Section 9. Clinical Considerations

9.1 Overview of Section

This section provides information on the clinical considerations for participants in HPTN 084-01. The Schedule of Evaluations in Appendixes I-V of the protocol indicates when specific clinical, counseling, and questionnaire procedures are required along with relevant laboratory testing.

Safety assessments will be obtained at every visit throughout the study. However, the IoR 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 conditions which may require follow-up.

Information pertaining to participant safety monitoring and AE reporting procedures are provided in Section 10 of this SSP manual. Information on performing laboratory procedures is described in Section 11 of this manual. Further instructions for the electronic data capture systems are provided in Sections 13 and 14 of this SSP manual and in any data communiqués.

The HPTN 084-01 study will begin with the Screening visit, followed for eligible participants by:

- Step 1 – Oral Run-in Phase: Oral Safety Visits (Week 0/Enrollment, Weeks 2 and 4)
- Step 2 – Injection Phase: First injection visit (Week 5), Safety visit (Week 6), Remaining injection visits (Weeks 9, 17, 25, 33), and remaining safety visits (Weeks 10, 18, 26, 34)
- Step 3 – Follow-up Phase: PK trough visit (+8 Weeks since last injection), and remaining safety visits (+12, +24, +36 and +48 Weeks since last injection).
    - NOTE: Step 3 should begin within and as close to 8 weeks after the last Step 2 injection at Week 33.

Any questions regarding the safety assessments and clinical management of participants in HPTN 084-01 should be directed to the HPTN 084-01 Clinical Management Committee (084-01CMC@hptn.org). See Section 9.9 of this SSP for further information about the CMC.

9.2 Participant-Reported Medical History 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 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).

Medical History should include, but is not limited to, symptoms, chronic conditions, and diagnoses that affect eligibility or participation in the study, bleeding history, concomitant medications, and a history of hospitalizations, surgeries, seizures, and allergies.

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, including severe cardiovascular disease. 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 AEs 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 must have a consistent method for documenting this information. In all cases, information obtained at Screening, Enrollment, and all follow-up visits must be documented in the participant's chart and on appropriate e-case report forms.

9.3 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 study product exposure. 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, (i.e. baseline sample prior to dosing) are considered pre-existing conditions and should be recorded as such. This includes depressive symptomology scoring from the Patient Health Questionnaire (PHQ) eCRF.

All ongoing conditions recorded as pre-existing are to be documented in the source documents and transcribed onto the Medical History e-CRF. This CRF 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 Medical History CRF 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 AEs. The purpose of grading a pre-existing condition is because the Medical History CRF serves as the "starting point" from which study clinicians must determine whether abnormal conditions, signs, symptoms, and findings identified during follow-up are AEs).

Helpful hint: Each site may wish to add a label to the front of the participant file noting baseline lab values and an alert value so that all % changes from baseline are easily compared when new results come in at follow up visits.

9.3.1 Medical History for Ascertainment of Eligibility

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

- At Screening, 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 Acetylsalicylic acid (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.

Guidelines for collecting the baseline medical history include:

- Probe for history of conditions by body system. Be thorough and ask open ended questions when possible.
- Document symptoms, illnesses, allergies, hospitalizations, and surgeries.
- Document both acute and chronic conditions, and both ongoing and resolved conditions.
- Signs and symptoms of acute HIV infection should be assessed:
    - Fever
    - Fatigue
    - Headache
    - Myalgia
    - Weight loss

- Pharyngitis or sore throat
- Lymphadenopathy
- Rash
- Diarrhea
- Oral or genital ulcers

- Site staff must 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 within 14 days prior to Enrollment. If a constellation of symptoms suggestive of acute HIV infection (per the judgment of the IoR or designee) are present at the Enrollment visit (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 of acute HIV infection, but whose HIV tests are NEGATIVE, may be re-screened for the study in consultation with the CMC, once appropriate testing has ruled out acute HIV infection.
- Otherwise, eligible participants with an exclusionary laboratory test result can be re-tested **once** during the Screening process, except for HIV and Hepatitis test results indicating exclusion. For Enrollment to proceed, non-exclusionary results from re-testing must be available and the Enrollment visit completed within 30 days from the initial Screening specimen collection date (see Protocol Section 5.1 for further information).
- Participants with clinically significant cardiovascular or liver disease (as per Section 3.2.6 and 3.2.9 of the protocol) cannot enroll and cannot be re-screened for the study.
- Participants with history of seizures cannot enroll.

NOTE: As in SSP Section 3, Table 3-2, any episode of seizure, independent of frequency (e.g. including just one episode) or timeframe (e.g. at any time during participant's life) is exclusionary.

9.3.2 Medical History at Enrollment

If new signs/conditions are identified at Enrollment, these newly identified conditions should be documented on the Medical History e-CRF as needed.

- Document whether each condition is currently ongoing; conditions ongoing at the time of Enrollment are entered on to the Medical History e-CRF. 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 (chronic, but not acute/present currently) at the time of Enrollment and should be entered on to the Medical History e-CRF, 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.
- Pre-existing Depressive Symptoms
- At the enrollment visit, we will be assessing participants for pre-existing depressive symptoms and suicidal ideation using the PHQ-9. A present or past history of depression does NOT exclude enrollment. However, proper management of current symptoms is important and should follow SSP guidance along with local referral for assessment and care. PHQ-9 scoring of depression severity for teens is as follows:

Score	Severity
0-4	None-minimal
5-9	Mild
10-14	Moderate
15-19	Moderately Severe
20-27	Severe

- Any participant scoring 10 or greater should be referred to an on-site clinician for further assessment. In addition, ANY positive response to suicide items (#9, #12, #13) requires same-day clinical assessment.
- Site staff should add the PHQ score to the AE log if the participant scores "mild" and above (e.g., scores 5-27).

9.3.3 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 conditions 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 (Enrollment)
- Was present at baseline (ongoing at Enrollment) BUT 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 AE but has increased in severity grade/frequency

At the participant's follow-up visits, retrieve the complete medical history source document and look up the Medical History e-CRF 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 MAY include reoccurrences of
- conditions/symptoms that were reported at baseline and had resolved at a prior visit (only if the condition has increased in severity grade or frequency since baseline).
- 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 completely resolved since the last visit should have their AE LOG updated with an "Outcome Date".

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 Medical History 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.

9.4 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. A physical exam may be conducted at the discretion of the IoR or designee during an interim visit in response to clinically indicated and/or reported symptoms.

9.4.1 Targeted Physical Exam for Ascertainment of Eligibility

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 084-01 protocol).

9.4.2 Complete Physical Exam at Enrollment

A complete physical exam is required at the Enrollment visit. A full physical will include the following:

- Height (measured each time BMI is calculated)

- Weight (see instructions in Section 9.4.4 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
- Pulmonary
- Abdomen
- Genital exam (if clinically relevant)
- Skin
- Neurological
- Extremities
- Mental status

Any abnormal findings must be documented on the Medical History e-CRF. It is important to grade these pre-existing conditions so that AEs can be reported if the severity or frequency of the pre-existing conditions increases.

- Body mass index (BMI) calculation is not needed at safety visits in Step 2, but since height may change in adolescents during follow-up, height must be measured each time BMI is calculated. Do not use the entry/baseline height measurement for subsequent visits. One of the reasons for this is to determine the appropriate needle size for the injections. A 23-gauge needle is recommended, however, other size gauges between 21-25 may be used. A 1.0 or a 1.5-inch needle is recommended for BMI < 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 for children and teenagers:

  https://www.cdc.gov/healthyweight/bmi/calculator.html.The BMI must be documented in the participant chart. The BMI must be documented in the participant chart.

9.4.3 Targeted Physical Exam at Follow-Up Visits

Targeted physical exams are performed at each follow-up visit. These exams are driven by the signs and symptoms that the participant reports. At a minimum, the participant must be weighed (see instructions in Section 9.4.4 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.

9.4.4 Instructions for Weight Collection

Collecting participants' weight is required as part of all physical exams (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 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 per manufacturer's instructions and 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 recorded at EVERY VISIT.

9.4.5 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 and any AE that leads to a study product hold (temporary or permanent) will be captured on the Adverse Experience (AE) Log e-CRF. For each AE, an assessment must be made by a study clinician of whether the event is related to the study product. Clinicians should review the relevant study product Investigator Brochures and Package Inserts to help make a determination. AEs will be

assessed as specified in the DAIDS Table for Grading Adult and Pediatric Adverse Events, corrected version 2.1, dated July 2017 and Version 2.0, January 2010 of the DAIDS EAE Reporting Manual.

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.

It is important to counsel participants prior to visits requiring lipid profile testing to fast for at least 8 hours prior to the visit. If the participant has not fasted for at least 8 hours, you may proceed with ALL study procedures except for the lipid profile testing. Reschedule the fasting profile within the next seven days or as soon as possible within the visit window. (If a sample cannot be obtained within this timeframe, contact the CMC for guidance on an acceptable timeframe to collect the sample.) 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).

See Section 10 of the SSP for more details regarding the reporting of AEs, as well as the HPTN 084-01 protocol Section 6.

9.4.6 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. Assessment of mental status, including mood, should be made. Any participants reporting depression must be assessed for suicide risk. Any neurologic symptoms should be documented on site-specific source documents (e.g. chart notes), and if Grade 1 or higher, on the AE e-Log as outlined in Section 6 of the protocol. This includes administration of the PHQ-9 e-CRF at Enrollment. Based on clinician's assessment, any symptoms of concern must be submitted to the CMC.

9.4.7 Injection site reaction (ISR) assessment

ISRs are prospectively assessed and captured on the Injection Site Reaction e-Log 1 week post-injection at Weeks 6, 10, 18, 26 and 34. ISR assessments are required at these visits and sites should document that ISR assessments were performed at these visits.

Please note that for data to be consistent across all sites, sites should not telephone participants the day after an injection. Instead, they should only assess any reactions at the visits specified in the Schedule of Evaluations (at Weeks 6, 10, 18, 26 and 34) UNLESS a participant contacts the site with any questions or concerns about an ISR. If a participant contacts the site, then the site may then choose to schedule an interim visit. Any ISR

symptoms noted during the interim visit will be documented on the Injection Site Reaction e-Log.

