A Multi-Center Trial of the
International Maternal Pediatric & Adolescent AIDS
Clinical Trials Group (IMPAACT)

IMPAACT P1090

A Phase I/II, open-label trial to evaluate the safety, tolerability, pharmacokinetics and antiviral activity of etravirine (ETR) in antiretroviral experienced HIV-1 infected infants and children, aged ≥ 2 months to < 6 years

MANUAL OF PROCEDURES (MOP)

Version 5.0
June 30, 2016

TABLE OF CONTENTS

APPENDICES

SUMMARY OF CHANGES

12/18/14	**Version 3.0 to 4.0**
Section	**Description of change**
2.1.2, 2.2, 3.4	Updated time period in which screening must occur prior to study entry
2.3, 3.9.3, 6.3.1 and Appendix IV	Replaced references to the University of North Carolina (UNC), Chapel Hill lab with University of Washington— Children's Hospital of Seattle
3.3, 3.4, 3.5, 3.6	Updated time period in which the Intensive PK Visit will occur
3.5	Information/instructions regarding the Intensive PK Visit at Day 14 consolidated into this section
3.6	New section re Intensive PK Visit following dose adjustment
6.2.3	Updated contact information for Laboratory Data Manager at FSTRF
Throughout	Updated email addresses, hyperlinks and references to appendices

6/30/2016	**Version 4.0 to 5.0**
Section	**Description of change**
6.3	Specimen volume column removed from Table 2., as volumes have been reduced across all visits to reduce the burden of collection on the youngest participants. Refer to Appendix IC.

List of Commonly Used Abbreviations and Definitions

ACTN	AIDS Clinical Trials Network
AE	Adverse Event
CDC	Center for Disease Control
CRF	Case Report Form
DAIDS	Division of Allergy and Infectious Diseases
DMC	Data Management Center
FSTRF	Frontier Science & Technology Research Foundation
HIPAA	Health Insurance Portability and Accountability Act
IATA	International Air Transport Association
ICF	Informed Consent Form
IMPAACT	International Maternal, Pediatric & Adolescent AIDS Clinical Trials Network
IND	Investigational New Drug
IRB	Institutional Review Board
LDMS	Laboratory Data Management System
LPC	Laboratory Processing Chart
PI	Principal Investigator
PID	Patient Identification Number
RCHSPB	Regulatory Compliance and Human Subjects Protection Branch
RSC	Regulatory Support Center
SAE	Serious Adverse Event
SES	Subject Enrollment System
SOP	Standard Operating Procedures

1.0 PROTOCOL OVERVIEW

1.1 Background

Etravirine (TMC125 from Janssen R&D) is a second generation NNRTI and has a diarylpyrimidine-based structure providing molecular flexibility relative to other NNRTIs, allowing etravirine to maintain its binding affinity for HIV-1 reverse transcriptase despite binding site changes induced by the presence of common NNRTI resistance mutations. Etravirine exhibits potent *in vitro* anti-HIV activity against wild type and against HIV isolates with NNRTI resistance mutations such as K103N, Y181C and Y188L.

Preclinical studies noted EC_{50} values for wild type laboratory and primary HIV-1 isolates of 0.9 to 5.5 nM (0.4 to 2.4 ng/mL) with little or no loss of activity against HIV-1 variants with the most common NNRTI related mutations. During *in vitro* testing, etravirine showed potent antiviral activity against a panel of >6000 recombinant clinical isolates resistant to at least one of the first generation NNRTIs, with EC_{50} values below 10nM for 83% of isolates and below 100nM for 98% of isolates. In addition, etravirine was noted to have an increased genetic barrier to the development of resistance compared to currently available NNRTIs. Non-clinical safety evaluations demonstrated that etravirine was safe for use in clinical testing.

Etravirine absorption is increased 50% when taken with a meal; peak plasma concentrations are found 2 to 4 hours post dose. The absorption is not affected when the drug is taken with proton pump inhibitors or H_2 blockers. Etravirine is a weak inducer of CYP3A4 and a weak inhibitor of P-glycoprotein, CYP2C9 and CYP2C19. Therefore it is subject to drug-drug interactions that may result in lower serum concentrations of drugs metabolized by CYP3A4 such as HIV protease inhibitors, if not boosted with ritonavir and higher concentrations of drugs metabolized by CYP2C9 and/or CYP2C19 and/or transported by P-glycoprotein.

1.2 Study Overview

IMPAACT P1090 is a Phase I/II, multi-center, open-label, non-comparative intensive PK and safety study of etravirine. All subjects enrolled into the study will be stratified at screening into one of three cohorts:

Cohort I: ≥ 2 year to < 6 years who are treatment experienced

Cohort II: ≥ 1 year to < 2 years who are treatment experienced

Cohort III: ≥ 2 months to < 1 year who are treatment experienced

1.3 Target Enrollment

This study will take place in multiple countries in North and South America, Asia and Africa.

Across all participating sites, target enrollment is for a total of approximately 50 subjects for 36 evaluable subjects. The study population will be HIV-infected treatment-experienced infants and children aged ≥ 2 months to < 6 years.

2.0 SCREENING

2.1 Introduction to Screening

The study screening lab and clinical procedures are also described in the P1090 Schedule of Evaluations (Appendix I of the P1090 protocol), which is available on the IMPAACT P1090 webpage (http://impaactnetwork.org/studies/P1090.asp).

Centralized reading of all study electrocardiograms is provided by eRT (Philadelphia, Pennsylvania). All participating sites must register with eRT and have an eRT provided-ECG machine onsite prior to screening. To facilitate this process, information detailing the registration process will be provided to domestic (US) and international sites as follows:

- Domestic: After protocol registration of P1090, the protocol CTS will send a message to the site with instructions for registration.
- International: Because shipments to international sites may be delayed due to customs or other issues, the protocol CTS will work with international sites on a case-by-case basis to schedule registration with eRT.

Sites may contact Megan Valentine, P1090 CTS, with questions (mvalentine@fhi360.org) about this process.

2.1.1 Screening and Enrollment Logs

Per the DAIDS policy for Essential Documents, study sites are required to document screening (including screening failures) and enrollment activity on screening and enrollment logs. Screening and enrollment/randomization logs may be separate or combined. A screened subject is defined as having signed the study consent.

Logs should include the following information:

- Initials of all patients screened for each study
- PID if patient receives one
- Date screened
- Date randomized
- If not randomized, indicate reason

For additional information, refer to the NIAID/DAIDS website http://www3.niaid.nih.gov/about/organization/daids/

2.1.2 Overview of Screening

- During this initial screening visit, detailed study information will be presented. Informed consent for screening and study participation should also be obtained. Screening must occur **60** days prior to entry.
- The child's parent/guardian will be encouraged to ask questions.
- If the parent/guardian needs additional time to consider the screening process, another visit will be scheduled and no procedures will be done.
- Ensure parent/guardian has authorized or denied authorization for use of samples for future studies.
- Provide parent/guardian with a copy of the signed informed consent that they can take home with them.
- Obtain parent/guardian authorization to obtain subject's medical record from private health care provider (if applicable)

- Ensure parent/guardian has signed medical release to obtain records of any AEs that might occur which necessitate medical record clarification or confirmation. Only those portions of the medical record that are pertinent to the study will be maintained in the study chart.

