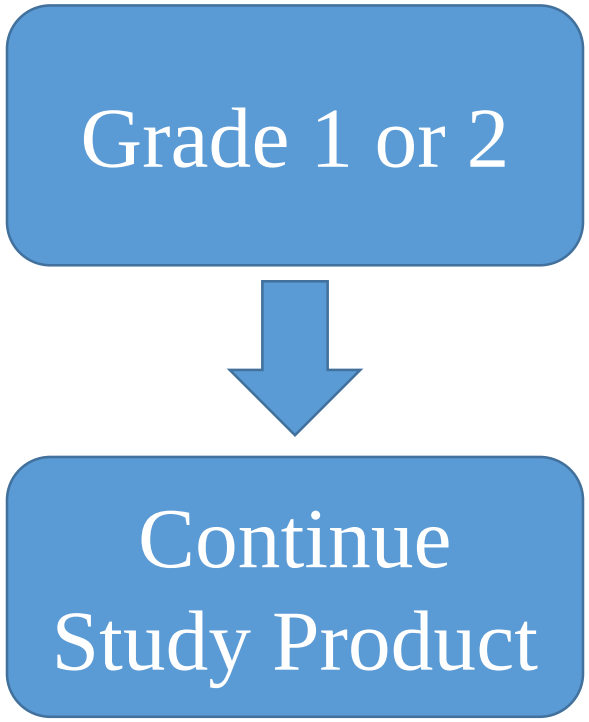
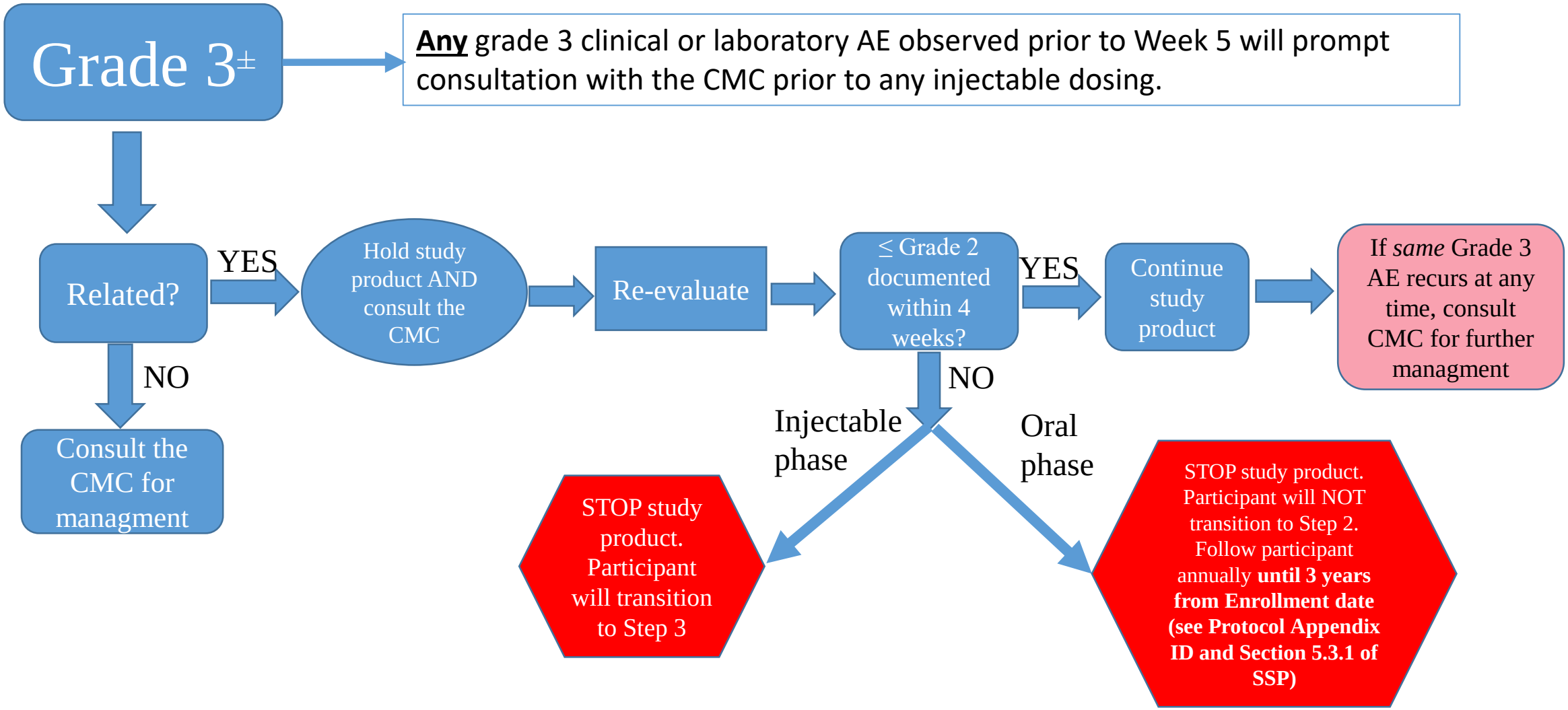
General Guidance*



*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.