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. See the last bullet in Section 9.6 of the SSP (below) for instructions to the participant upon leaving the clinic following an injection.

Participants should be instructed to contact the site regarding any ISRs of concern (and they may take a non-identifying picture if they wish and send it to the site or return for an interim/unscheduled visit). **Per the HPTN 084-01 Protocol, Toxicity Management Appendix V, 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 experienced 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 due to 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.

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 the appropriate section of Appendix VI of the HPTN 084-01 protocol, *"Guidance for Injection Site Reactions (**ISRs)"*** prior to discontinuation of Step 2 procedures.

9.4.8 Concomitant medications

Sites must document on the Concomitant Medications Log all medications/preparations (prescription and non-prescription) including alternative/complementary medications/preparations (e.g., herbs, vitamins) taken by study participants within 30 days prior to Enrollment and anytime thereafter during study participation.

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 he/she 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, record any new medications provided to the participant by study staff, and actively ask the participant whether he/she is 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 Log. To help ensure accurate reporting of concomitant medications information, participants should be encouraged to bring all medications to all study visits.

9.4.8.1 Precautionary and Prohibited Medications

In order to avoid AEs caused by drug interactions, whenever a concomitant medication is taken, site staff must review the concomitant medication's and study product's most recent 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 precautionary or prohibited drug listed in the cabotegravir IB, it is required that the HPTN 084-01 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 (as of the time this section of the SSP was written) are listed below.

Cabotegravir:

- 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® or generic (TDF/FTC)*:

- 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)

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

** If sites choose to procure generic TDF/FTC, they must follow the appropriate DAIDS policy (No.: DWD-POL-RA-014.02) to procure it, when such products have not been approved or tentatively approved by the U.S. FDA.*

9.4.8.2 Considerations for Co-Administration of Precautionary and Prohibited Medications

Site physicians must refer to the IB of CAB and Truvada when prescribing concomitant medications and consult the CMC when prescribing medications carrying precautionary status.

- Consult the CMC for instructions when a participant or provider decides it is in the participant's best interest to initiate Post-Exposure Prophylaxis.
- If use of a prohibited medication is needed for treatment of a condition (including but not limited to TB or LTBI), the participant transitions to Step 3 (exits the study if the treatment occurs in Step 1), following that Schedule of Evaluations, then exits the study. Please consult the CMC.

9.5 Transition from Step 1 to Step 2

Step 1, the Oral Run-in Phase, is included in the study to ensure that each participant is able to tolerate cabotegravir and that no participants have a negative reaction which would preclude moving into Step 2, the (active) Injection Phase.

Oral Study Product Adherence
It is critical that participants have taken cumulatively 50% or greater (equivalent to 14/28 days) of their oral study product during Step 1. Adherence must be verified by discussion with the participant and by pill count by site staff at Weeks 2 and 4. If less than 50% of the doses were taken during Step 1, the site IoR (or designee) should contact the CMC at 084-01cmc@hptn.org for further guidance.

Participants should bring their pills to every study visit in Step 1. Staff should attempt to observe participants swallow their study pill at Weeks 2 and 4 visits.

Safety Considerations
Sites must ensure that ALL information/laboratory results are available from all previous visits, including Week 4, and are within permissible limits prior moving into Step 2. In addition, at least one Week 5 HIV test must be negative prior to providing the Week 5 injection.

9.6 Injection Administration Instruction

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.

An instructional video for administering IM injections in the gluteal muscle can be found on https://www.hptn.org/research/studies/084-01. This video is provided as an example only. Sites should use their clinical judgement and be guided by participant preference regarding which approach (ventrogluteal or dorsogluteal locations) 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. Document in the participant's file.
- Prior to administering the injection, and as part of the targeted physical exam, assess whether the participant has had a buttock implant or fillers since previous visit. If implant/filler is present, do not administer injection. Inform the CMC.
- 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 should be calculated at each injection visit. If a participant experiences 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 study product 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, paracetamol, 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.

9.7 Schedule of Injections

The injection schedule is included in the Appendix II SOE tables. The initial injection is scheduled for Week 5 of the study. A loading dose is scheduled four weeks later, at Week 9. Subsequent injections will be given every eight weeks for the duration of Step 2. In general, attempt to perform the injection as close to the target date as possible.

9.7.1 Week 5 Visit Window Considerations

The target day for the Week 5 Visit is Day 35, with an allowance of + 3 days. Should this window be violated, contact the CMC for advice. The date of the first injection (Week 5) re-sets the visit schedule from that point forward (i.e. Week 6 will always be one week after Week 5 - even if Week 5 is a Week early or late).

9.7.2 Injection Visit Window Considerations

Timeliness of injections and adherence to visit windows must be carefully explained to participants. If participants present to the clinic outside of the visit windows (see Section 13 of this SSP for visit windows), contact the CMC for guidance. Injections may never be given with less than three weeks between them.

9.7.3 Missed or Late Injections

First, CONTACT THE CMC.

Visit windows are contiguous. The following principles will be considered when advising sites on how to address missed injection visits.

- The interval between injections: Injections should ideally not be closer than 3 weeks apart. Longer delays between injections may require participants to be re-loaded.
- The visit schedule: The team should attempt to get the participant back onto their visit schedule; this may require the use of interim visits.
- The availability of safety assessments: Prior to injection, a recent set of safety bloods should be available to confirm that it is safe to administer injections. At a minimum, HIV testing should be performed.

In general, if it has been >15 weeks since a participant's prior CAB LA injection, a reload of CAB LA injections (two injections, 4 weeks apart) will take place. The participant will then continue Step 2 or transition to Step 3 four weeks later. Contact the CMC for guidance regarding all reloading cases.

The site must consult the CMC regarding possible re-loading of the participant with delayed or missed visits.

9.8 Specimen Collection

Blood and urine will be collected throughout the study. The protocol outlines the clinical procedures and corresponding testing to be performed according to Section 5.0 of the HPTN 084-01 protocol. 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 Screening, GC/CT testing will be performed using urine or vaginal swabs. (See Section 11 of this manual for further information.)
- At visits where a fasting lipid profile will be taken, participants should be fasting for at least 8 (preferably 12) hours before sample collection. Additional details are provided in Section 9.4.5 (above).
- 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 modified Schwartz equation. The formula is in Section 11.3.4, "Creatinine Clearance", of the SSP (Laboratory and Specimen Management Procedures Section). Continue using the Schwartz equation for participants even after they turn 18.

9.9 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 084-01 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, and representatives from the HPTN LOC, HPTN LC, and the HPTN SDMC. The CMC has a primary responder who is "on call" and is responsible for soliciting input and initially responding to site queries within a 24-hour time period.

Sites that plan to conduct visits during off hours (nights or weekends) should notify the CMC and their local laboratories in advance so that a responder will be available, and samples will be able to receive and processed within protocol requirements.

Sites should be mindful that throughout the HPTN 084-01 protocol and associated protocol appendices, as well as the SSP manual, are examples of situations and AEs that require consultation with the CMC.

Queries from sites are submitted to the following email alias list: 084-01CMC@hptn.org.

Queries must be formatted to include the information outlined below.

- Include "084-01 CMC: [Insert PTID] – [One-line summary of query – for example – "Elevated ALT Grade 3" 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: 084-01 CMC: Participant 103-000011 – Elevated ALT Grade 3

Body of email:

Site name and number: Site 103 – Prevention Clinic

Person submitting query: Felicity Bones, Study Coordinator

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

Query Type: Initial submission

Reason for query: 16 year old participant week 2 on oral study medication found to have Grade 4 CK elevation after rigorous exercise regimen 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, Rifampin, PZA, Ethambutol

Denies alcohol, other recreational drug use.

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

	AST	ALT	CK	creatinine
Reference Ranges*	10-40 U/L	9-46 U/L	21-215 U/L	0.60-1.35 mg/dL
4/16/17 W2	812 (G4 25xULN)	225 (G3 7xULN)	7100 (G4 20x ULN)	0.97
3/23/20 Entry W0	15	15	43	0.97
3/19/20 screen	16	15	49	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. Keeping this documentation will help explain to monitors why the site followed a particular course of action.

9.10 Toxicity and Clinical Management

Sites should regularly consult the HPTN 084-01 protocol Appendix VI – 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 VI of the Protocol refers to several instances where the CMC must be contacted in the case of AE management and grading. ForAEs that require CMC consultation, the CMC should be notified as soon as possible after site awareness, ideally within 3 business days.

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.

9.10.1 Liver toxicities/ damage

In addition to the diagrams at the end of this SSP section, sites should consider and investigate any potential causes leading to liver damage. In the event of permanent discontinuation for liver criteria, the site should run the following tests:

- Hep A IgM
- Hep B sAg; Hep B cAb
- Hep C RNA
- Hep E IgM
- CMV IgM
- EBV IgM
- RPR and syphilis screening
- Tox screen
- ANA; a-smooth muscle Ab; type - anti-liver kidney microsomal Ab, total IgG

- APAP (acetaminophen) level of reported use
- Review of any herbal meds and supplement use

9.11 HIV Considerations During Study Conduct

At all follow-up visits (including safety visits during Step 2), HIV test results from previous visits and at least one HIV test result, inclusive of HIV viral load RNA testing, from the current visit must be available and reviewed by designated staff. All HIV test results must be confirmed to be negative/non-reactive prior to study product administration.