2.2 Obtaining a Screening Slot

- Sites MUST have IRB, Protocol Registration Office (PRO) and Ops center* approval prior to consenting and screening a subject.
  *NOTE: Ops center approval is required only for NIAID sites.
- Sites should email the team at impaact.teamP1090@fstrf.org to request a screening slot. Please note it is NOT necessary to provide PID numbers in your email to the team, however, a PID is recommended. If no PID has been assigned, then sites should provide the age of the subject. The site number, cohort requested, as well as prior and current ARV experience is also required. IF while the subject is on the waiting list for an enrollment slot, the subject has a milestone birthday that will change the cohort assignment, it is the site's responsibility to notify the DMC data manager to request a cohort assignment change.
- The team will review the status of the study and decide whether the subject may be screened or not. Sites MUST wait to receive permission from the protocol team in order to proceed with screening evaluations.
- Sites will be asked to complete the screening evaluations within a defined period of time (the team will inform you of this time frame, but generally 2 weeks is allocated from the time when the slot is granted to the screening visit). Sites should contact the team with any screening timeline deviations. Slots will be recalled if deviations from the time line are not approved by the protocol team. Sites then have **60** days after screening to enroll the subject.
- If an enrollment slot is not currently available for the subject, the subject will be entered onto a waiting list and will be notified when a slot does come available.

2.3 P1090 Screening Procedures

The following procedures should be completed to screen the subject for the P1090 study:

a) Request a slot from the DMC protocol data manager by emailing the study team (impaact.teamp1090@fstrf.org).

b) Obtain Informed Consent
Documentation of the informed consent process is achieved by having the informed consent form (ICF) signed by the minor subject's parent or guardian; however, the process of obtaining informed consent should be documented in the research record.

Sites should see page 19 of the DAIDS Source Documentation Requirements SOP for more information:
https://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/sourcedocappndx.pdf

The web site for the DAIDS Essential Documents SOP is:
https://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/essentialdocpolicy.pdf

c) Medical history, physical exam

d) Evaluations for CDC classification

e) Electrocardiogram (ECG)
    - As noted: centralized reading of all study electrocardiograms is provided by eRT. All sites must have an eRT-provided ECG machine prior to screening. Please see the start of Section 2.1 for more information.

f) Blood draws for hematology, chemistries, lymphocyte subsets and coagulation assays
    - Refer to the Schedule of Evaluations (Appendix I of the protocol) and the Lab Processing Chart (LPC) for further information on specific tests and blood volumes and processing.

g) Urinalysis

h) HIV-1 RNA PCR viral load
    - Only the Abbott platform may be used for this protocol
    - If your lab is not VQA approved for the Abbott platform, please contact the P1090 team for guidance.
    - If you are using the UNC Retrovirology lab for Abbott RNA PCR, please remember to include a completed Specimen Testing Requisition Form (see Appendix IV of the MOP) when you ship a VL specimen

i) Real time HIV genotyping for resistance testing (if sufficient blood is collected)
    - This specimen MUST be sent in REAL time to the appropriate location (see Appendix II of the P1090 protocol and the P1090 LPC).
    - Depending on the location of the clinical site, the closest specialty laboratory for genotyping may be in-country or specimens may need to be shipped out of the country for testing (refer to the Lab Processing Chart and Appendix II of the P1090 protocol).
    - When shipping a specimen for genotyping, please remember to include the following documents:
        - LDMS shipping manifest
        - Specimen Testing Requisition Form (see Appendix IV of the MOP)
    - Genotype specimens should be shipped to the following locations (see Appendix II of the protocol and the LPC):
        - US sites: **University of Washington— Children's Hospital of Seattle**
        - South American sites: FioCruz, Brazil
        - Africa sites: CLS, Johannesburg SA
        - Thailand sites: PHPT, Chiang Mai
    - Once a site ships a genotyping specimen for testing, an email should be sent to the team informing them of the PID number, site number and

shipment date so that we can track the specimen and the results. Emails should be sent to impaact.teamp1090@fstrf.org.
- Turnaround time for the genotyping results will vary for each specialty lab, but is typically approximately 2-3 weeks from initial shipment.

j) HIV Phenotyping
- At screening, blood should be processed for resistance testing (phenotyping).
- Phenotype specimens should be shipped to the following locations (see Appendix II of the protocol and the LPC):
    - US sites / Brazil: Monogram Biosciences
    - All other sites: BRI repository
- This specimen should be shipped in real time, so that results can be made available in order for the subject to be eligible for entry.
- Once a site ships a phenotyping specimen for testing, an email should be sent to the team informing them of the PID number, site number and shipment date so that we can track the specimen and the results. Emails should be sent to impaact.teamp1090@fstrf.org.
- Turnaround time for phenotyping is 3-6 weeks.

Further details can be found in the Lab section of the MOP (Section 7.0), in the Laboratory Processing Chart (LPC), and in the Schedule of Evaluations (Appendix I) of the P1090 protocol.

2.4 Screening Failures

If a subject consented for the study fails to meet all of the inclusion/exclusion criteria to participate in the study, or fails screening evaluations, the subject will be considered a screen failure. The reason for screen failure should be documented appropriately in the source documentation and the Screening Failure/Non-Enrollment Tracking CRF must be entered into the DMC database.

3.0 PROTOCOL IMPLEMENTATION

3.1 Recruitment of Study Subjects

This is a multi-site study. Approximately 50 subjects will be recruited from outpatient clinics at specific sites in the United States, South America, Asia and Africa. Each site will be required to obtain team approval of a site implementation plan (SIP) before they can start enrolling in the study, as well as all local and national approvals.

3.2 Obtaining an Enrollment Slot

Sites interested in enrollment subjects for possible enrollment into IMPAACT P1090 should send an email to the team at impaact.teamP1090@fstrf.org indicating the candidate's screening number, PID# (if no PID# is assigned, provide patient age only) and cohort number. Slots will be granted based on the date a slot was requested. Sites MUST receive authorization from the protocol team before proceeding with screening. It is the site's responsibility to ensure the subject is potentially eligible for the study.

Enrollment slots will only be granted to a site once the site completes the following procedures:

- Sites MUST email the team to request a screening visit
- Sites should then wait to receive permission from the team to proceed with the screening visit (within 48-72 hours)
- Sites MUST email the protocol team to accept the screening slot
- Sites must complete the screening visit within two weeks of approval of the slot

If the subject passes the screening evaluations and study inclusion criteria, the site may email the team to request permission to enroll the subject into the study. Sites should contact the protocol team at impaact.teamp1090@fstrf.org with any screening timeline deviations. A slot may be recalled if deviations from the timeline are not approved by the protocol team. Study drug(s) must begin within 72 hours of enrollment.

NOTE: IF while the subject is on the waiting list for an enrollment slot, the subject has a milestone birthday that may change the cohort assignment, it is the site's responsibility to notify the DMC data manager.

3.3 General Information Regarding Clinic Visits

3.2.1 Windows for Clinic Visits

- Entry (Day 0) must be completed within **60** days of the screening visit.
- The intensive PK visit must be completed within **the Day 14 (± 4 days) window** after the subject starts study drug.
- Study visits on weeks 4, 8 and 12 should all be completed within a one (1) week window (±1 week).
- Study visits on weeks 16, 24, 32, 40 and 48 should all be completed within a two (2) week window (±2 weeks).
- After week 48, study visits for long-term follow-up are every 12 weeks and should be completed within a (2) week window (±2 weeks).

3.2.2 Medications Allowed During the Study

The following medications should be recorded in the CRFs during the first 48 weeks on study drug:

- Use of prescription, non-prescription and herbal medications
- Non-pharmacological treatment/procedures

Minimum documentation must include:

- Name of the medication or treatment
- Dose, Route and Frequency
- Start and Stop Date of Medication
- Indication for Medication or Treatment

For a list of disallowed medications, please refer to Section 4.32 of the P1090 protocol document.

3.2.3 Emergency Plan for After Hours

Study subjects should be informed of the procedures for reaching a study staff member out of normal clinic hours. Each site should have an emergency plan in place for evaluation and management of sick children for after hour's sick visits, as

per the Standard of Care at the site. The subject/caregiver should know exactly how they can reach medical help in an emergency situation.