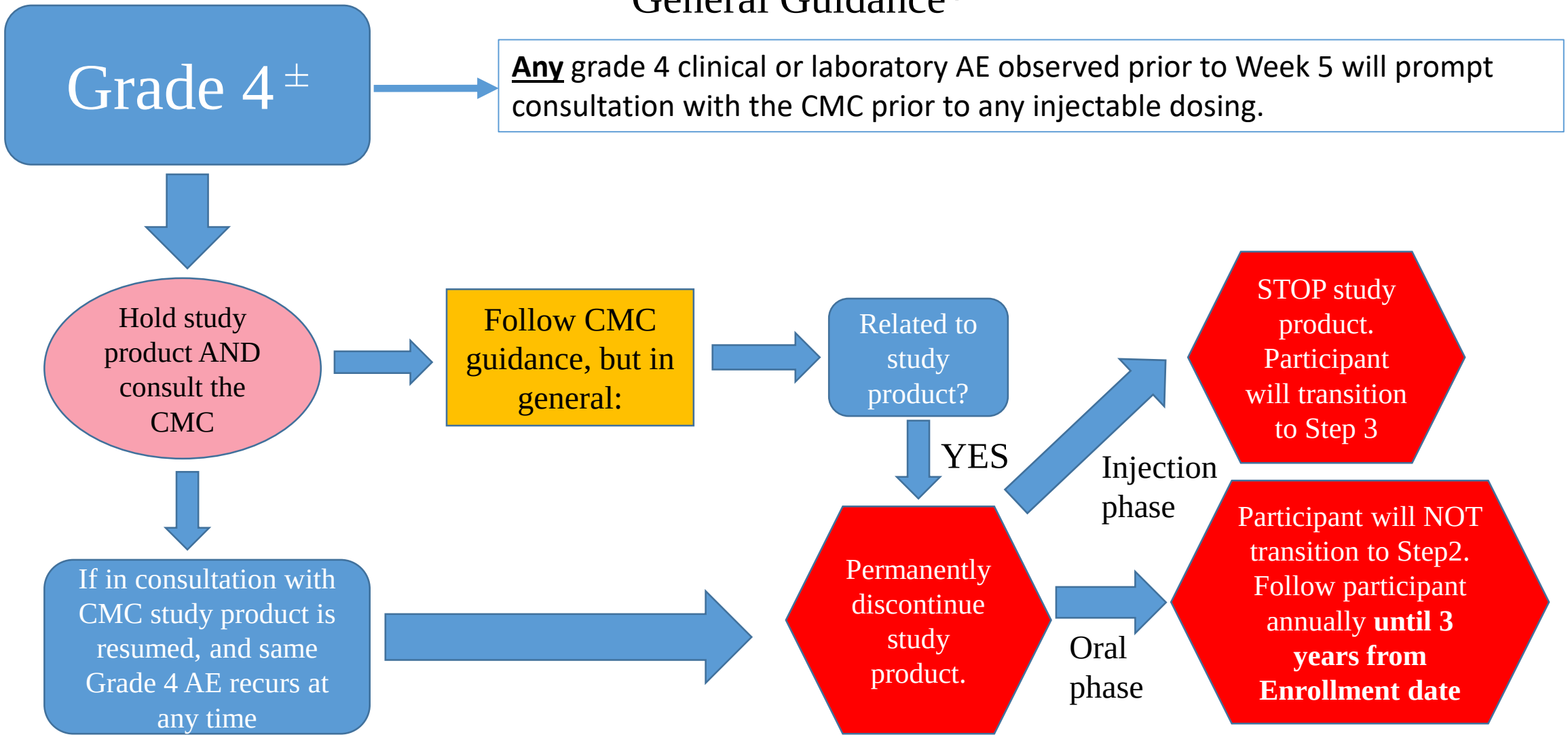
General Guidance*



*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

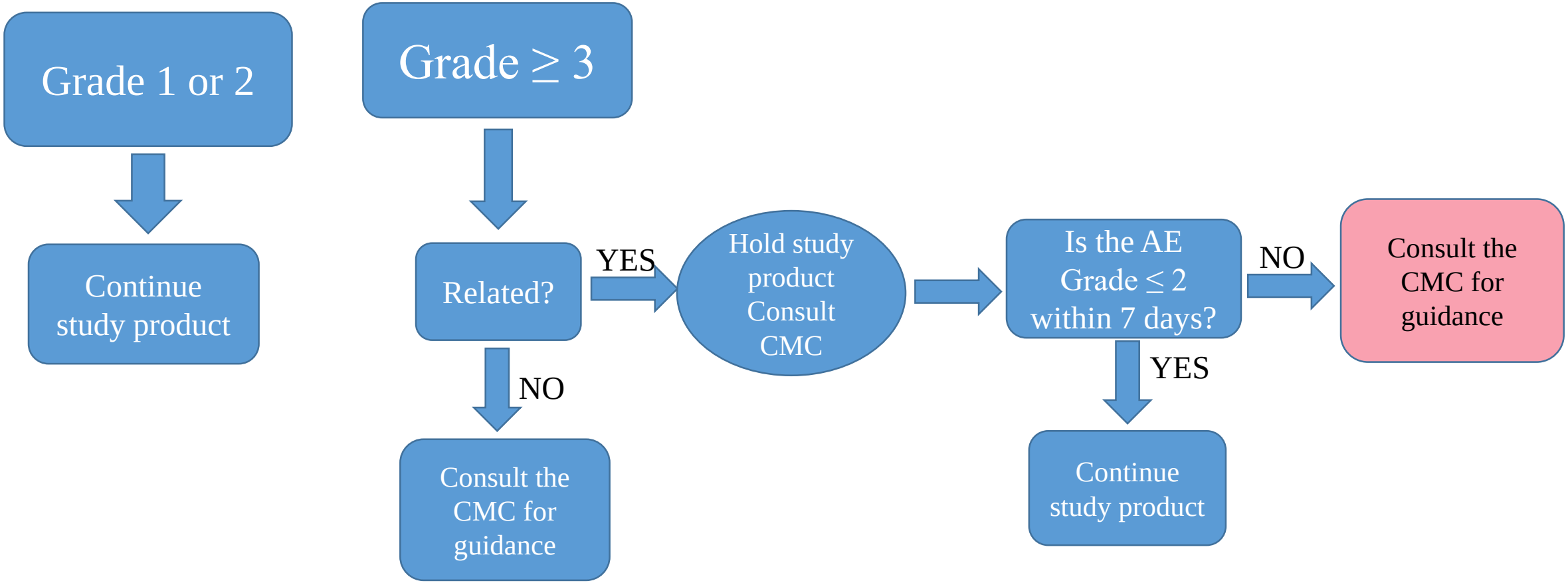
General Guidance*



*If condition is addressed on Appendix III tables, follow specific guidance

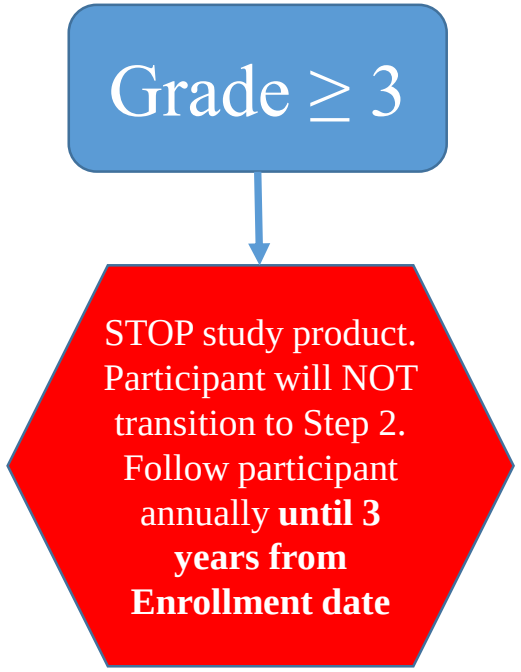
± At Week 0 (study enrollment), consult the CMC for guidance regarding follow up and ongoing study product administration

Specified Toxicities
Nausea, Vomiting, and Diarrhea*



*For all grade levels, treat symptomatically

Specified Toxicities
ALT
Oral Phase (Step 1)