Positive/Reactive HIV Test

If a participant has a reactive or positive HIV test, product will be held. Further testing for confirmation of HIV infection will be done per Appendix IV of the Protocol. Procedures for participants who have a reactive or positive HIV test during follow-up are described in Section 5.11 of the Protocol. **Notify the CMC** before confirming HIV infection**.**

Confirmed Seroconversions

Further considerations for participants that have confirmed HIV-infection during each study Step include:

Step 1: Conduct an in-clinic interim visit to –

- Permanently discontinue oral study drug
- Retrieve and quarantine remaining study drug
- Provide post-test counselling for the participant
- Discuss disclosure to the consenting adult, if appropriate
- Facilitate timely access to HIV care and treatment per site-specific SOPs Terminate the ppt from the study, once access to HIV care is confirmed

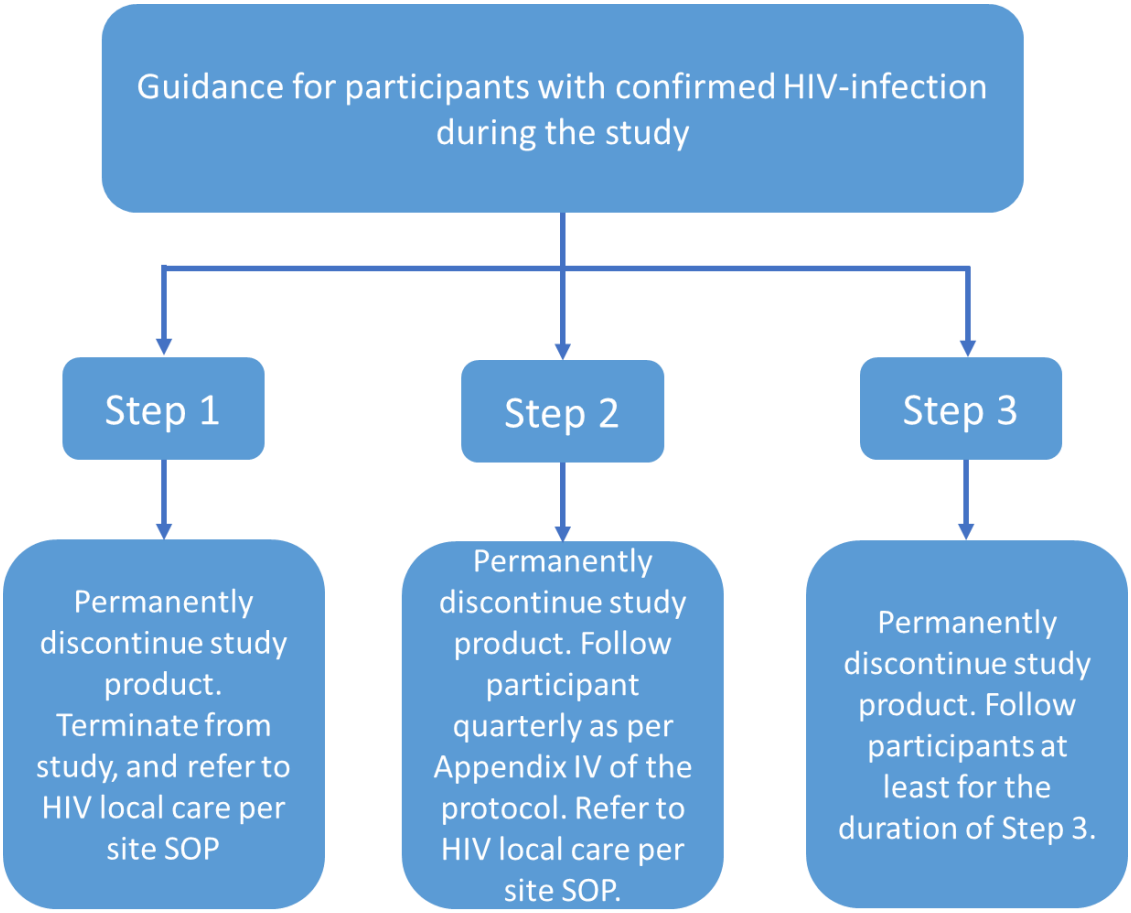
Step 2: Conduct an in-clinic interim visit to –

- Permanently discontinue injectable study drug
- Provide post-test counselling for the participant
- Discuss disclosure to the consenting adult, if appropriate
- Facilitate timely access to HIV care and treatment per site-specific SOPs
- Transition to Step 3 for 48 weeks of observational follow-up
    - Complete the procedures from both Appendix III and IV

Step 3: Conduct an in-clinic interim visit to –

- Permanently discontinue open label oral PrEP
- Provide post-test counselling for the participant
- Discuss disclosure to the consenting adult, if appropriate
- Facilitate timely access to HIV care and treatment per site-specific SOPs
- Complete follow-up in Step 3
- Complete the procedures from both Appendix III and IV

Please refer to the diagram below for a visual of how to proceed with participants confirmed to be HIV infected during each Step of the study.



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, in Section 9.3.1.

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.

9.12 Sexually Transmitted Infections (STIs)

Section 5.12 of the HPTN 084-01 protocol and Section 11 of the SSP should be followed for procedures regarding testing for GC/CT and syphilis. As noted in the HPTN 084-01

protocol, treatment for STIs will be provided per local guidelines (and may include referral for treatment).

Symptomatic or other screening for STIs beyond what is required by the protocol can be done at a site's discretion and cost. Costs associated may come out of each site's respective per participant study reimbursements.

9.12.1 Hepatitis B and Hepatitis C

Section 5.13 of the HPTN 084-01 protocol and Section 11 of the SSP should be followed for procedures regarding Hepatitis B and Hepatitis C testing.

Of note, persons with a positive HBsAg test and/or a positive HCV antibody test will be excluded from the study. If the HBsAg test is positive, then the hepatitis B virus is present in the blood. This means that the participant has either an acute or chronic hepatitis B infection. Participants who do not have evidence of immunity to HBV will be provided HBV vaccination.

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 084-01, 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).**

9.13 Tuberculosis

As noted above in Section 9.4.8.1, rifampicin, rifapentine and rifabutin are contraindicated to concurrent use with cabotegravir. If TB treatment is required and rifampicin, rifapentine or rifabutin use is planned, CAB oral and/or injections (study product) must be permanently discontinued. In Step 1, the participant will terminate the study. In Step 2, the participant will transition to Step 3 for follow-up on open label oral PrEP.

9.14 Pregnancy

If a pregnancy test is positive **DO NOT OFFER** the study product at that visit (injections or pills).

9.14.1 Required Confirmatory Testing for Pregnancy

All participants who test positive for pregnancy (blood or urine or reported by the participant between study visits) will be administered open label TDF/FTC for four weeks (until a confirmatory test takes place) and have their oral CAB or CAB LA injections withheld, depending on their current Step of the study. Refer to protocol section 5.15, protocol Appendix V, and inform the CMC within 7 days of awareness.

9.14.2 Unconfirmed Pregnancies (I.E. only one positive pregnancy test)

If pregnancy is not confirmed on subsequent testing, Step 1 participants will exit the study, per protocol Section 5.15. Site staff will refer to their SOP for detailed management. If in Steps 2 or 3, participants with pregnancies not confirmed (pregnancy testing negative) 4 weeks after an initial positive pregnancy test may resume study medications in consultation with the CMC (I.E., this will be decided on a case-by-case basis.)

9.14.3 Confirmed Pregnancies

All (confirmed) pregnant participants will be placed on open-label TDF/FTC for the duration of the pregnancy. No participant with a positive pregnancy test will be administered CAB or CAB LA.

Participants with confirmed pregnancy after four weeks in Step 1 will permanently discontinue oral CAB, will be referred for care, will skip Step 2, and their visit schedule will change to being seen on the study only once every 12 weeks during the pregnancy (see protocol Appendix V).

Participants with confirmed pregnancy after four weeks in Step 2 will discontinue CAB LA and move to quarterly procedures, as seen in protocol Appendix V. Participants with confirmed pregnancy after four weeks in Step 3 will switch to the Schedule of Evaluations in protocol Appendix V, as well. Site staff will refer to their SOP for detailed management.

All participants who are confirmed pregnant must be referred for an Ultrasound and evaluation by an obstetric specialist at about 12-14 weeks gestational age, for other testing, counseling, and management. Further biochemical blood tests may be done as indicated. The preceding services will be covered by the study. All findings and pregnancy outcomes will be collected and reported. The site IoR or designee will refer pregnant participants to all applicable pregnancy-related services and will provide a letter to obstetric services detailing participation in the trial; however, sites will not be responsible for paying for pregnancy-related care. The site IoR or designee will counsel any participants who become pregnant regarding possible risks to the fetus according to site-specific SOPs.

Participants with confirmed pregnancies may still have the option to join the HPTN 084 OLE. Please contact the HPTN 084-01 CMC in the case of participants who are pregnant, but want to remain on injections by transitioning to HPTN 084 OLE.

9.14.4 Completed Pregnancies - Post Pregnancy/Breastfeeding

Participants who become pregnant during the study will not resume study product (CAB), but will be followed for 48 weeks post-last injection. All pregnancy outcomes will be reported on relevant CRFs. Outcomes meeting criteria for expedited AE (EAE) reporting also will be reported.

9.15 Enrollment violations

When an enrollment violation is discovered, the Protocol Chairs, DAIDS Medical Officer and Statistician must be in agreement to let the participant continue in the study. A

regulatory note to file will be written, signed by all three parties, filed in the site's regulatory files and submitted to DAIDS/RAB by the LOC, and to applicable local regulatory authorities by applicable site staff.

Appendix 9a: HIV testing log template for positive or indeterminate results

The subject line of the email: 084-01 CMC: Participant 333-333-33333 – Positive HIV RNA PCR test

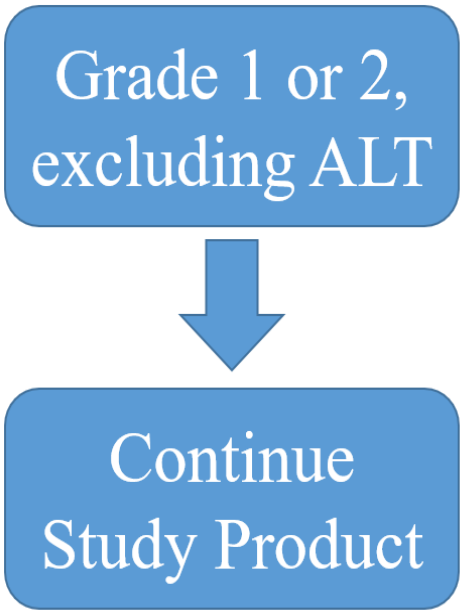
Body of email:

Site name and number:	Nowhere CRS	31033
The person submitting the query:	Zeb McGillicuty	
PTID	333-33333-3	
Study Step:	Step 2	
Study Week:	Week 33	Visit code: XX
Date of Visit:	31-OCT-2020	
Date of Last CAB-LA injection:	N/A - on open label PrEP	
Contraception method in use:	XX (or 'Currently pregnant with EGA XX/40')	
Query Type:	Initial Query	
Reason for query:	(1) CMC notification of positive HIV RNA PCR test (2) Study product action (3) Site plan for confirmatory HIV testing	
A 16-year-old participant's HIV RNA PCR test for week 33 was reactive. The result was released to the site today. She reported flu-like symptoms 3 weeks prior to the week 33 visit. She denies having unprotected sex in the past month. The pregnancy test was negative and the rapid HIV test was not reactive at the week 33 visit. We called the participant to schedule her to come next week for HIV confirmatory testing per Appendix V. Please advise if our plan is in order.		