3.3 Subject Withdrawal

Regardless of the reason for withdrawal, study personnel are responsible for identifying all subjects who withdraw and documenting the reason and date of termination.

- Parents/guardians may withdraw their child from the study at any time.
- Study personnel should attempt to collect final data from subjects who are withdrawn early.
- Study personnel will record the date and reason for withdrawal in the subject's source record, and on the subject case report form.
- In general, the investigator should not withdraw a subject unless that subject is lost to follow up or is noncompliant with the protocol.
- If the subject is withdrawn from the study drug due to an adverse event (AE), the subject should be followed by the clinical site until the AE resolves (per Schedule of Evaluations, Appendix IE).

3.4 Enrollment/Entry

- Please note there will be a waiting list for enrollment into this study if we do not have sufficient slots available in a cohort at any particular time.

- The team will notify sites in real time regarding the status of the mini-cohorts and the full cohorts (i.e. open or closed).

- If the subject is eligible for enrollment (based on the screening results), sites may enroll the subject as they would normally through the enrollment system.

  NOTE: Subjects may NOT enroll in the study if they are currently taking any of the drugs listed in Section 4.32 of the P1090 protocol "Disallowed Medications". If a subject is taking any of the medications listed in Section 4.31 of the P1090 protocol "Precautionary Medications", alternative treatments should be sought. Sites should contact the protocol team at impaact.teamp1090@fstrf.org if treatment with any of the listed medications is necessary for clinical care.

- Once the subject has been enrolled into the P1090 study, the following procedures should be completed:
  - Entry visit should be completed within **60** days of the screening visit.
  - Refer to Schedule of Evaluations, Appendix I (P1090 protocol) for required clinical and laboratory evaluations for each specific cohort and stage.
  - Study drug should also be distributed at this visit.
  - The subject should be scheduled to come back for the Intensive PK visit **on Day 14 (± 4 days).** The intensive PK should be scheduled such that a witnessed dose of ETR is taken approximately 12 hours after the previous dose. PK dosing within a range of 11-13 hours after the previous dose is acceptable.

3.5 Intensive PK Visit on Day 14 (± 4 days)

General Comments

- We anticipate that each institution will likely have their own policy on the maximum number of times it is acceptable to attempt a blood draw outside of a medical emergency, however, the team suggests no more than 2-3 attempts by each of 2 phlebotomists (maximum of 6 tries).
- Sites should refer to Appendix I in the P1090 protocol (Schedule of Evaluations) for required clinical and laboratory evaluations for each specific cohort and stage.

Prior to the Intensive PK Visit

- At Entry (Day 0), remind the subject that they will undergo the intensive PK visit on **Day 14 (± 4 days)** and they will need to come to the clinic in order to complete the 12-hour PK sampling.

- At 7 days prior to scheduled PK visit, contact the subject to remind them of the following:
    - The visit dates and times for the PK visit
    - No missed dose(s) of etravirine during the 7 days prior to the scheduled PK visit; otherwise the PK visit needs to be rescheduled
    - Record the actual dose (in mg) taken, actual date and time of the etravirine doses on the 7 days (total of 14 doses since etravirine is taken twice a day) prior to the scheduled PK visit. The dose of etravirine taken prior to the PK visit should be taken at approximately the same time of the scheduled PK visit. The actual dose taken needs to be recorded in the unit of mg, not number of tablets, number of packets, or volume of solution.

- At 1 day prior to the scheduled PK visit, the subject should be contacted by phone to ensure the following:
    - Confirm there was no missed dose during the 7 days prior to the PK visit. If there is any missed dose(s) of etravirine during the 7 days prior to the PK visit, please reschedule the PK visit within **the Day 14 (± 4 days) window.**
    - Remind the subject that they will be provided breakfast when they arrive at the clinic, as part of the intensive PK visit.
    - Remind subject to bring their etravirine medicine for dosing on both days of the PK sampling visit and not to take the dose until the pre-dose PK blood sample is taken under observation at the physician's clinic.

On the Day of the PK Visit and Before Starting the PK Collection

- Subjects should not have missed any of their etravirine doses in the 7 days prior to the intensive PK visit.
- Clinic staff should review any subject documentation of prior dosing; collect undocumented information by oral interview. Example templates are available in Appendix I of the MOP to assist subjects with keeping track of previous dose and meal information. Sites may print copies of these templates should they wish to provide subjects with a collection tool.

Intensive PK Collection

- The team suggests that a heparin/saline lock be used for the intensive PK procedure.

- Collect the pre-dose PK sample as close as possible to 12 hours after the subject's last dose of etravirine (within a target window of 11 to 13 hours).
- Subjects should receive a breakfast appropriate for their age. WITHIN thirty (30) minutes of breakfast, the PK medications should be administered followed by the PK sampling at the specified time points.
- Subjects may resume unrestricted food intake 2 hours after their dose of ETR at the intensive PK visit.
- Administer etravirine dose and record actual dose, date and time of the dose administration. The actual dose taken needs to be recorded in the mg unit, not number of tablets, number of packets, or volume of solution. Also record whether the dose was taken as a whole tablet or dispersed.
- If the subject vomits <15 minutes after taking study drug, the dose should be repeated.
- Record whether or not the subject vomited more than 15 minutes after dosing:
    - For subjects who vomited ≥15 mins but < 4 hours after dosing, or who cannot complete the PK that day for any other reason, the PK should be cancelled and MUST be rescheduled AND completed within the **visit window**
    - For subjects who vomited ≥4 hours after dosing, the drug should be absorbed and the intensive PK can continue.
- Collect the PK samples at time points specified in the footnotes in Appendix I of the P1090 protocol.
    - The 9 hour blood draw has a window of 8-10 hours. NOTE: If necessary to meet specific blood volume constraints for an individual participant, the 1 hour post-dose blood draw and/or 9 hour blood draw can be deleted.
    - The 12 hour blood draw has a window of 11 to 13 hours.
- Remember to complete the time unit in the LDMS (see Laboratory Processing Chart for more information).
- Record in the CRF:
    a) The dates, times, and amounts (in the unit of mg) of the three doses of etravirine administered prior to the PK visit and the dose administered at the PK visit; the actual dates, times, and doses should be recorded even if they are off-schedule. Also record whether the dose was taken as a whole tablet or dispersed.
    b) The actual PK sampling dates and times should be recorded even if they are off-schedule.

<u>When should an intensive PK visit be rescheduled?</u>

- If a dose was missed on any one of the 7 previous days
- The pre-dose sample was not be taken in the 11-13 hour target window
- The subject did not take the etravirine dose in the clinic
- The subject vomited within 4 hours after dosing

<u>What is the timeframe for rescheduling an intensive PK visit?</u>

- The intensive PK visit MUST be rescheduled AND completed within **Day 14 (± 4 days) window** of the original intensive PK visit. If this timeline cannot be met, sites should contact the team for guidance (impaact.teamp1090@fstrf.org).

3.6 Intensive PK Visits Following Dose Adjustment

Participants who have had individual dose adjustment for low or high AUCs or due to mini or full cohort failure will be asked to return to clinic for an intensive PK evaluation between Day 7-14 on the new dose. Procedures are the same as per section 3.5. A full

Intensive PK will be expected for participants who have had individual dose adjustments. Participants who have had dose adjustments as a result of cohort failure will have a truncated intensive PK evaluation with samples collected at the following time points: Pre-dose, 2 and between 3-5 hours post-dosing.

Note that a repeat EKG is required at the time of a PK visit required for in the event of dose adjustment.