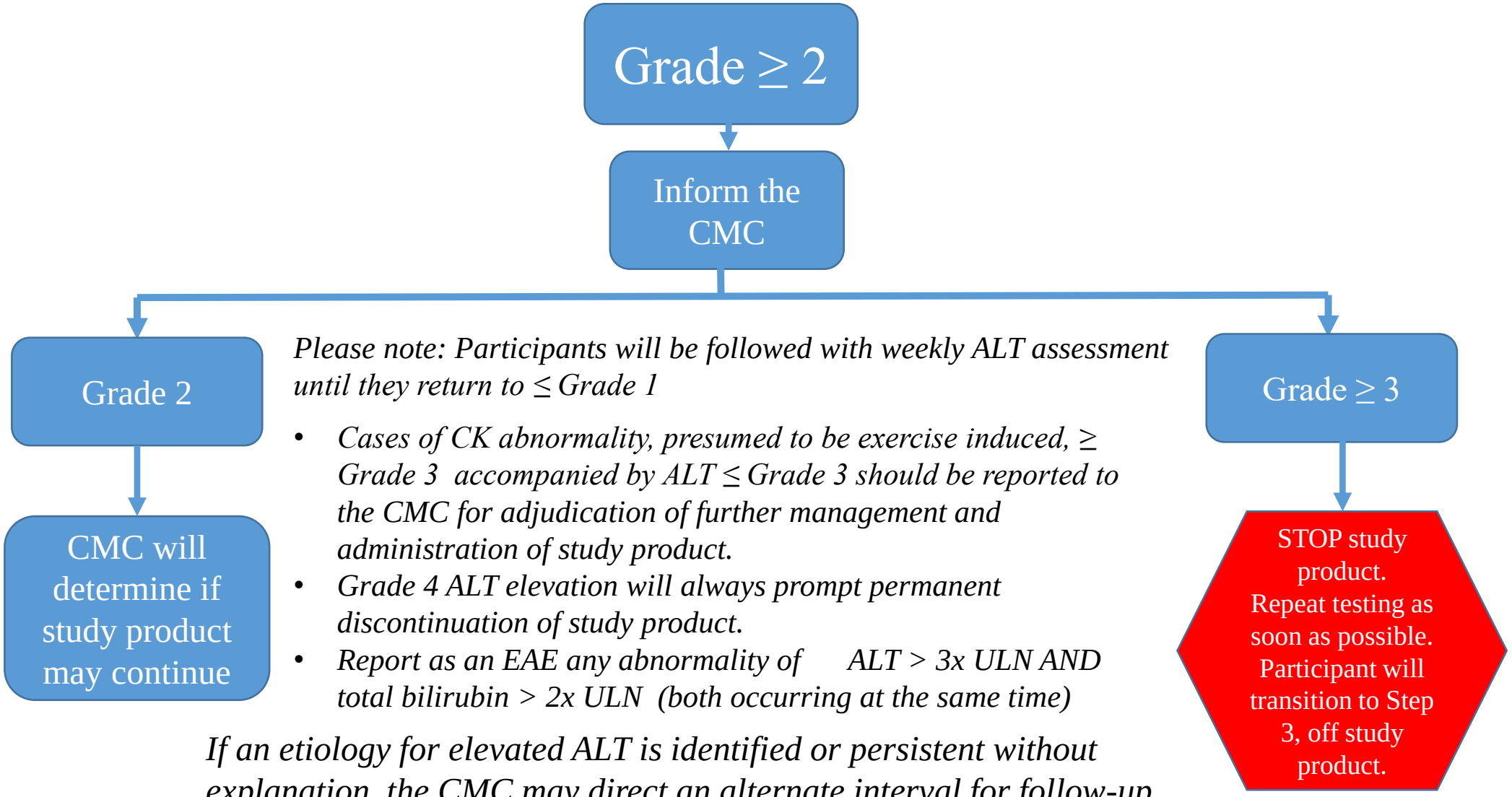


Please note: All cases should be reported to the CMC. Participants will be followed with weekly ALT assessment until they return to ≤ Grade 1

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)



Please note: Participants will be followed with weekly ALT assessment until they return to ≤ Grade 1

- *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)*

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)

Participant discontinued product during Step 2 due to ALT elevation

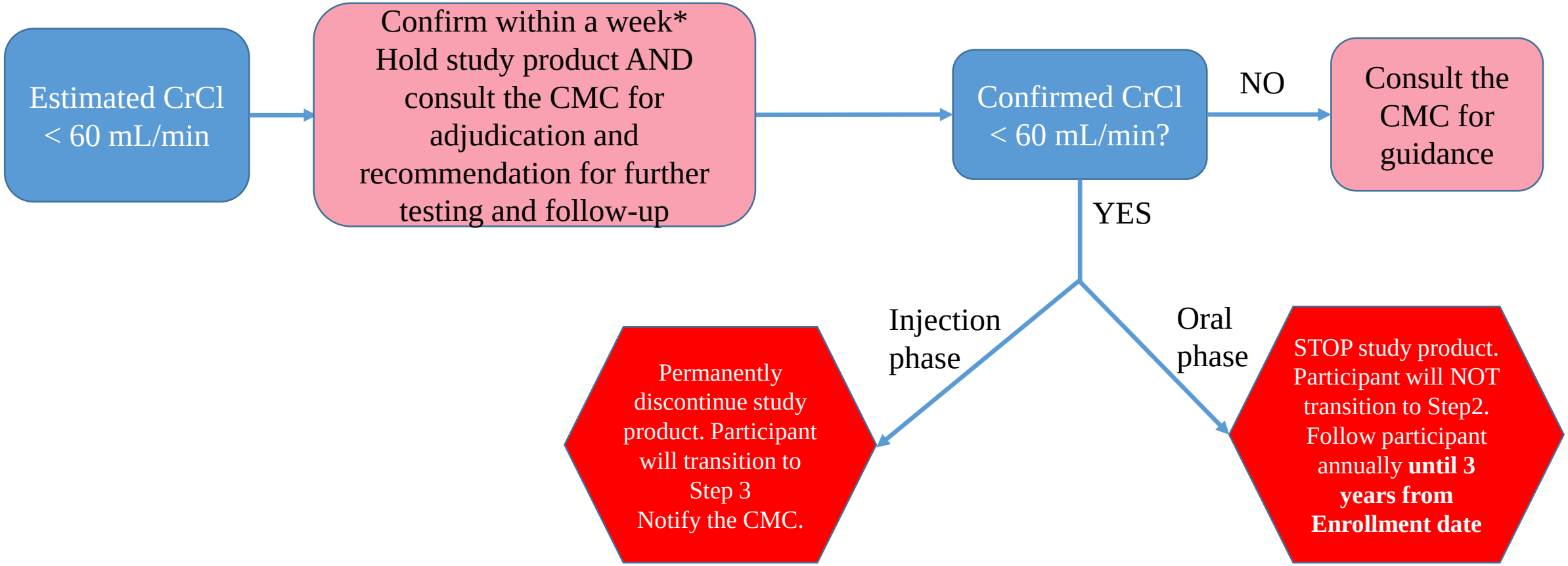
Participants will be followed per the Schedule of Procedures and Evaluations for Step 3 **except** for provision of study product.