PTID:		Person Submitting the results		
HIV Test	Week 33 October 31, 2020	Confirmatory Visit DATE TBA	Post Product-Hold Visit	Comments
HIV Rapid Test (1)	Unigold-rapid UNREACTIVE			
HIV Rapid Test (2)	NA			
HIV ELISA 4th Gen				
HIV Discriminatory Test (Geenius)				
HIV RNA Test	POSITIVE			
HIV DNA Test				
CD4				
DBS				
Plasma storage				
HIV resistance testing				

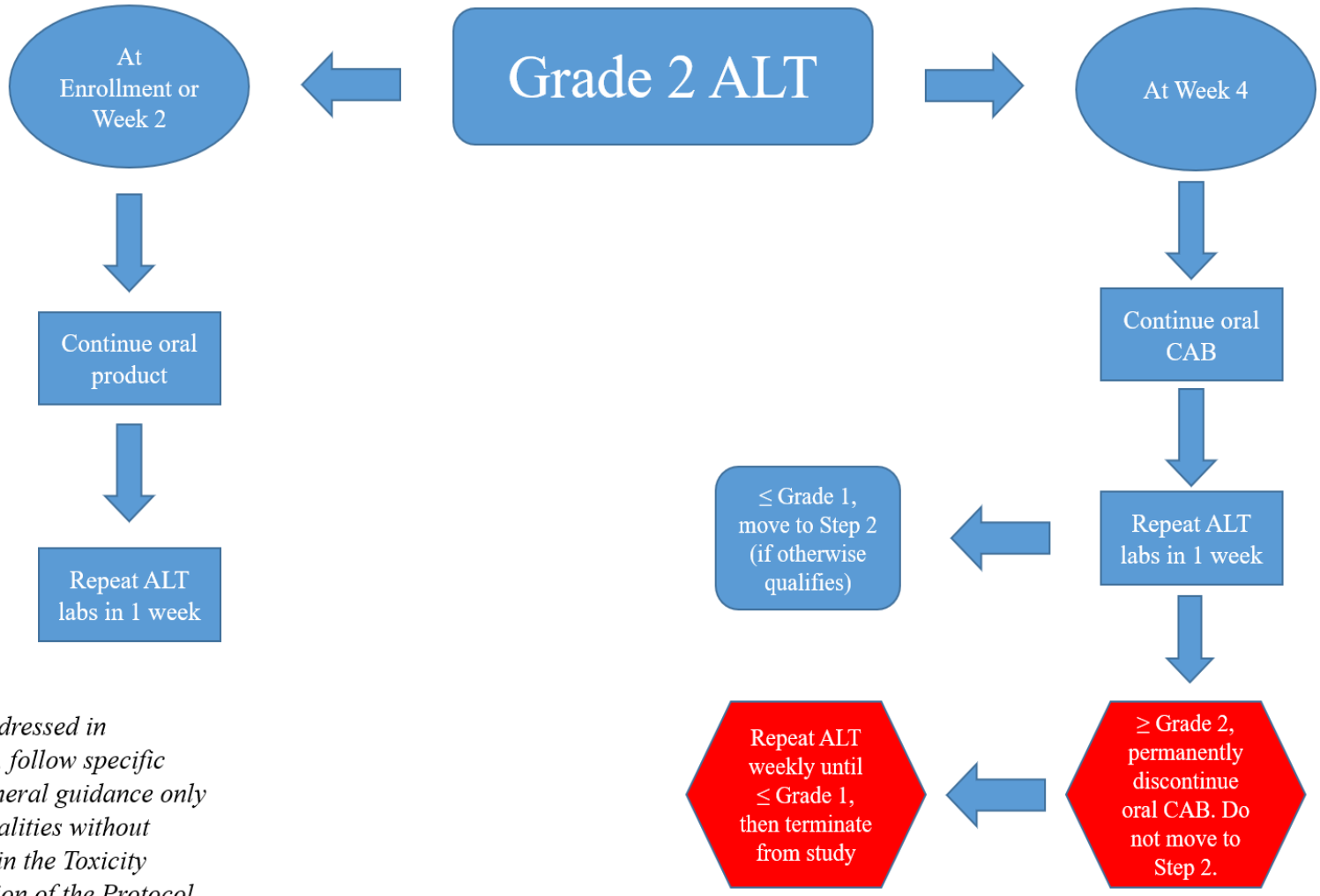
Appendix 9b: Toxicity Management Diagrams

General Guidance* - Step 1

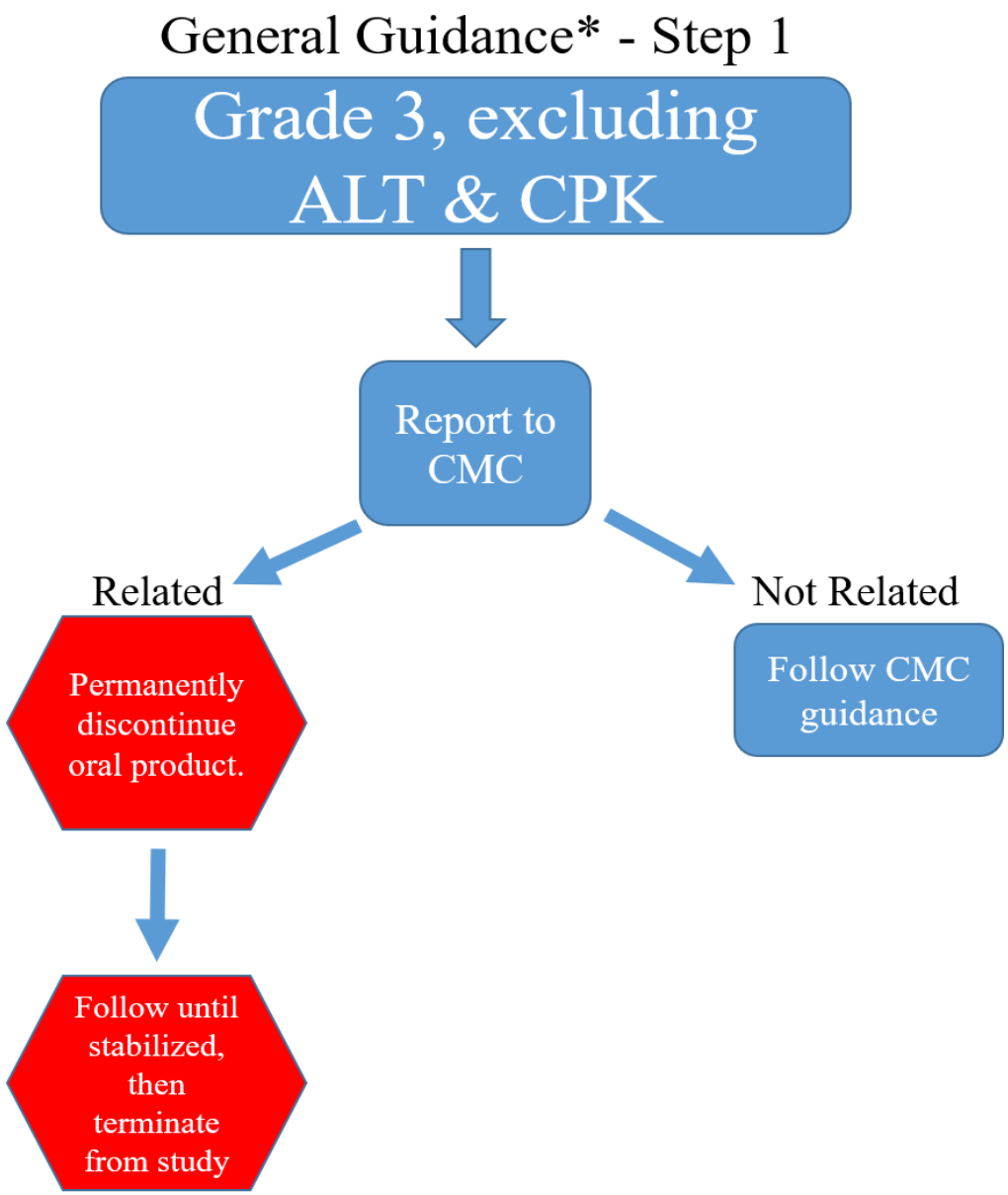


*If condition is addressed in Appendix V tables, follow specific guidance. This general guidance only applies to abnormalities without specific guidance in the Toxicity Management Section of the Protocol.