3.7 Study Visits – Weeks 4, 8, 12, 16, 24, 32, 40, 48

- Refer to Schedule of Evaluations, Appendix I (P1090 protocol) for required clinical and laboratory evaluations for each specific cohort and stage.
- Please note that weight should be obtained and recorded as part of the physical exam performed at each visit. Remember that any change in the subject's weight may require a change in medication dose. If a dose change is required based upon weight increase/decrease, weight change is listed as a reason for change on the treatment record form. In this case, the team should be contacted to obtain a new dose (impaact.teamp1090@fstrf.org).

3.8 Population PK Visits

3.8.1 Before the Population PK Visit

NOTE: Subjects DO NOT need to be fasting prior to any of the population PK visits.

- Provide subjects with a diary card at the visit before the PK sampling visit.
- Instruct the subject that he/she must record the time they took their dose of etravirine on each of the 7 days prior to the PK sampling visit on the diary card.
- Please note that subjects must take their etravirine dose in the 7 days prior to the PK sampling visit at a time in the day that corresponds to the time their next visit is scheduled.
- Please note that if a subject misses any of the 3 doses prior to the population PK, the population PK should be rescheduled.
- Sites are recommended to call the subject at 7 days and then 1 day prior to the PK visit with reminders concerning dose times. Remind them to take their dose of etravirine on the day of the population PK sampling visit under observation at the clinic.

3.8.2 Virologic Failure

- Review the diary card prior to collecting any blood sample.
- Collect the post-dose PK sample at any time.
- Note the time of the last dose and the blood draw.

3.8.3 Week 4 Population PK

- Review the diary card prior to collecting any blood sample.
- Collect the post-dose PK sample at 1 to 4 hours after the subject's dose of ETR.

3.8.4 Week 8 Population PK

- Review the diary card prior to collecting any blood sample.
- Collect the post-dose PK sample at 4 to 8 hours after the subject's dose of ETR.

3.8.5 Week 12 Population PK

- Review the diary card prior to collecting any blood sample.

- Collect the post-dose PK sample at 8 to 12 hours after the subject's dose of ETR.

3.8.6 Week 24 Population PK

- Review the diary card prior to collecting any blood sample.
- Collect the post-dose PK sample at 1 to 4 hours after the subject's dose of ETR.

3.8.7 Week 48 Population PK

- Review the diary card prior to collecting any blood sample.
- Collect the post-dose PK sample at 8 to 12 hours after the subject's dose of ETR.

3.8.8 Missed Doses/Vomiting Prior to a Population PK

- If a dose was missed on any one of the 3 previous doses, the population PK sample does not need to be drawn; the remainder of the study visit should be completed as usual.

3.9 Virologic Failure

If a subject appears to be experiencing virologic failure (as defined in Section 6.3 of the P1090 protocol), the following procedures should be completed:

3.9.1 Consult the Subject

- Inadequate adherence is a common cause for virologic failure, and should be explored as a first step in the management of study subjects (e.g., at the first indication of inadequate virologic response or rebound).

- Upon notification that a subject's HIV-1 RNA plasma level qualifies them as a suspected virologic failure, the investigator should query the subject regarding intercurrent illness, recent immunization, or interruption of therapy.

3.9.2 Perform Confirmatory VL Sampling

All cases that meet a criterion for suspected virologic failure must be confirmed by a second Viral Load measurement performed at least 1 week but not more than 4 weeks apart from the date of the original sample, unless one of the extenuating circumstances outlined below applies:

- Confirmatory testing should be scheduled 2 to 4 weeks following resolution of any intercurrent illness, during which time the subject should receive full dosing of etravirine.
- Confirmatory testing should be scheduled at least 4 weeks following any immunization, during which time the subject should receive full dosing of etravirine.
- If therapy is interrupted due to toxicity management, non-compliance, or other reasons, confirmatory testing should be scheduled 2 to 4 weeks following resumption of full dosing of etravirine.
- The subject should have received full doses of etravirine for at least 2 weeks at the time confirmatory plasma HIV-1 RNA is done.

3.9.3 Managing Confirmed Virologic Failure

- IF this second viral load confirms the initial suspected virologic failure, the subject should have the appropriate clinical and laboratory evaluations performed (refer to Virologic Failure column in Appendix I of the P1090 protocol).
- Genotyping/phenotyping blood specimen:
    - At virologic failure, blood should be collected for genotyping and for phenotyping.
    - A **genotyping** specimen MUST be collected and batch shipped quarterly to the appropriate location (refer to the Lab Processing Chart and Appendix II of the P1090 protocol):
        - US sites: **University of Washington-Children's Hospital of Seattle**
        - All other sites: BRI Repository
    - A **phenotyping** specimen MUST be collected and batch shipped quarterly to the appropriate location (refer to the Lab Processing Chart and Appendix II of the P1090 protocol):
        - US sites: Monogram Biosciences
        - All other sites: BRI Repository
    - When shipping a specimen for genotyping, please remember to include the:
        - LDMS shipping manifest
        - Specimen Testing Requisition
    - Once a site ships a genotyping specimen for testing, an email should be sent to the team informing them of the PID number, site number and shipment date so that the team can track the specimen and the results. Emails should be sent to (impaact.teamp1090@fstrf.org).
    - Turnaround time for the genotyping results will vary for each specialty lab, but is typically approximately 2-3 weeks from initial shipment. Results from the genotyping will be made available to the investigator as soon as they are available.
    - The plasma specimen for HIV phenotyping should be stored at the local site until requested for batch shipment.
    - Please email the team with any questions (impaact.teamp1090@fstrf.org).
- It is up to the site investigator to determine whether it is in the best interests of the subject to have study drug (etravirine) withdrawn. Section 6.3 of the P1090 protocol explains the subject's protocol-based treatment options if they reach virologic failure. Please email the team with any questions – (impaact.teamp1090@fstrf.org).
- Every effort should be made to perform the assessments outlined for the 'Virologic Failure' visit before the subject is withdrawn from the study.

3.10 Management of Abnormal QTc or PR intervals noted on ECG

Participant management of these abnormal ECG readings should be governed by best clinical practices and the guidelines in Section 6.15 of the protocol. If the local reading suggests Grade 3 or above, sites should request a turnaround time of 24 hours for the ECG

interpretation from the centralized reading service (eRT). Such requests may be made of eRT Customer Care 24 hours a day, 7 days a week at the following toll-free numbers:

- Argentina: 0800 6660824
- Brazil: 0800 8919075
- South Africa: 0800 995609
- Thailand: 001800 4915201
- United States: 1 800 704 9698

When the call is answered, select Option 1 to request a STAT report.

Please be sure to have your ERT study name (P1090), Portal account login or the Ticket number for an existing case available, if necessary.

You may also access the Help Desk at the following website:
http://www.ert.com/clinical/contact-customer-care/

3.11 Early Discontinuation of Study Drug ('Off Study Drug/On Study')

Study drug should be discontinued early for any of the reasons described in Section 6.8 of the P1090 protocol. Please refer to Schedule of Evaluations Appendix IE of the P1090 protocol for a schedule of evaluations for these subjects.

If a subject meets any of the criteria for discontinuing study drug before the end of the study, the site should complete the following procedures:

- Subjects should come off study drug immediately
- If the subject is experiencing an adverse event, the subject should be followed and remain on study until the adverse event resolves or until there is satisfactory clinical stabilization. During this time, the subject may be asked to come back to clinic as often as the site investigator feels is necessary for safe monitoring of the adverse event. Once the adverse event is resolved, the subject can come off the study entirely.
- If the subject is coming off study for any reason other than an adverse event, the subject should be asked to come back to clinic once more; 4 weeks after the subject has stopped taking study drug.
- Refer to Schedule of Evaluations, Appendix IE (P1090 protocol) for required clinical and laboratory evaluations for subjects who discontinue study treatment early.

