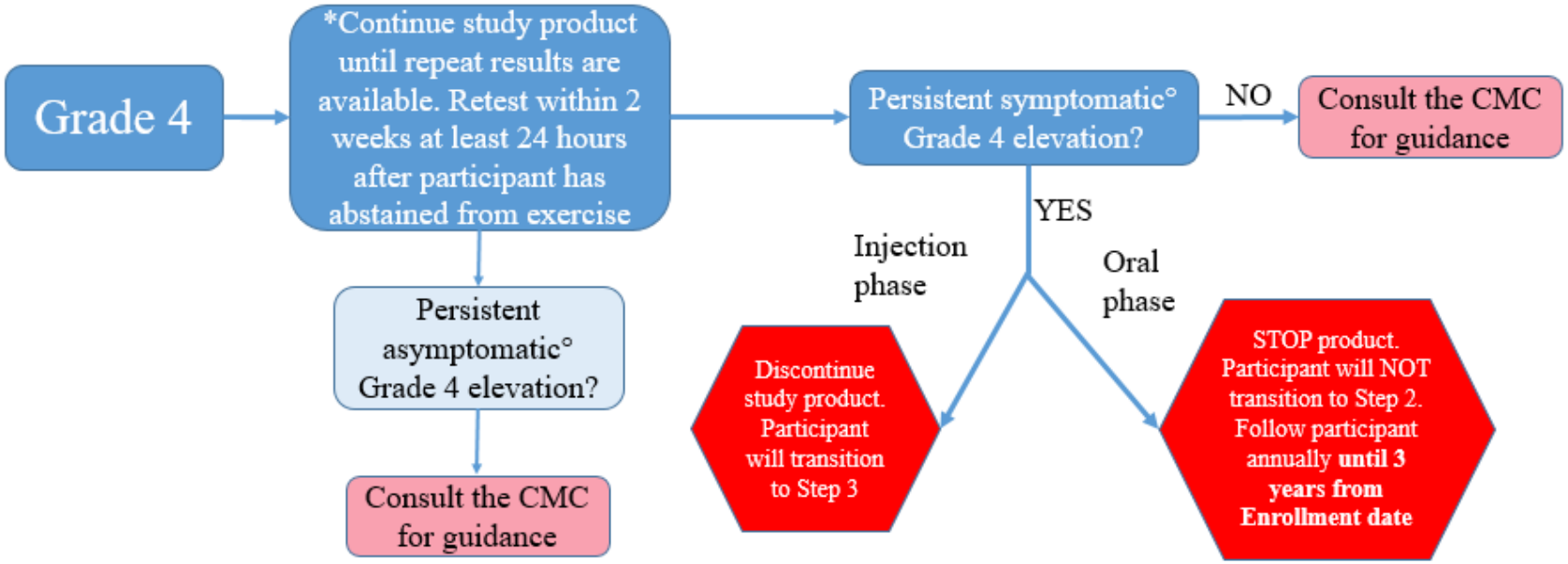
Creatinine Phosphokinase (CK or CPK)



*Use of products know to cause increase of CPK and physical activities proceeding CPK evaluation should be obtained

Specified Toxicities

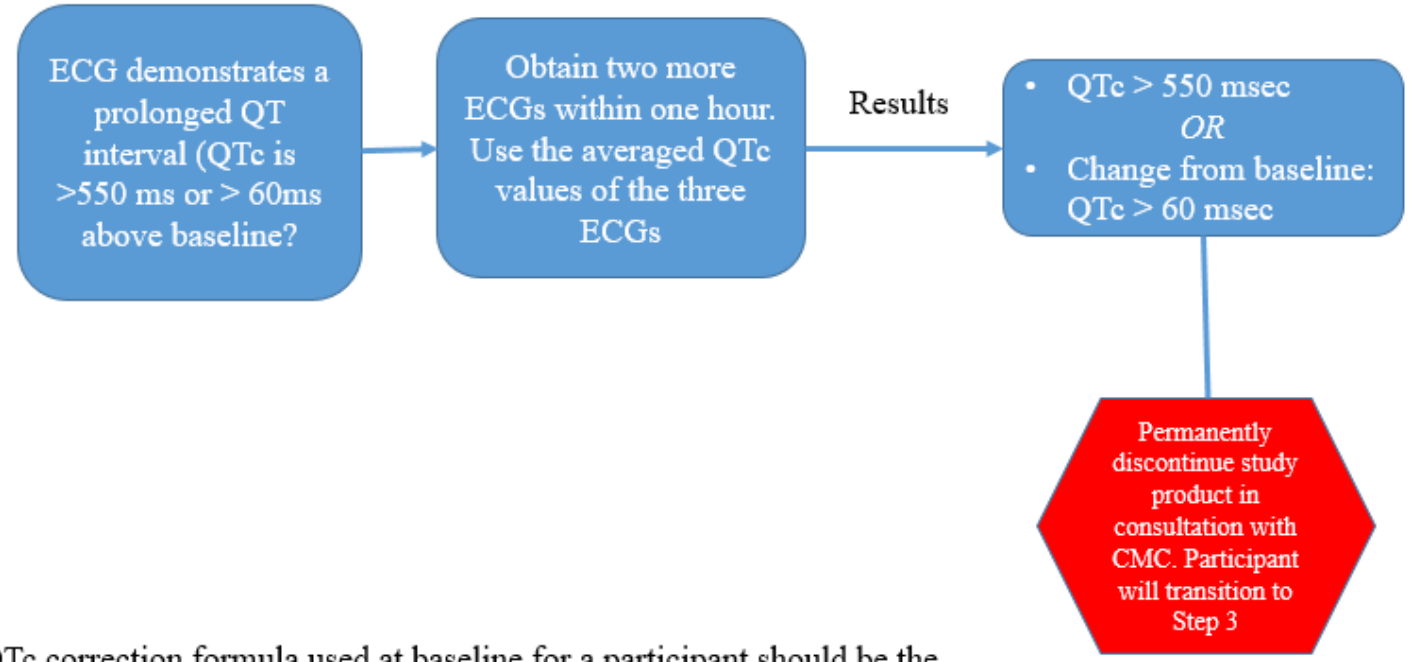
Creatinine Phosphokinase (CK or CPK)