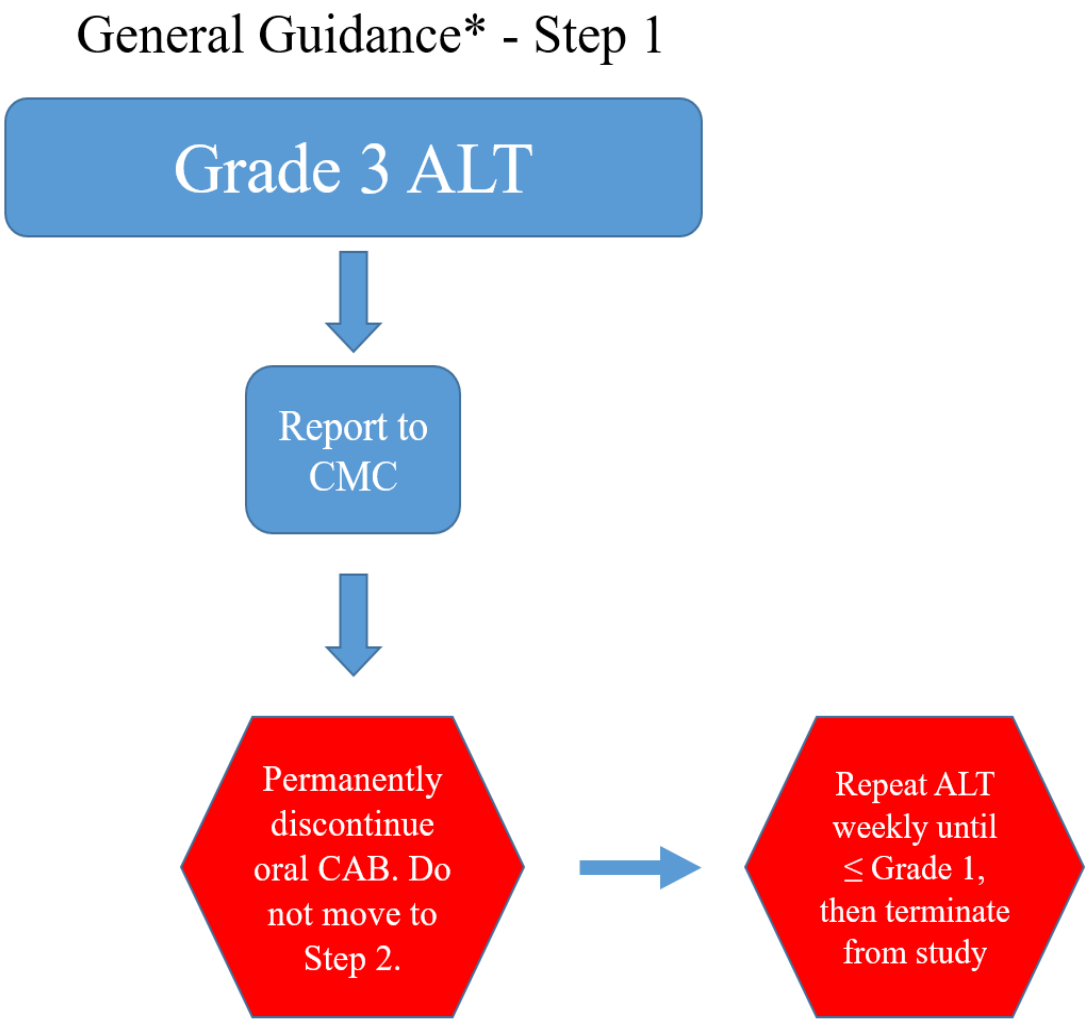
General Guidance* - Step 1



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



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



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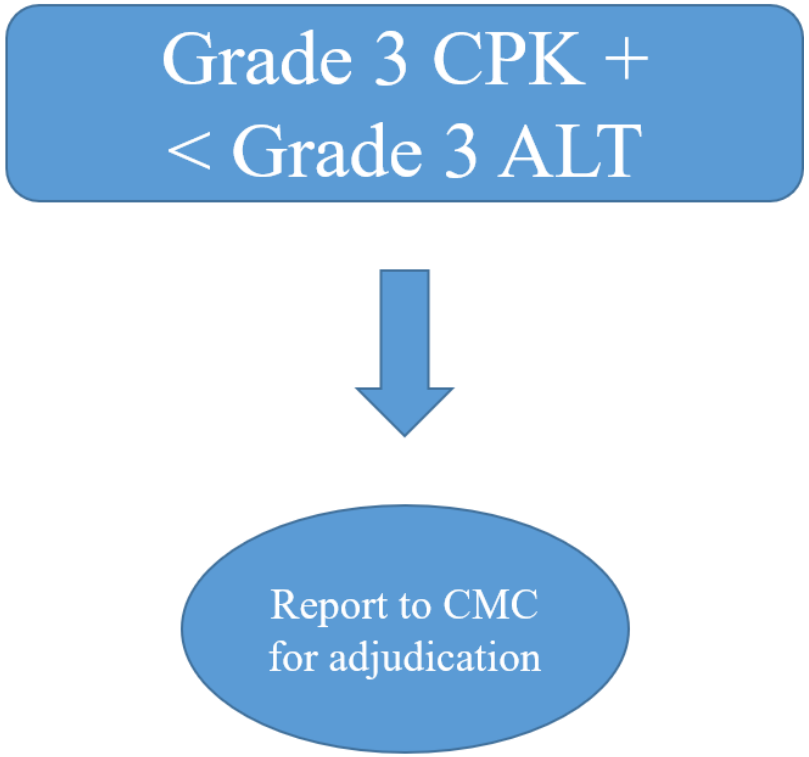
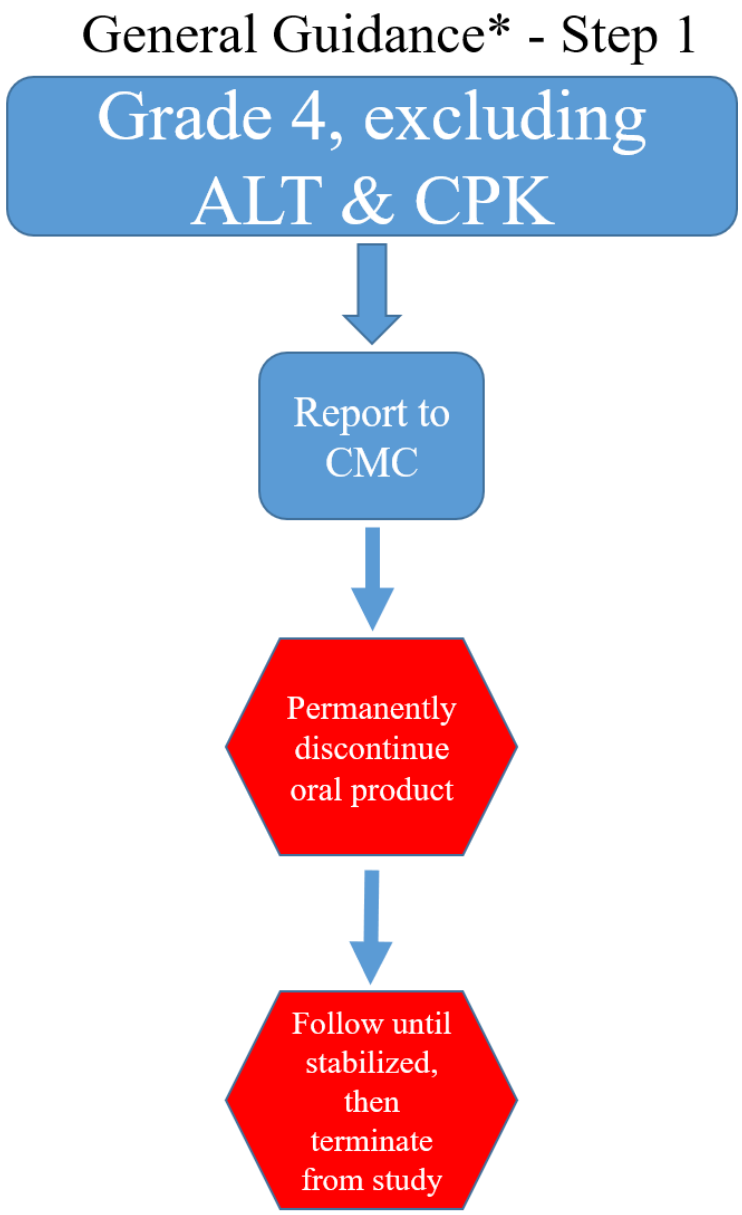
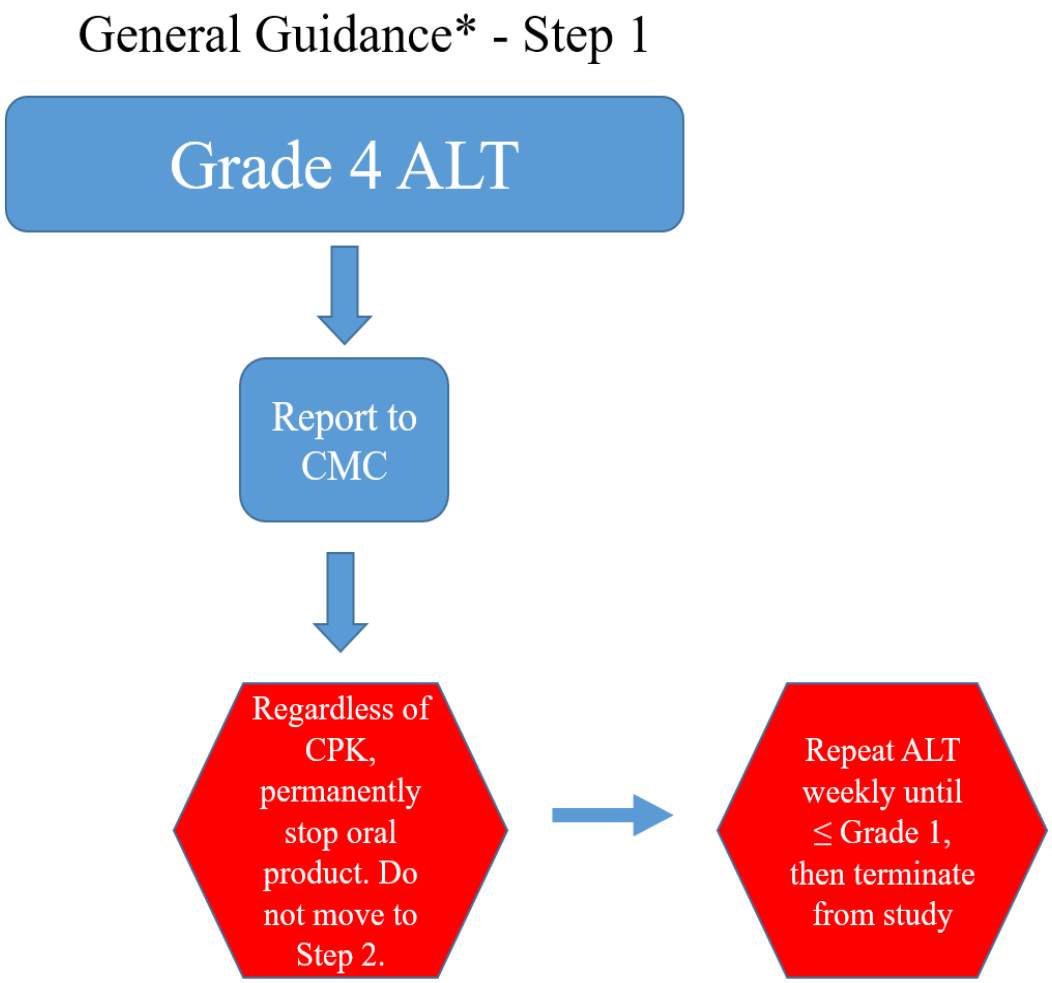
General Guidance* - Step 1