3.12 Early Discontinuation from Study ('Off Study')

- A subject should be discontinued from participation in the study for any of the reasons described in Section 6.9 of the P1090 protocol.
- Refer to Schedule of Evaluations, Appendix IA-ID (P1090 protocol) for required clinical and laboratory evaluations for each specific cohort and stage for "Early Study Discontinuation".
- Every effort should be made to perform the evaluations described in the 'Early Study Discontinuation' visit before the subject comes off the study.

3.13 Long Term Follow-Up

Provided that the overall data for this drug appear to be generally favorable, each subject who successfully completes 48 weeks of etravirine treatment will continue to receive etravirine and be followed on study for long term safety follow-up for up to 5 years, or until any one or more of the following events occur within the 5 years:

- The age-appropriate formulations provided by the study are available locally from another source (e.g. government programs, pharmaceutical drug access programs, aid programs, assistance programs etc) to all subjects in each specific country ; OR
- Until subjects are no longer deriving benefit; OR
- Until subjects meet a protocol-defined reason for discontinuation; OR
- Pharmaceutical development of etravirine for that age cohort is terminated

Once subjects enter the long term safety follow-up phase, they will be seen in clinic for safety visits and laboratory evaluations, as per Appendix **IE**. Sites should record any laboratory results, diagnoses etc. that are recorded as part of standard of care as well as perform the study mandated HIV-1 RNA assay (See Appendix **IE**).

Subjects in countries where etravirine continues to be unavailable locally at the end of the planned 5 year long-term safety follow-up program will be provided the drug either through a P1090 protocol amendment or through other sources, such as another Janssen-sponsored program, government programs, and aid and assistance programs.

Subjects who are withdrawn from study drug in the first 48 weeks of study will not enter long term follow-up (Appendix **ID**), but will be followed for safety for 4 weeks, as per Appendix 1E. Additionally, any AEs will be followed until satisfactory clinical resolution (i.e. value returns back to subjects baseline value) or stabilization (to be agreed upon with the sponsor). All grade 3 and grade 4 lab abnormalities and lab abnormalities resulting in an increase of 2 DAIDS grades from baseline will be followed until return to baseline or within 1 grade from baseline.

4.0 PHARMACY CONSIDERATIONS

4.1 Study Product Considerations

<u>Splitting 25 mg scored etravirine study drug tablet into two equal half-tablets.</u>

The study participant or caregiver should be instructed on how to split the scored 25 mg etravirine tablet if needed to obtain the desired dose per dosing instructions by the site pharmacist and as noted in the Drug Dosing Table, Appendix III of the protocol to ensure patient safety and minimize chance of error and adverse events.

Precautions should include, but may not be limited to, the following:

The scored 25 mg etravirine tablet should split consistently into equal parts using either the fingers or a tablet cutting device. Use of a device is preferred if feasible to help improve the accuracy of each half tablet.

Pharmacists or the designated, trained study staff should ensure that the subject or the subject's caregiver:

- Understands the purpose for splitting tablets.
- Understands the intended dose and treatment regimen.
- Is physically able to easily and accurately split the scored 25 mg etravirine tablet into two equal parts. The pharmacist or the designated, trained study staff should suggest the use of a tablet cutting device when appropriate.
- Is instructed to take the second half of the split tablet for the next dose that requires a half tablet.
- Is encouraged to report any problems with splitting the tablets or ingesting the split tablets to the site study clinician and site pharmacist.

4.2 Instructions for the Caregiver

General Instructions & Safety Information

It is important that the medicine be stored away from children so that they do not accidentally take a dose that is not meant for them or so that they do not take an overdose.

If you have any questions or instructions about these instructions, please talk to the study staff, who can help you.

Should my child eat before taking etravirine tablets?

Your child should be a given a meal approximately 30 minutes before taking their etravirine medication. Your child should not take the etravirine study medication on an empty stomach.

What should I do with the little pouches that are in the bottle of etravirine tablets?

The little pouches in your medicine bottle are called desiccant pouches. The pouches contain a drying agent. They help collect any moisture in the bottle and so make sure the tablets stay in the right conditions. The bottle should be kept tightly closed in order to protect from moisture and the desiccant pouches must always be kept in the bottle. DO NOT open these packages and DO NOT eat them. Do not take the tablets out to put them in another bottle or pillbox.

What should I do if my child cannot swallow the etravirine tablets?

If your child cannot swallow a whole tablet by mouth, you may put the tablet in a container with at least 1 teaspoon (5mL) of sterile water or other safe drinking water. The tablet-water mixture should be stirred for about 1 minute. The tablet-water mixture can then be further diluted with a beverage (see list below) but there should not be more than 2 tablespoons (30mL) of the added drink.

Warm or fizzy drinks (for example: soda, hot tea etc) MUST NOT be used to take the etravirine study drug medicine. Etravirine can be taken with any of the following beverages:

- Water that is safe to drink (If necessary, sterile water will be provided by the study staff for the purposes of this study)
- Mineral water that is safe to drink
- Orange juice

- Milk (whole milk, skim milk or chocolate milk)
- Various infant formula

For infants, it is recommended to put the tablet in approximately 2 teaspoons (10mL) of liquid (such as formula or milk). Once mixed, the infant should be given the study medicine mixture by mouth, to drink right away.

After the infant has taken the mixture, an additional 1 teaspoon (5mL) of water, juice, milk or infant formula should be added to the container and this rinse should also be given to the child to make sure that the entire dose is consumed. The tablet-water mixture should be given the child right away and all the dose of study drug medicine should be swallowed; it is not allowed to take only some of the dose of medicine.

What do I do if my child only needs half a tablet?

If your child only needs to take a half of a tablet, you will need to cut the tablet. You can break the tablet using your fingers or by using a tablet cutter as instructed by the study staff. You can then save the other half in a container until your child's next dose.

Below are suggestions for cutting the tablets and for cleaning the tablet cutter.

Manual tablet splitting instructions:

- Wash your hands in clean water. Be sure to completely dry your hands before taking any tablets out of the bottle.
- Place one scored, 25 mg etravirine tablet with the scored side facing up on a clean, dry hard surface.
- Place two fingers, one on each side of the scored tablet.
- Press down on each side of the scored tablet (towards the edge of the tablet) while applying equal pressure until the tablet splits along the scored line into two equal parts.

Tablet cutter instructions:

- Insert the tablet into the tablet cutter.
- Place the tablet with the scored side of the tablet facing up on the "V" shaped holder of the tablet cutter.
- Position the tablet such that the scored line on the tablet is in line with the blade and the tablet can be cut along the scored line on the tablet.
- Close and press cover to split tablet.
- Open and remove the split tablet.
- After cleaning, close cover and store in closed position.
- Store the tablet cutter in a secure place away from children as the cutter is sharp and must be handled with care.

Tablet cutter cleaning instructions:

- After each use, wash with clean water, preferably warm, clean water to remove any leftover powder or particles.
- Open tablet cutter about halfway.
- Flush tablet cutter with clean water, preferably warm, clean water, to rinse.

- Stand the tablet cutter on end in a partially open position to air dry in a secure place away from children.

Can I cut several tablets in half and put them back in the bottle so I do not have to cut them every day?

No, do not cut the tablets in half in advance. Cut the tablet when needed. You can then save the other half in a container until your child's next dose. Keep all etravirine study drugs away from children.

What should I do if my child misses their usual dose of etravirine study medication?

If your child misses a dose of etravirine study medication and if it is within 6 hours of the usual time they take it, you should give your child the missed dose of study medication following a meal as soon as possible. Your child should then take their next dose of etravirine study medicine at the normal time.