- Participant will be followed annually until three years from the date of Enrollment.
- The timepoint during Step 2 that a participant transitions to Step 3 will determine whether they will be asked to attend annual visits following the completion of Step 3.
- If the completion of open label TDF/FTC for Step 3 post-dates three years from the date of Enrollment, no further annual follow-up is required. All such cases must be reported to the CMC.

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.

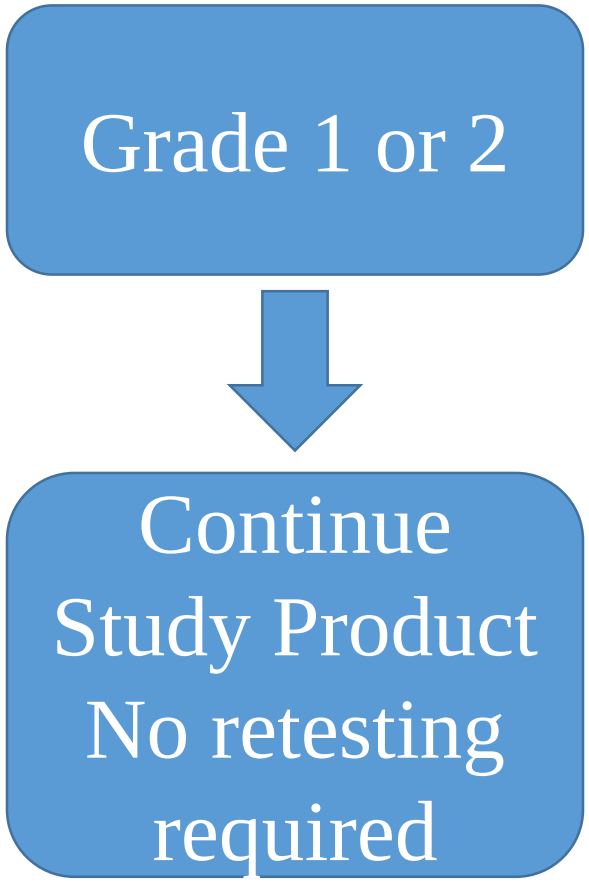
NOTE 2: Calculated creatinine clearance must be performed at every visit where chemistry testing is being performed, using the Cockcroft-Gault formula.

Specified Toxicities
Creatinine Clearance

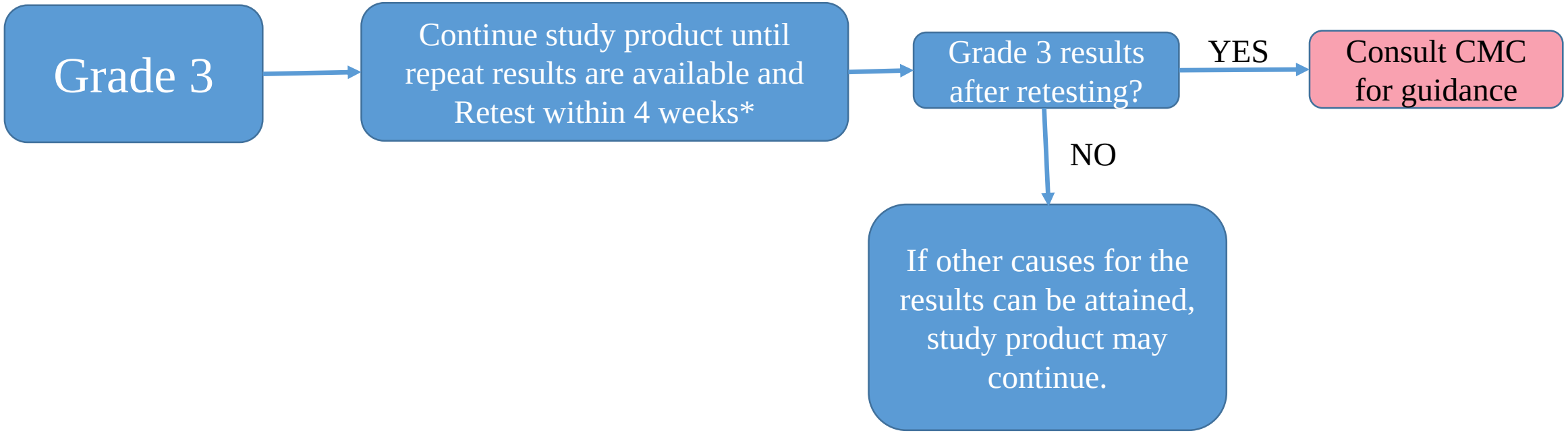
- Adverse events related to creatinine clearance should be based on examination of BOTH the absolute creatinine clearance AND the change in creatinine clearance from baseline (Enrollment/ Visit 2.0).
- When gradable, only the higher grade of these two assessments should be entered on the Adverse Event 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)