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



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



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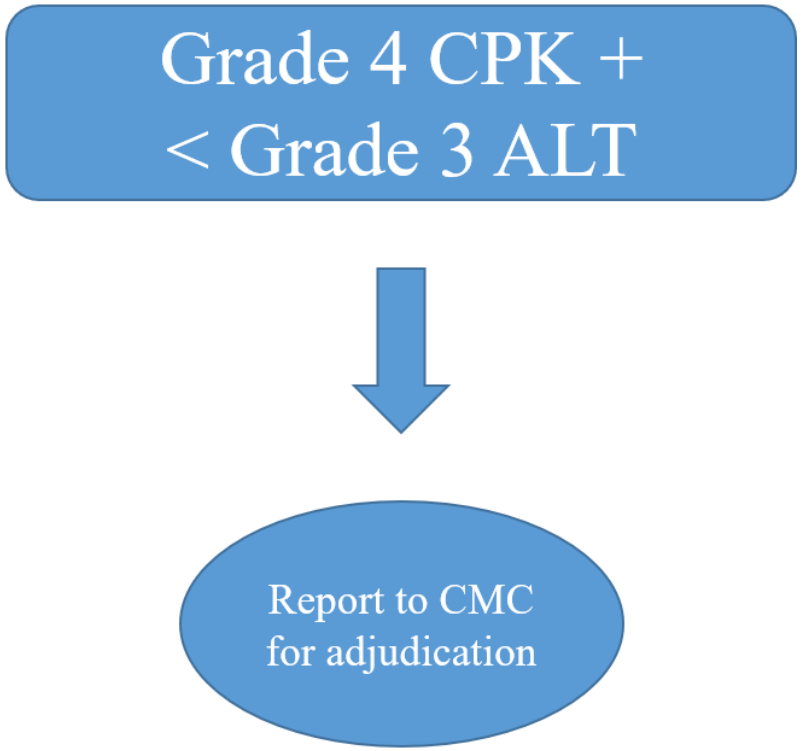
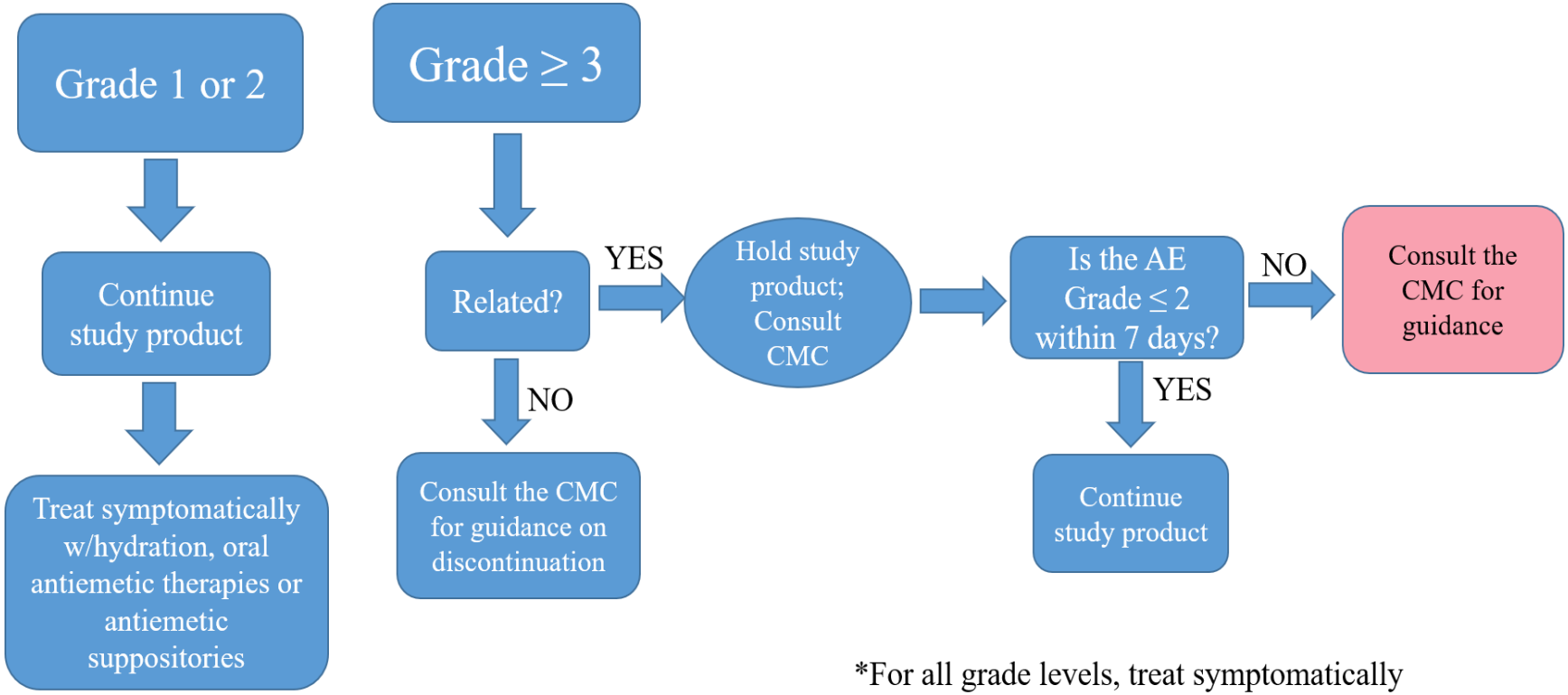
General Guidance* - Step 1



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

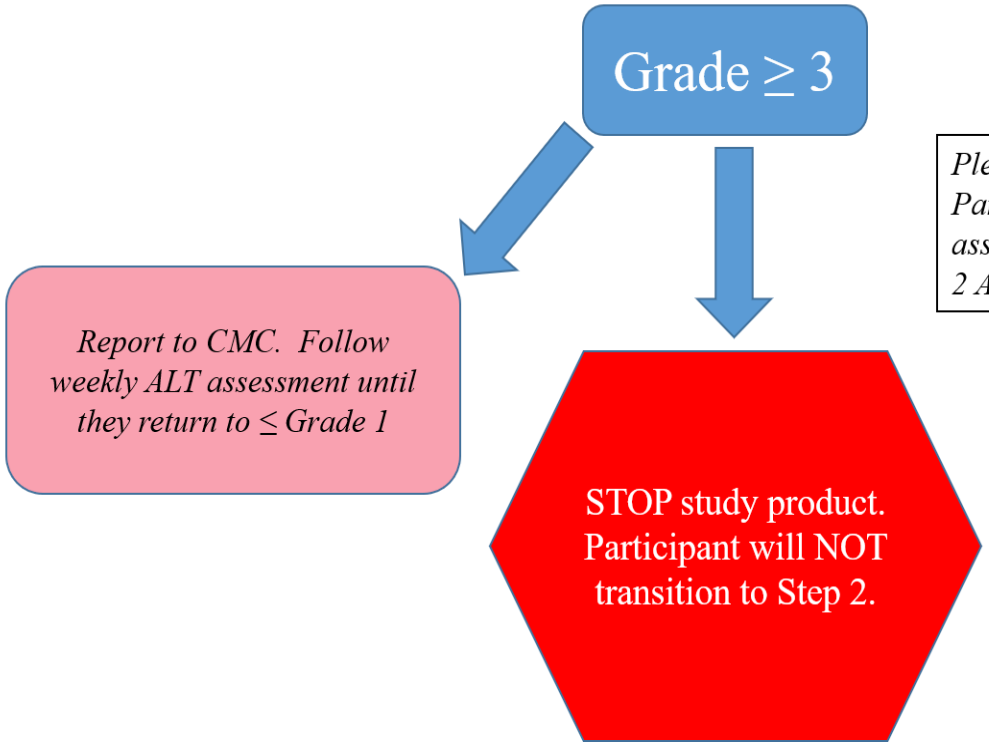
Specified Toxicities

Nausea, Vomiting, and Diarrhea*



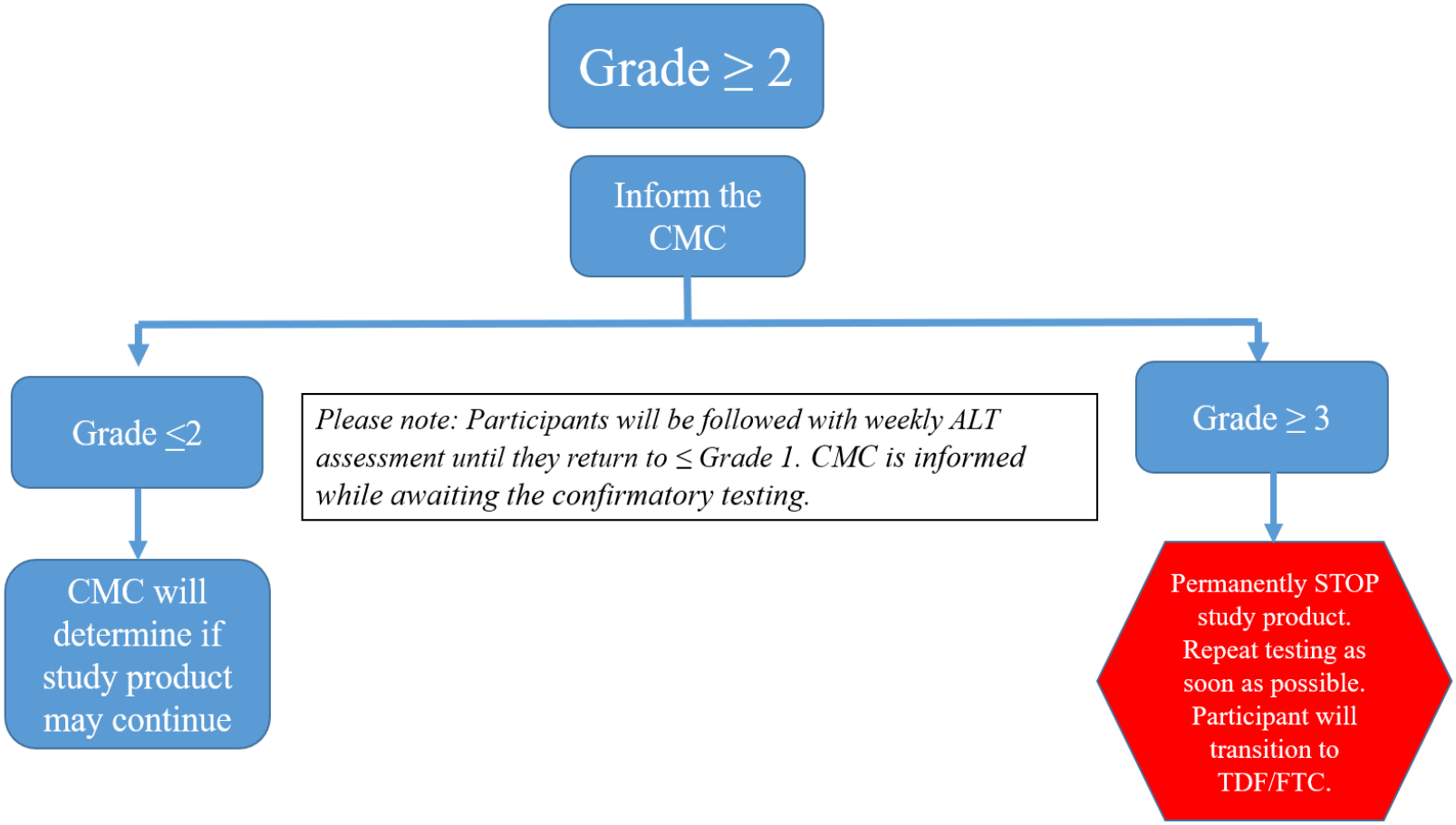
*For all grade levels, treat symptomatically