If your child is not able to take their missed dose of etravirine study medication within 6 hours of the normal time he/she takes it, you should not give your child the medicine and should wait and give them their next dose of etravirine study medicine at the normal time.

What should I do if my child doesn't take the full dose of his/her etravirine study medication?

If your child does not take the whole dose of study medicine (for example, if your child refuses to take all the medicine and some is then left in the container) then you should wait 15-30 minutes and then try to give your child the rest of the dose. If your child is still not able to take the rest of the study medicine, be sure to write it down and let the study team know.

What should I do if my child vomits after taking his/her etravirine study medication?

If your child vomits within 15 minutes of taking the etravirine study medicine, you should try to give your child another full dose of etravirine study medicine.

If your child vomits more than 15 minutes after taking the study medicine, you should NOT try to give your child another dose. Instead, be sure to write it down, let the study team know and wait to give your child his/her next dose as usual.

Do the tablets need to be refrigerated?

No. The etravirine tablets should be kept at room temperature 15°to 30°C (59° to 86°F). The tablets should not be kept in the refrigerator. The tablets must also be kept in the bottle that the pharmacist gave them to you in. The bottle should be kept tightly closed in order to protect from moisture and the desiccant pouches should be kept in the bottle. The study medicine bottle must be kept away from places that might get too hot (such examples are: a cabinet next to an oven, in direct sunlight, in a hot vehicle etc.

5.0 ADVERSE EVENTS (AEs)

5.1 Overview

An adverse event is any untoward, medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this

treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally assiciated with the use of an investigational product, regardless of the causal relationship.

This includes:

- Any clinically significant worsening of a pre-existing condition
- Any episode of overdose or abuse of a drug or investigational product

5.2 Reporting of Adverse Events for P1090

Adverse events, pregnancies and laboratory abnormalities meeting pre-defined criteria will be reported promptly by the investigator as summarized in the following table once the investigator determines that the event meets the protocol definition for that event:

EVENT	TIME FRAME	DOCUMENTATION	REPORT TO
SAE	3 days	EAE Form	RSC
Grade 3 Toxicity	1 day	e-mail	Protocol Team
Grade 4 Toxicity	1 day	e-mail	Protocol Team
	3 days	EAE Form	RSC

5.3 Causality Assessment

Grade 3 and 4 AEs will have their relationship to study drug assessed using the following terms below. The site and the team will both make assessments as to the relationship of the adverse event to the study drug.

Definitely related: Clear-cut temporal association, and no other possible cause.

Probably related: Clear-cut temporal association and a potential alternative etiology is not apparent.

Possibly related: Less clear temporal association; other etiologies also possible.

Unlikely related: Temporal association between the AE and the vaccine or the nature of the event is such that the vaccine is not likely to have had any reasonable association with the observed illness/event (cause and effect relationship improbable but not impossible).

Not related: The AE is completely independent of vaccine administration, and/or evidence exists that the event is definitely related to another etiology.

5.4 Serious Adverse Events

5.4.1 Definition

A serious adverse event is an AE occurring at any time from entry through follow-up, whether considered related to the investigational vaccine or not, that meets one of the following conditions:

- Death during the protocol-defined surveillance period

- Life threatening: defined as an event that places a subject at immediate risk of death at the time of the event and does not refer to an event that hypothetically might have caused death were it more severe
- Hospitalization[1] during the period of protocol-defined surveillance: defined as inpatient hospitalization or prolongation of existing hospitalization
- Results in a congenital anomaly or birth defect
- Results in a persistent or significant disability or incapacity; defined as a substantial disruption of the study participant's ability to carry out normal life functions.
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious AE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention.
- Life threatening refers to immediate risk of death from the event as it occurred. It does not include an experience that had it occurred in a more severe form might have caused death but as it actually occurred did not create an immediate risk of death.

1. Hospitalization is to be considered a serious adverse event only in the event of an overnight admission. An elective hospitalization for a pre-existing condition that has not worsened does not constitute an SAE.

6.0 SPECIMEN COLLECTION and PROCESSING

6.1 Introduction

This section contains instructions related to collection and processing of P1090 specimens. For detailed information on tests and specimens required for each visit, please refer to the P1090 Schedule of Evaluations (Appendix I) of the P1090 protocol (www.impaactgroup.org)

Regardless of where tests are performed, personnel who collect specimens and/or perform assays must be trained in proper collection, handling, testing and associated QA/QC procedures prior to performing the tests for study purposes. Training documentation must be available for inspection at any time.

All laboratory activities should be conducted in accordance with accepted Good Clinical Laboratory Practice (GCLP), the IMPAACT and ACTG Network Laboratory Joint Laboratory Manual and site-specific Standard Operating Procedures (SOPs) for proper collection, processing, labeling, and transport of specimens. Transport of all specimens must comply with federal, state, local, IATA and ACTG/IMPAACT specimen shipping regulations.

As the transmission of HIV and other blood-borne diseases can occur through contact with contaminated needles, blood and blood products, appropriate precautions should be employed by all personnel when drawing blood and handling clinical specimens for this study in both the clinical and laboratory setting, as recommended by the Centers for Disease Control and Prevention (CDC). Respiratory infections may be transmitted by droplet aerosolization and fomites. All study staff should take appropriate precautions when collecting and handling biological specimens. Guidance on Universal Precautions/ Body Substance Isolation is available from the US Centers for Disease Control and Prevention: http://www.cdc.gov/ncidod/dhqp/bp_universal_precautions.html

Additional laboratory reference information can be found in the joint ACTG/IMPAACT Laboratory Manual, which is available at:
http://www.hanc.info/labs/Pages/actgimpaactlabmanual.aspx

6.2 General Overview and Guidelines

Key elements of specimen management include collection, transport, storage and shipping. Also essential for clinical trials is a Chain of Custody which refers to the tracking of specimens and results.

It is essential that all staff collecting P1090 specimens have been trained in proper collection techniques, container types, and any special requirements. Specimens must be transported within predefined time limits to the laboratory under proper conditions. The remainder of this section provides information intended to standardize specimen collection and laboratory procedures across sites.

6.2.1 Specimen Chain of Custody

All IMPAACT sites must have a Standard Operating Procedure (SOP) for Chain of Custody in place. The Chain of Custody must track when specimens are transferred between clinics, processing units, and laboratories. Internal movements of specimens within the same laboratory do not need to be tracked. Laboratories with Laboratory Information Management Systems (LIMS) or the Laboratory Data Management System (LDMS) may be able to track most Chain of Custody information electronically. Tracking forms with specific information must accompany specimens. Required information includes the following: the PID/SID, collection time and date, and visit code for each specimen. Subject names or initials may NOT be used on research samples or the accompanying tracking forms.

6.2.2 Labeling Specimens

All samples collected at a study visit must be labeled at the time of collection with the PID, visit number, and collection date. If collecting PK specimens, time and time unit are also required. PID and visit numbers may be pre-printed on these labels; however study staff must write the specimen collection date and time (if needed) on each label. Information on the specimen containers must match the information on the tracking forms. All samples must be entered into the LDMS system and aliquots must be labeled using standard LDMS-generated barcode labels.

6.2.3 Laboratory Data Management System (LDMS)

The LDMS must be used at all sites to track the collection, storage, and shipment of the laboratory specimens. Detailed instructions for use of the LDMS are available at:
http://www.fstrf.org/ldms

All sites should upgrade to the most current version of the LDMS as soon as possible. For supported label and printer options, refer to the product listing documents located on the LDMS Client Reference Guides page on the FSTRF Portal. Contact LDMS user support for further information.