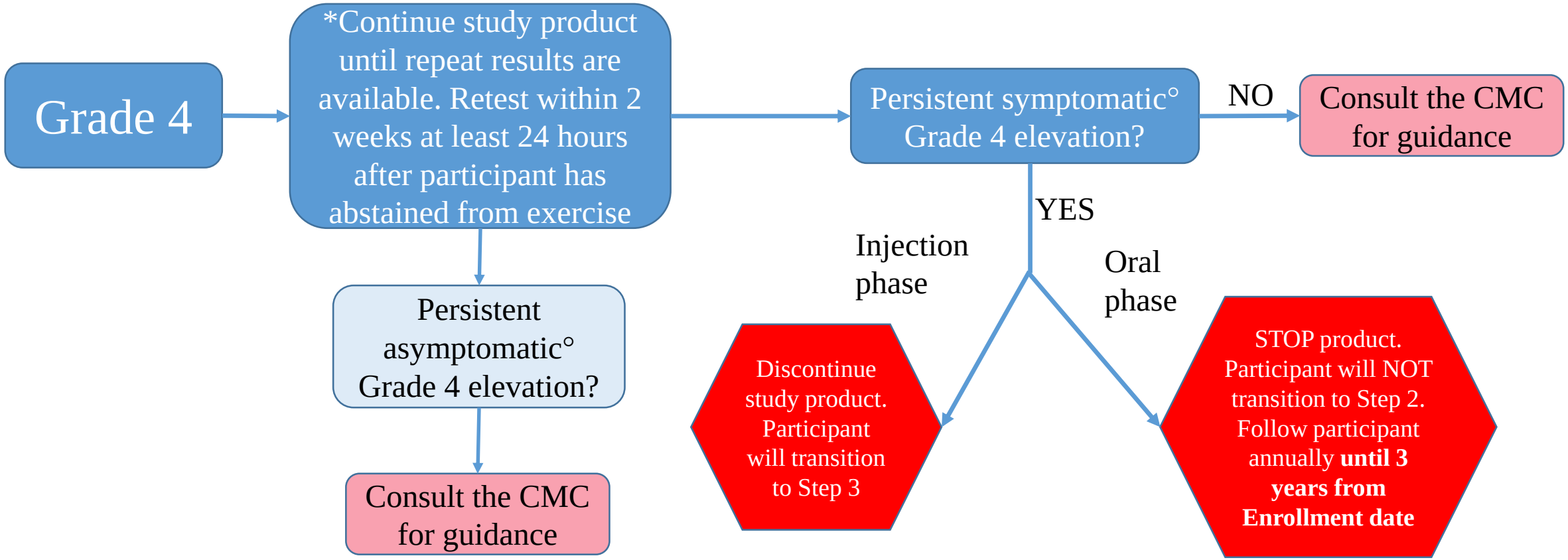


Specified Toxicities
Creatinine Phosphokinase (CK or CPK)



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

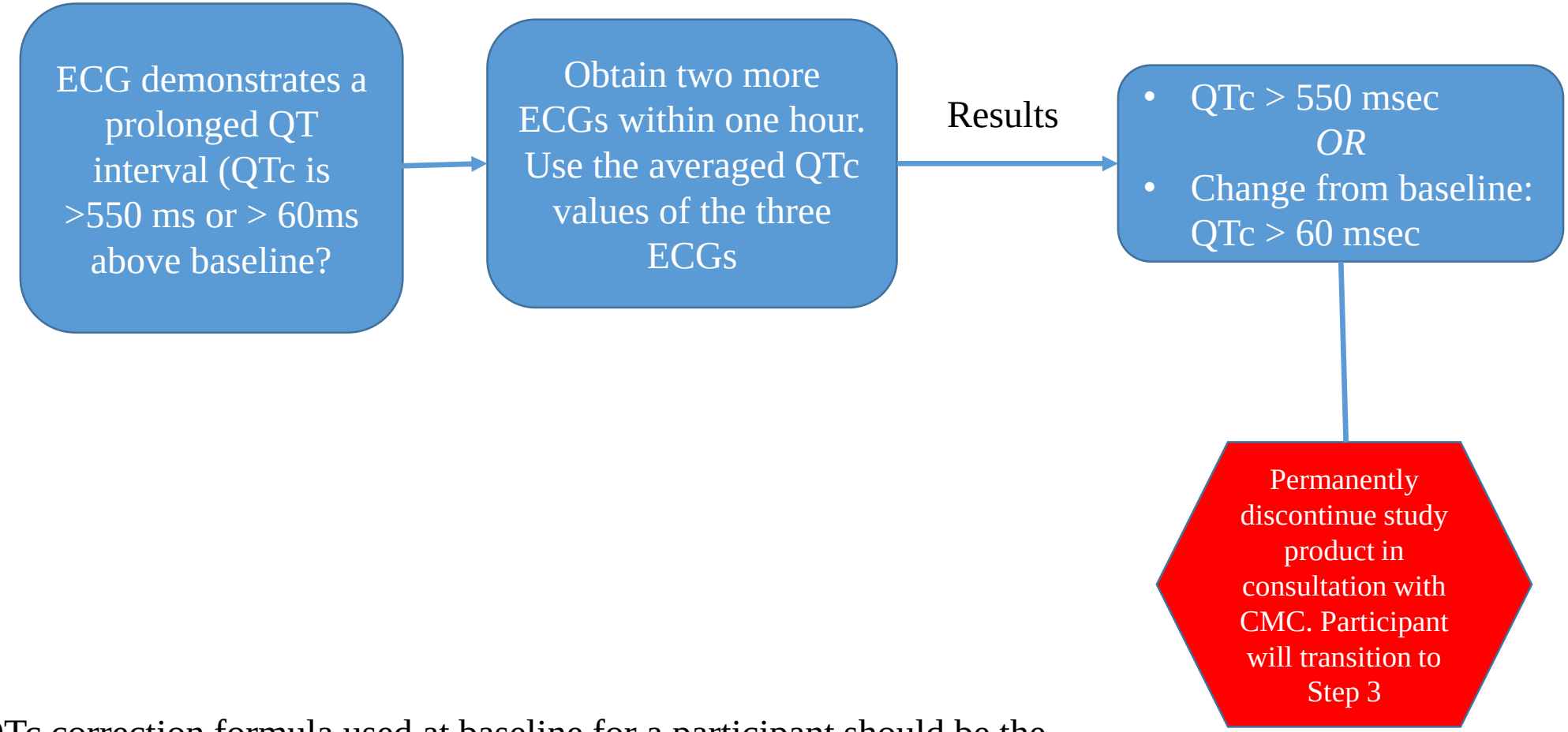
Specified Toxicities
Creatinine Phosphokinase (CK or CPK)