*Use of products know to cause increase of CPK and physical activities proceeding CPK evaluation should be obtained

° Myalgias, muscle pain, dark urine, or clinically significant changes in creatinine clearance, defined in consultation with the CMC

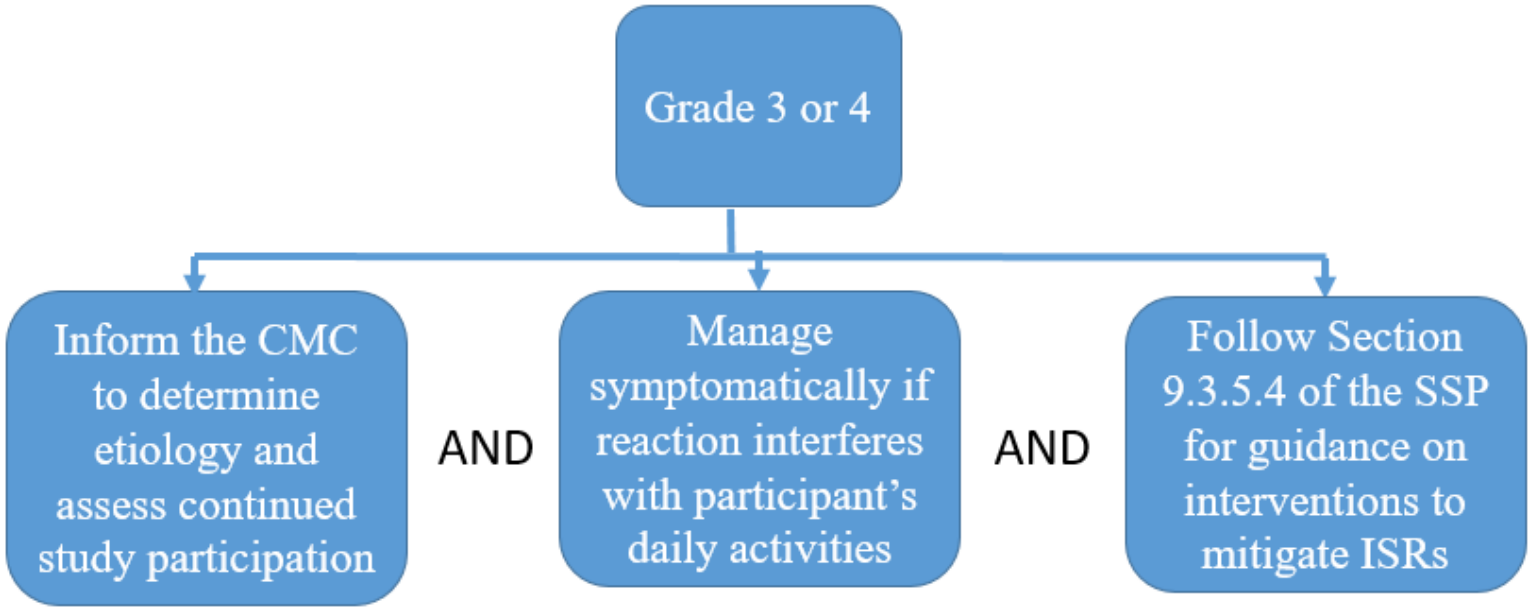
Specified Toxicities
QTc*



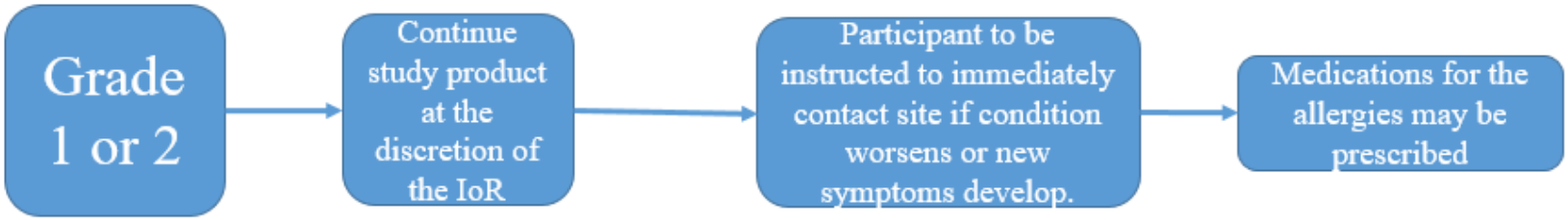
*QTc correction formula used at baseline for a participant should be the same formula throughout the study.

Specified Toxicities

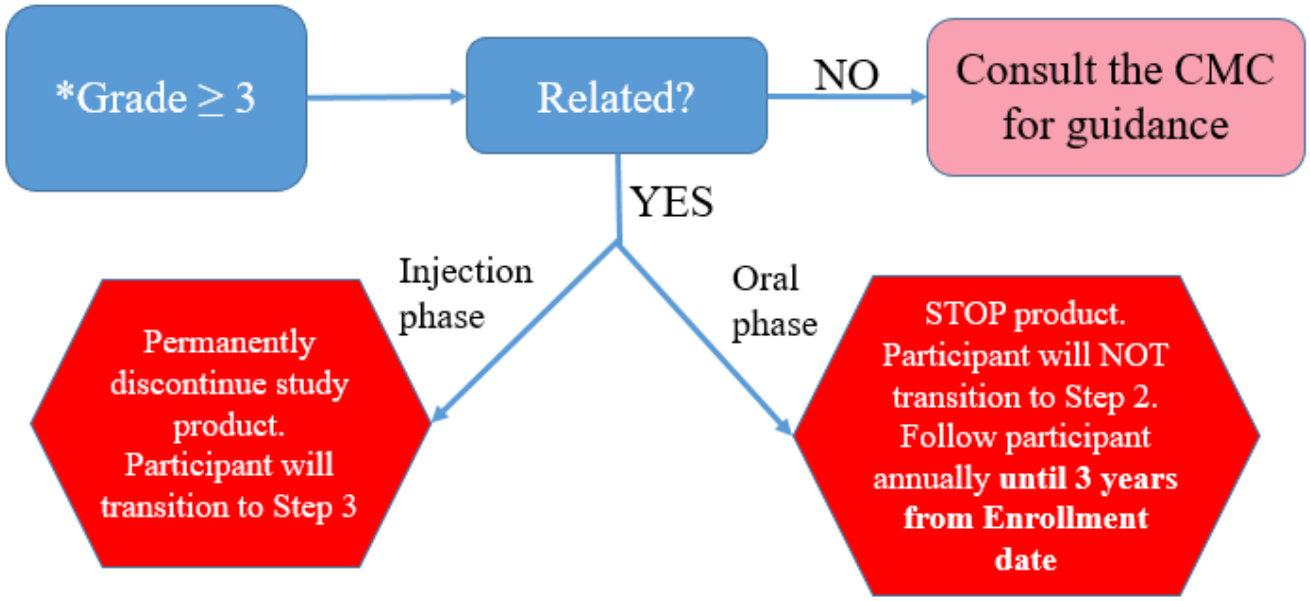
Injection Site Reactions (ISRs)



Specified Toxicities
Allergic Reactions



Specified Toxicities
Allergic Reactions



*Treat participants as appropriate and followed until resolution of the AE.

General Toxicity Management Considerations

- Participants who discontinue study product for any reason (other than HIV infection) during Step 1 will be followed annually until 3 years from Enrollment date (see Protocol Appendix ID and SSP Section 5.3.1 for procedures to be performed in these cases).
- Participants who discontinue study product for any reason (other than HIV infection) during Step 2, will transition to Step 3.
  - Depending on the toxicity (e.g. decreased renal function), Step 3 follow-up may be "off" study product.
- Always consult Appendix III of the Protocol for specific toxicity management guidance and detailed information.
- Contact the CMC for guidance on toxicity and product use management, and general questions related to participant safety.
- For protocol-required consultations, contact the CMC ideally within 72 hours of site awareness of the AE in question.
- **All** AEs will be followed until resolution or stabilization.
- The IoR has the discretion to hold study product at any time to safeguard participant's safety. When product is held for conditions not described in the protocol, the CMC must be informed.