Specified Toxicities
ALT
Oral Phase (Step 1)



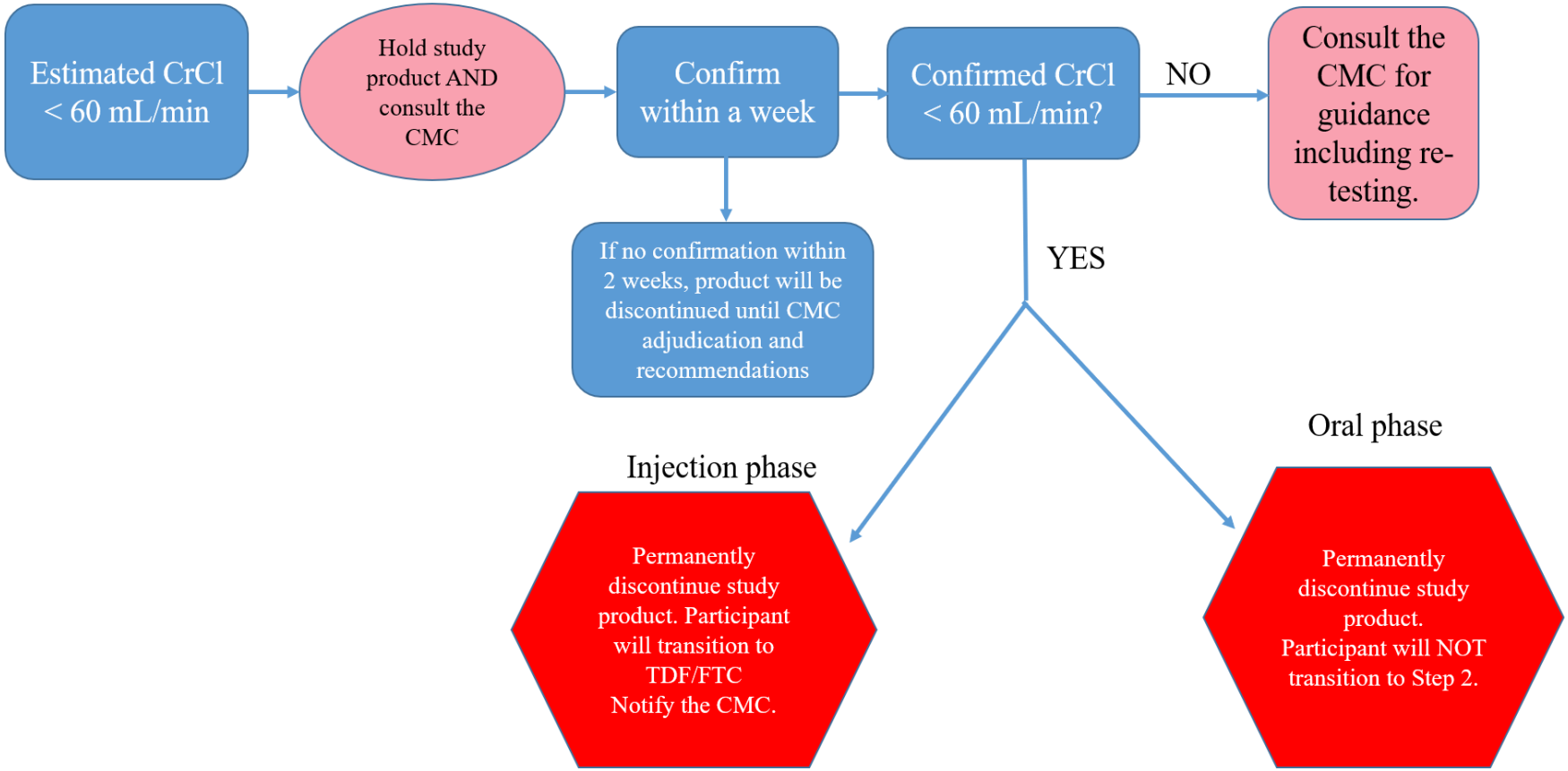
Please note: All cases should be reported to the CMC. Participants will be followed with weekly ALT assessment until they return to ≤ Grade 1. (For Grade 2 ALT in Step 1, see slide 2.)

Specified Toxicities
ALT
Injection Phase (Step 2)