*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

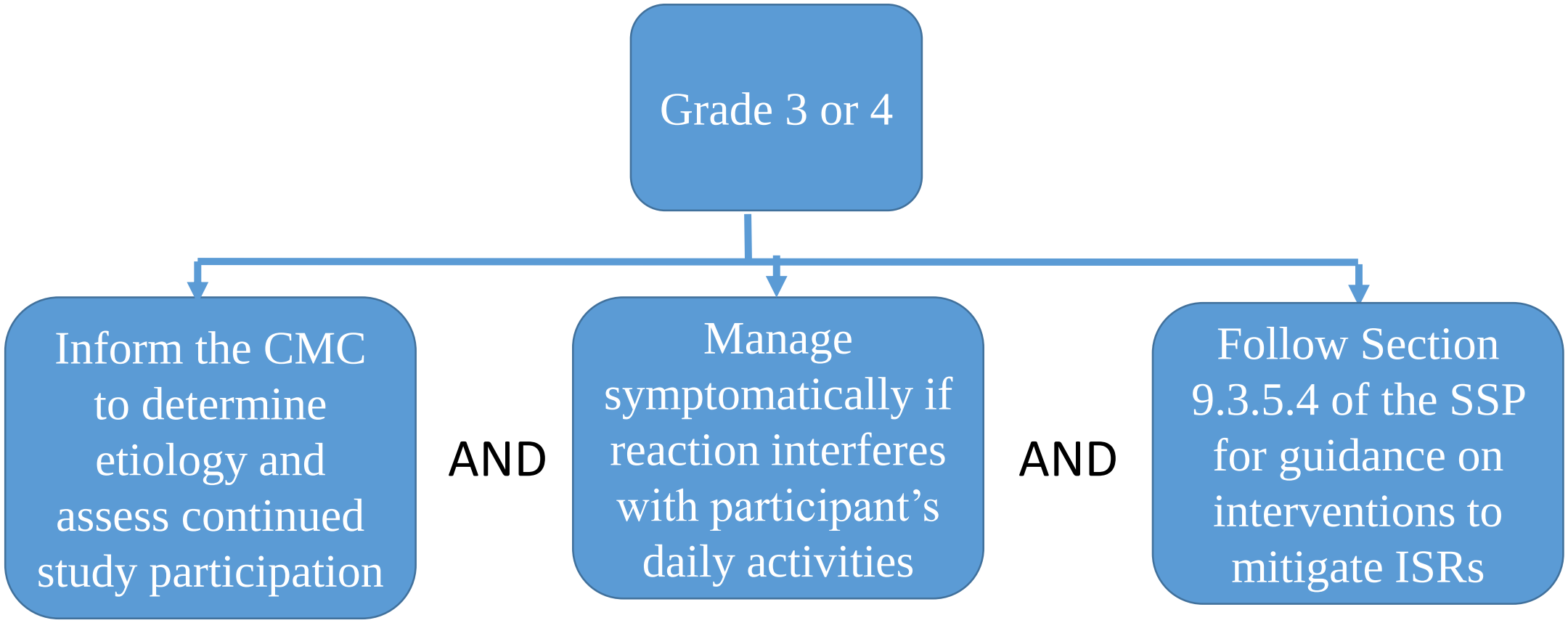
Specified Toxicities
QTc*



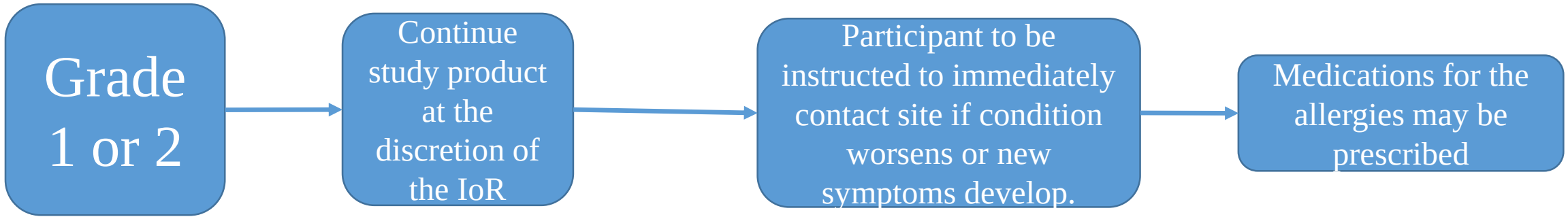
*QTc correction formula used at baseline for a