Questions about LDMS, shipping and storage for this protocol should be raised with the Laboratory Data Manager at FSTRF:

Oswald Dadson, FSTRF
Phone: (716) 834-0900, extension 7238
Email: dadson@fstrf.org

24-Hour LDMS User Support

Technical support is also available from LDMS User Support. Usual business hours from LDMS user support are 12 AM - 6:00 PM Eastern Time in the US (ET) Monday through Friday. During business hours, please contact LDMS User support as follows:

Email: Ldmshelp@fstrf.org
Phone: (716) 834-0900, extension 7311
Fax: (716) 898-7711

Off-Hours Contact Information

If you are locked out of your LDMS or are experiencing errors that prevent you from completing your LDMS lab work during off-hours, page LDMS User Support using the LDMS Web Pager utility. Alternatively, you may e-mail the paging system directly at ldmspager1@fstrf.org. Please allow at least 15 minutes to get a response before sending another e-mail to the paging system.

Additional Resources:

LDMS website:
http://www.fstrf.org/ldms/

FSTRF portal:
http://www.fstrf.org/portal/

6.3 Specimen Collection Procedures

Table 2 outlines all samples required by the P1090 protocol. The table identifies the type of collection tube, the amount and type of specimen to be processed and stored, and the required tests.

6.3.1 HIV-1 RNA Assay

For this study, the Abbott platform only may be used for the HIV-1 RNA PCR assay. If your local laboratory does not run the Abbott platform, you can visit the HANC website to obtain a list of labs that are certified to run the Abbott platform. Sites should contact the team if they have any questions - impaact.teamp1090@fstrf.org

If sites are planning to use the **Seattle Children's Research Institute (SCRI) Lab** for performing viral load assays, they should be sure to include the specimen shipping requisition form in Appendix IV of the MOP.

HANC Laboratory Resources site:
https://www.hanc.info/labs/labresources/Pages/informationActgImpaactLabs.aspx

Table 2. Specimen Collection and Testing Summary

Assay / Procedure	Collection Container	Specimen Type	Additional Information
HIV GENOTYPING (SCREENING)	EDTA	Plasma	Real time shipping
HIV GENOTYPING (VIROLOGIC FAILURE)	EDTA	Plasma	Shipped in batches quarterly
PHENOTYPING (SCREENING)	EDTA	Plasma	Real time shipping
PHENOTYPING (VIROLOGIC FAILURE & EARLY D/C)	EDTA	Plasma	Shipped in batches quarterly
HIV-1 RNA VIRAL LOAD	EDTA	Plasma	Real time – Abbott assay only
CYP GENOTYPING	EDTA	Packed whole Bld.	Shipping in batches
CHEMISTRIES	NON / SST	Serum	Real time – local laboratory
HEMATOLOGY	EDTA	Whole Blood	Real time – local laboratory
CHOLESTEROL / TRIGLYCERIDES	NON/SST or Li-Heparin	Serum or plasma	Real time – local laboratory
COAGULATION ASSAYS	NaCitrate	Plasma	Real time – local laboratory (domestic sites only)
LYMPHOCYTE SUBSET	EDTA	Whole Blood	Real time – local laboratory
URINALYSIS	n/a	Urine	Real time – local laboratory
PELLETS / PLASMA FOR STORAGE	EDTA	Plasma/PBMC pellets	Shipping in batches
INTENSIVE PK SPECIMENS	EDTA	Plasma	Blood volume to be collected changes with the cohort; Real time shipping
POPULATION PK SPECIMENS	EDTA	Plasma	Blood volume to be collected changes with the cohort; Shipped at the end of the study per team instructions

6.4 Specimen Processing Procedures

For laboratory processing instructions for specimens, please refer to the Laboratory Processing Chart which is located on the P1090 IMPAACT webpage:
http://impaactnetwork.org/studies/P1090.asp

6.5 Shipping Procedures

For additional shipping instructions and addresses, please refer to the P1090 Laboratory Processing Chart (LPC) available on the P1090 IMPAACT webpage:
(http://impaactnetwork.org/studies/P1090.asp). If you have additional questions, please contact the team at impaact.teamP1090@fstrf.org

6.5.1 Instructions for BRI 'Pass-Through' Specimens

This process is to be used ONLY for the following laboratories and specimens:

- Phenotyping (ALL non-US sites)
- Intensive PK assays (ALL non-US Sites)
- Population PK assays (ALL non-US Sites)

a. When creating the LDMS shipping batch select the appropriate testing laboratory as the shipment destination based on the P1090 LPC:
   - Phenotyping – Monogram Biosciences – Lab code 903
   - Intensive PK assays – University of Colorado, Denver – Lab code 533
   - Population PK assays – University of Colorado, Denver – Lab code 533

   IMPORTANT: When preparing the LDMS shipment as a 'pass-through', DO NOT select lab 999 (BRI) as the destination. BRI is not the final destination for any 'pass-through' specimens

b. Pack the specimens as you normally would and address the Safety Pack/World Courier Secondary Packaging and specimen freezer boxes to the final shipment destination of Lab code: 903 or 533

c. Be sure to include the correct "Pass Through" shipping notification inside the box addressed to BRI. The shipping notifications can be found in Appendix II and III of the MOP. Refer to the figure below on shipping.

d. Be sure to send the LDMS shipping manifest and any necessary CRFs to the testing lab.

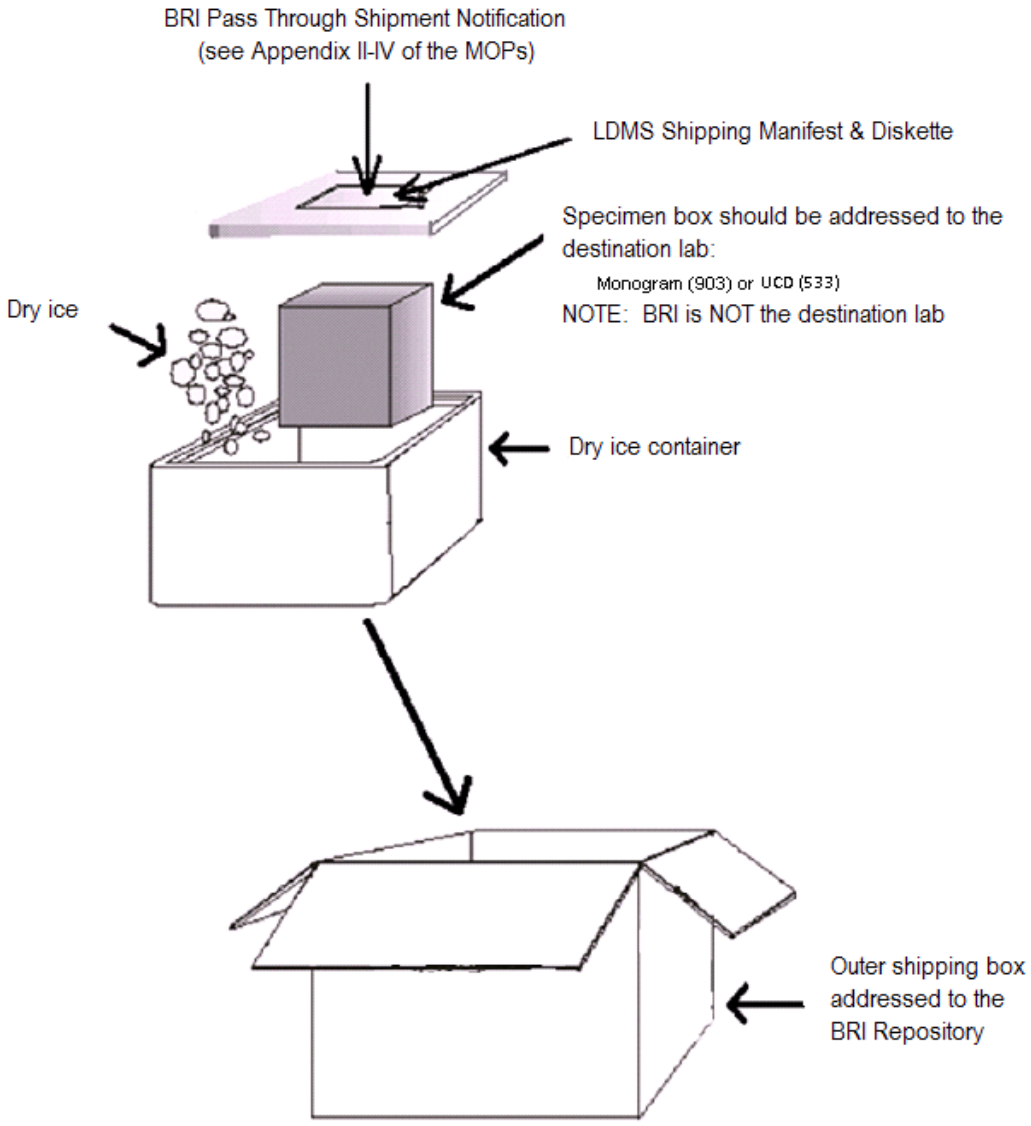
e. Please indicate this is a "Pass Through" shipment to Lab XXX in the Explanation section of the Shipment Form.

