IMPAACT 2007 CLINICAL MANAGEMENT CONSIDERATIONS

VERSION 1.0, 13 APRIL 2016

LOA #1, 12 AUGUST 2016

CLINICAL MANAGEMENT

- All pre-existing conditions and adverse events occurring in study participants must be source documented:
  - Clinical description
  - Severity grade of each event
  - Relationship to maraviroc
  - Onset and resolution dates
- All must be followed to resolution or stabilization
- CRFs used to record safety outcomes must be keyed within 48 hours of availability

SEVERITY GRADING

Grade	Definition
1	Mild
2	Moderate
3	Severe
4	Potentially life-threatening
5	Results in death

Grade adverse events per **Version 2.1** of the DAIDS Toxicity Table Per CM #1

SEVERITY GRADING

Grading of infant malnutrition is as follows:

Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
WHO weight-for-length Z score <-1 to >-2	WHO weight-for-length Z score <-2 to ≥-3	WHO weight-for-length Z score <-3	WHO weight-for-length Z score <-3 with life-threatening consequences

GRADATION OF RELATIONSHIP ASSESSMENT FOR AE

Relationship Category	Definition
Definitely related	The event and administration of the medication are related in time, and a **direct association** can be demonstrated.
Probably related	The event and administration of the medication are reasonably related in time, and the event is **more likely** explained by the medication than other causes.
Possibly related	The event and administration of the medication are reasonably related in time, and the event can be explained **equally well** by causes other than the medication.
Probably not related	A potential relationship between the event and the medication could exist (.e., the possibility cannot be excluded), but the event is **most likely** explained by causes **other** than the medication.
Not related	The toxicity is **clearly explained by another cause** not related to the medication.

This classification applies for AE documentation (i.e. source documentation and CRFs) and management, but does NOT apply for EAE reporting.

TOXICITY MANAGEMENT GUIDELINES

- Refer to protocol Section 8

  Email questions to Core Team: impaact.core2007@fstrf.org
- Section 8.2, per LoA #1, provides general guidance on management of events by cohort and includes more specific guidelines for ALT, AST, and total bilirubin abnormalities.
- Any infants who discontinue administration of maraviroc will remain in follow-up and per the relevant Schedule of Evaluations in Appendix I with the exception that no further PK sampling will be done.

TOXICITY MANAGEMENT GUIDELINES

Site Investigators should notify the Core Protocol Team by e-mail within three business days of site awareness of any confirmed Grade 1 ALT, ≥ Grade 2 ALT or AST and any Grade 3 or higher adverse event regardless of relationship to maraviroc occurring throughout follow-up. This notification should include the diagnoses or symptom, grade, and relationship assessment. *(See LoA #1, Section 7.1.1)*

IMPAACT 2007 EXPEDITED ADVERSE EVENT REPORTING

EXPEDITED ADVERSE EVENT REPORTING

Refer to protocol Section 7.3 for complete instructions

- The serious adverse event category (SAE) Reporting Category, as defined in *Version 2.0, DAIDS EAE Manual.*
- Reporting only for infants
- The study drug for reporting is maraviroc solution
- The EAE reporting period for this study begins at the time of administering the first dose of study drug and continues through the end of study follow-up.

SERIOUS ADVERSE EVENT (SAE)

An AE that:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

SERIOUS ADVERSE EVENT (SAE)

- Medical and scientific judgment should be exercised in deciding whether other AEs not listed above should be considered serious.
- Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the outcomes listed above should usually be considered serious.

MAPPING RELATIONSHIP CATEGORIES TO RELATIONSHIP CATEGORIES FOR EAE REPORTING

Relationship Category	Maps To	Relationship Category for EAE Reporting
Definitely related		**Related**
Probably related		**Related**
Possibly related		**Related**
Probably not related		**Not Related**
Not related		**Not Related**

QUESTIONS