participant should be the same formula throughout the study.

Specified Toxicities

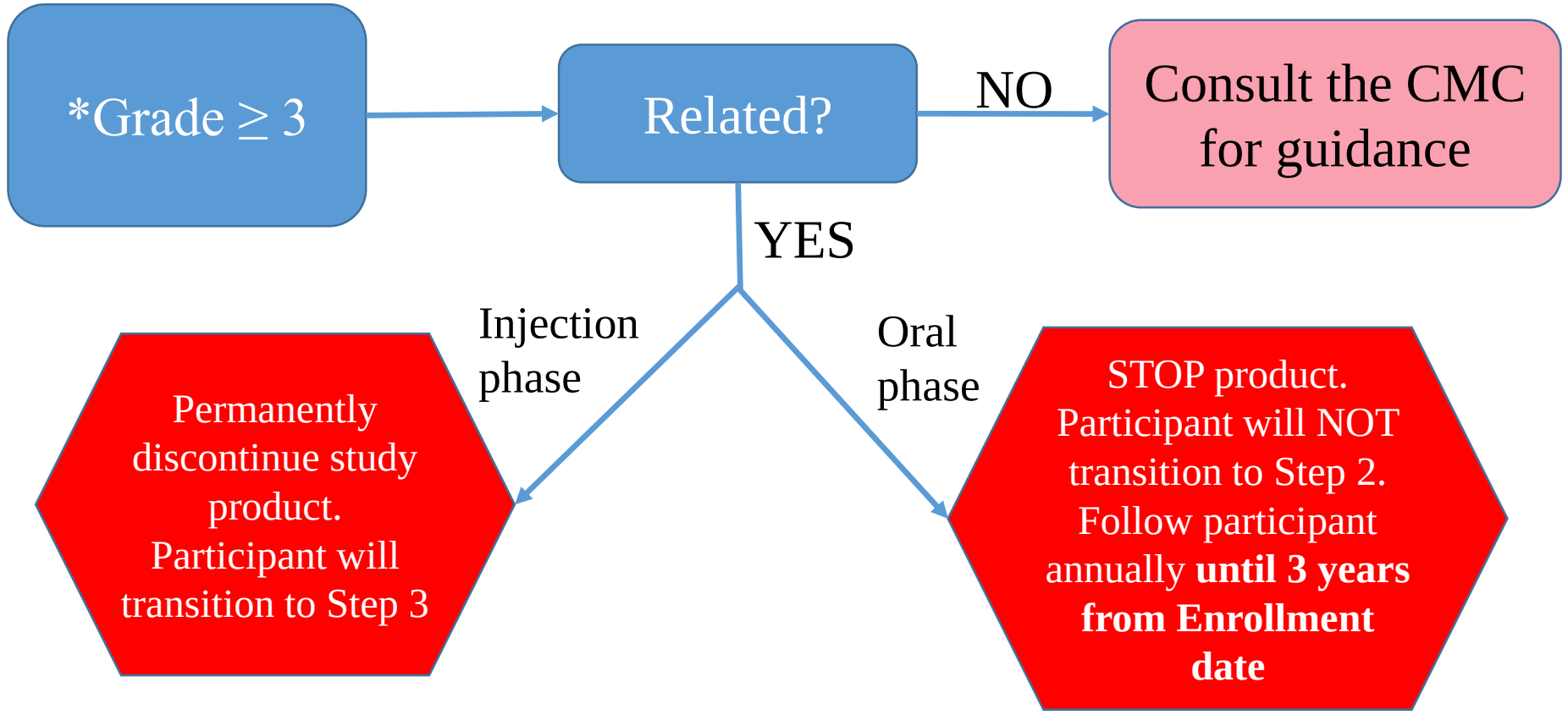
Injection Site Reactions (ISRs)



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.