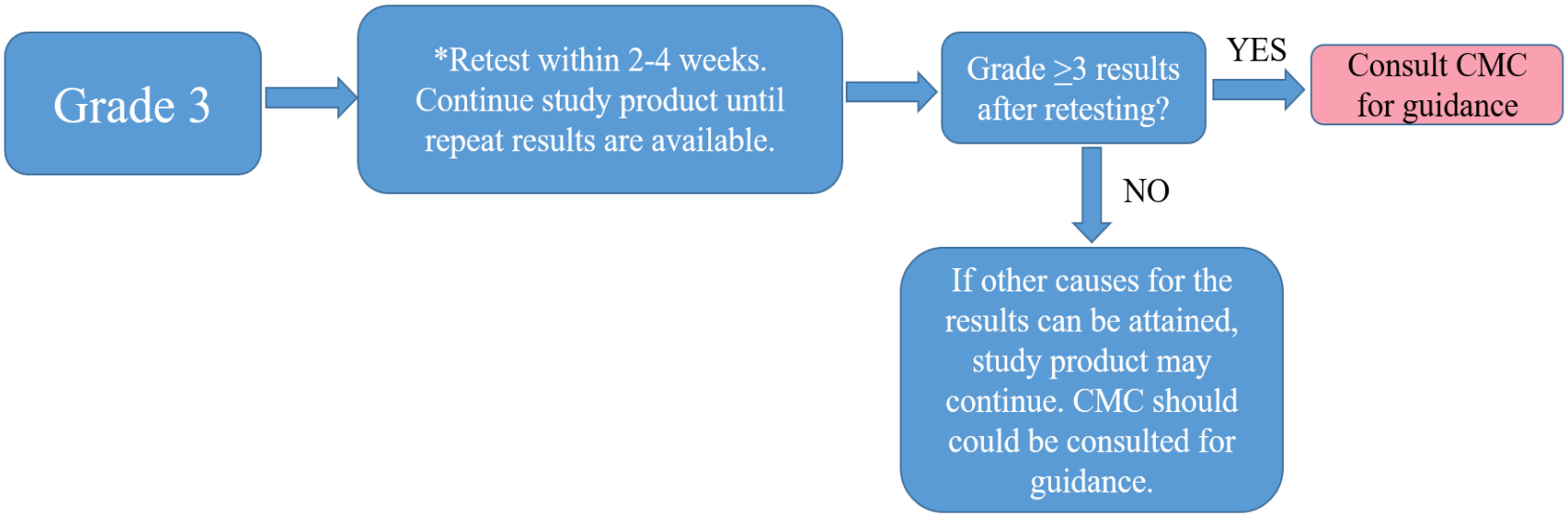
Specified Toxicities

Creatinine Clearance



Specified Toxicities

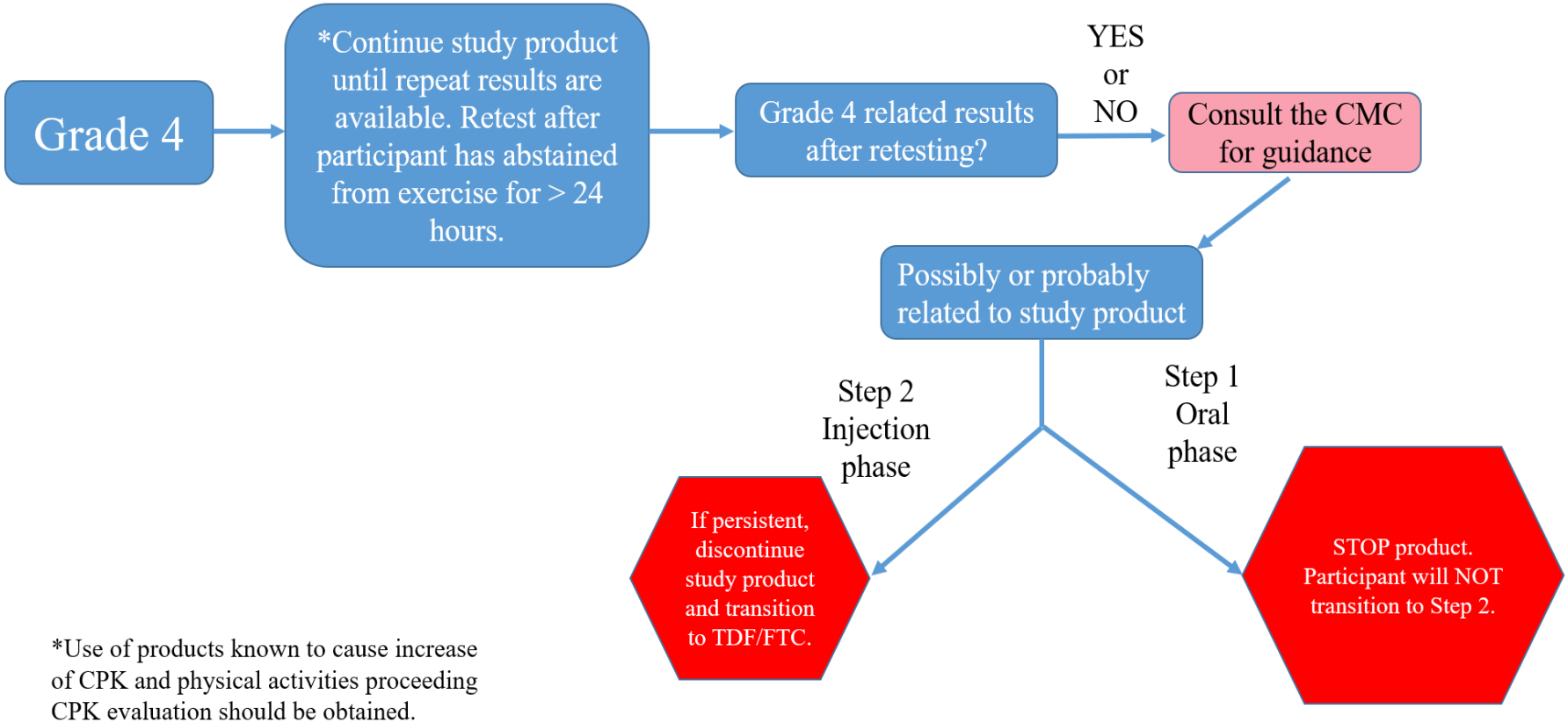
Creatinine Phosphokinase (CK or CPK)



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

Specified Toxicities

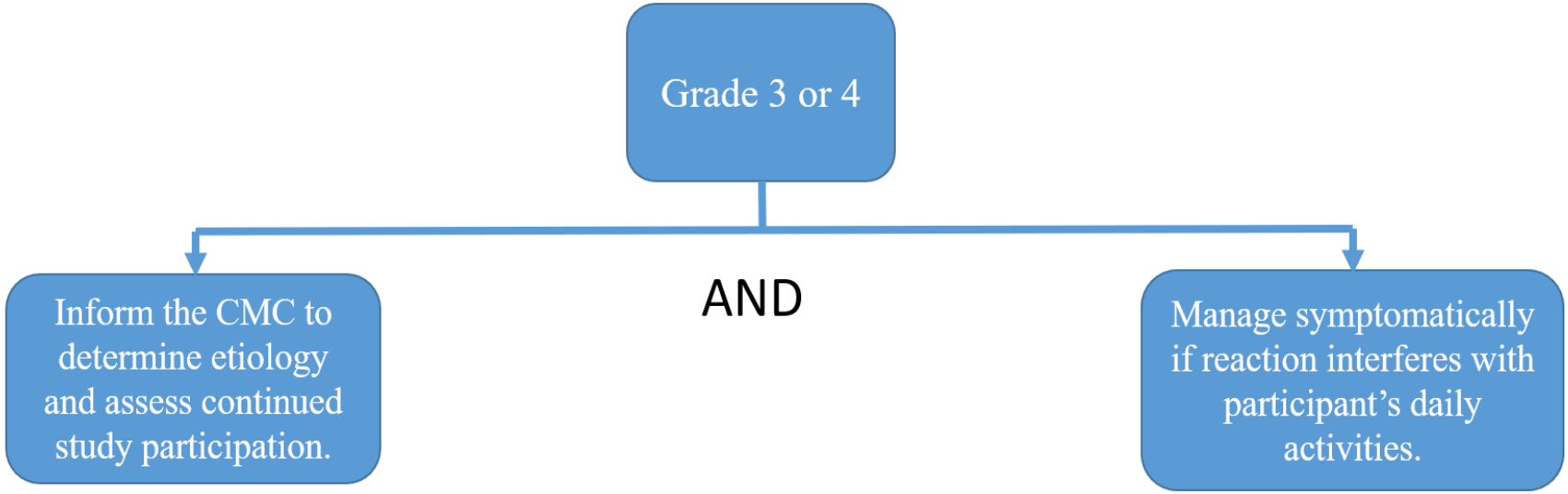
Creatinine Phosphokinase (CK or CPK)



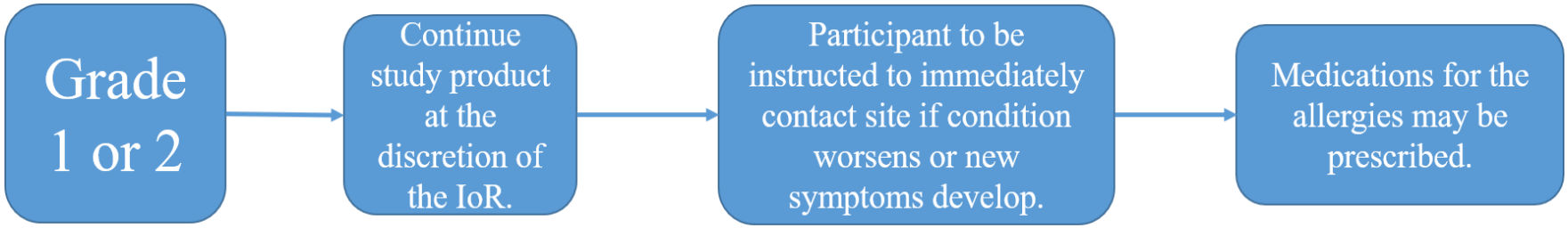
*Use of products known to cause increase of CPK and physical activities proceeding CPK evaluation should be obtained.

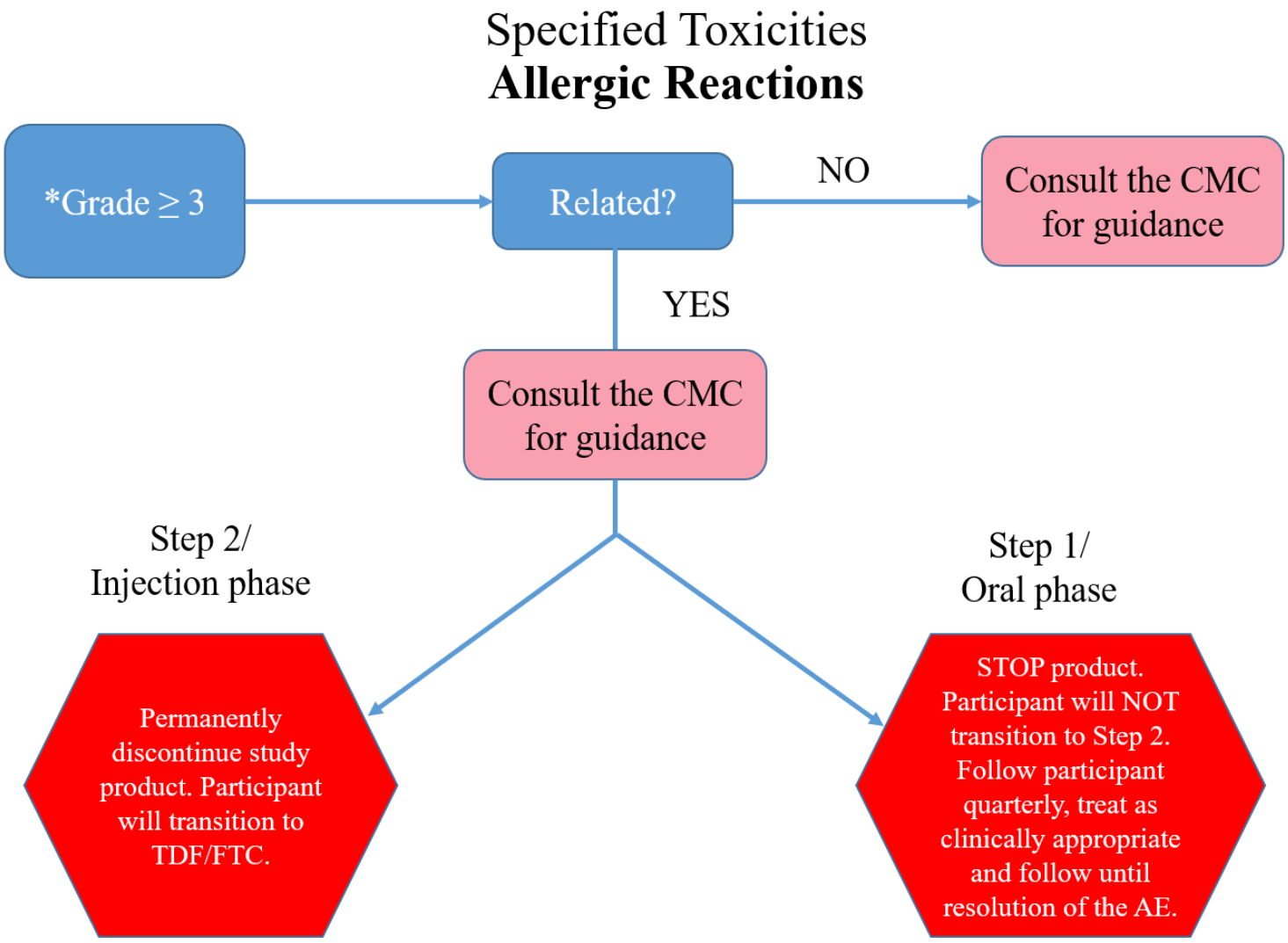
Specified Toxicities

Injection Site Reactions (ISRs)



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 instructed to return all study products as soon as possible.
- For management of participants with AEs in Step 2, see Appendix VI (Toxicity Management).
- Always consult Appendix VI 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 should be informed.