f. Please contact BRI directly for their current CDC Import Permit (BRIRepository@aol.com).

g. Place this fully packed and addressed shipment within a box and address the outer box to the BRI repository:

Biomedical Research Institute
c/o John C. Ward, Jr.
12264 Wilkins Avenue, Bay F
Rockville, MD 20852

Phone: (301)881-7636
Fax: (301)770-9811
Email: BRIrepository@aol.com



6.6 Additional Resources

ACTG/IMPAACT Laboratory Manual:
http://www.hanc.info/labs/Pages/actgimpaactlabmanual.aspx

ACTN Specimen Processing Guide:
http://www.hanc.info/labs/Pages/actgimpaactlabmanual.aspx

ACTN Guidelines for Shipping Diagnostic Specimens:
http://www.hanc.info/labs/Pages/actgimpaactlabmanual.aspx

ACTN Guidelines for Shipping Infectious Substances:
http://www.hanc.info/labs/Pages/actgimpaactlabmanual.aspx

IMPAACT Specimen Repository (BRI) Shipping Guidelines:
http://impaactnetwork.org/about-us/LabCenter/SpecRepository.htm

7.0 DATA MANAGEMENT

7.1 Assignment of a Patient Identification Number (PID)

The PID is assigned at the site from a list that is generated by the DMC (FSTRF) and sent to the sites. If a subject has been on another IMPAACT or ACTG study, the same PID is carried with them for use in the new study; a new PID number would not be assigned.

7.2 Source Documents

Demographic, sample collection, clinical examination, and AE data must be collected and recorded by the Investigator's designated personnel, directly on chart documents or investigator spreadsheets, and maintained as source documents.

Medical charts and/or subject charts, temperature cards, and any other collection tool may be used for verification of information recorded in the source documents or on Investigator spreadsheets.

All documentation must be made available to the monitor at scheduled monitoring visits.

7.3 Case Report Forms

Site staff can find the schedule of case report forms for this study on the FSTRF website (www.fstrf.org).

7.4 Resources

Questions regarding data mangement, case report forms etc should be directed to the P1090 Data Manager, Bobbie Graham, who can be reached via the contact information below:

Bobbie Graham,
FSTRF
4033 Maple Road
Amherst, NY 14226
Phone: (716) 834-0900 ext. 7265
Fax: (716) 834-8675
Email: bgraham@fstrf.org

Additionally, you may access the FSTRF website for additional information and resources at www.fstrf.org.

APPENDIX I

P1090 PK Medication Log

Subject PID: _____

Date of visit	Previous etravirine dosing	Date taken (mmm/dd/yyyy)	Time taken (hh:mm)	Dose taken (mg)
Example: APR/11/2012	*7 days before the PK visit*	*APR/04/2012*	*7:30*	*30*
	6 days before the PK visit	*APR/05/2012*	*8:25*	*30*
	5 days before the PK visit	*APR/06/2012*	*8:10*	*30*
	4 days before the PK visit	*APR/07/2012*	*8:10*	*30*
	3 days before the PK visit	*APR/08/2012*	*7:30*	*30*
	2 days before the PK visit	*APR/09/2012*	*8:25*	*30*
	1 day before the PK visit	*APR/10/2012*	*8:10*	*30*
Intensive PK	7 days before the PK visit			
	6 days before the PK visit			
	5 days before the PK visit			
	4 days before the PK visit			
	3 days before the PK visit			
	2 days before the PK visit			
	1 day before the PK visit			
Week 4	7 days before the PK visit			
	6 days before the PK visit			
	5 days before the PK visit			
	4 days before the PK visit			
	3 days before the PK visit			
	2 days before the PK visit			
	1 day before the PK visit			
Week 8	7 days before the PK visit			
	6 days before the PK visit			
	5 days before the PK visit			
	4 days before the PK visit			
	3 days before the PK visit			
	2 days before the PK visit			
	1 day before the PK visit			
Week 12	7 days before the PK visit			
	6 days before the PK visit			
	5 days before the PK visit			
	4 days before the PK visit			
	3 days before the PK visit			
	2 days before the PK visit			
	1 day before the PK visit			
Week 24	7 days before the PK visit			
	6 days before the PK visit			
	5 days before the PK visit			
	4 days before the PK visit			
	3 days before the PK visit			
	2 days before the PK visit			
	1 day before the PK visit			

Date of visit	Previous etravirine dosing	Date taken (mmm/dd/yyyy)	Time taken (hh:mm)	Dose taken (mg)
Week 48	7 days before the PK visit			
	6 days before the PK visit			
	5 days before the PK visit			
	4 days before the PK visit			
	3 days before the PK visit			
	2 days before the PK visit			
	1 day before the PK visit			
Virologic Failure	7 days before the PK visit			
	6 days before the PK visit			
	5 days before the PK visit			
	4 days before the PK visit			
	3 days before the PK visit			
	2 days before the PK visit			
	1 day before the PK visit			

APPENDIX II

Phenotyping Specimens

BRI PASS THROUGH NOTIFICATION

P1090 Pass-Through Samples

LDMS Inventory/
BRI Storage Not Required

Phenotyping specimens

Ship to **Lab 903: Monogram**

Attn: Monogram Biosciences, Inc.
345 Oyster Point Blvd.
South San Francisco, CA 94080-1913

PHONE: (650) 866-7482
FAX NUMBER: (650) 624-4457

Email: **receiving@MonogramBio.com**

APPENDIX III

Intensive PK Specimens

BRI PASS THROUGH NOTIFICATION

P1090 Pass-Through Samples

LDMS Inventory/
BRI Storage Not Required

Intensive PK Specimens

Ship to **Lab 533 :**
University of Colorado Denver

Attn: Lane Bushman
COLORADO ANTIVIRAL PHARMACOLOGY LABORATORY
UNIVERSITY OF COLORADO DENVER
Skaggs School of Pharmacy,
Room 4410, V20-C238
12850 E Montview Blvd
Aurora, CO 80045

PHONE: (303) 724-6132
FAX NUMBER: (303) 724-6135

Email: lane.bushman@ucdenver.edu

APPENDIX IV
P1090 Specimen Testing Requisition

IMPORTANT: Please use this form when shipping specimens to **Seattle Children's Research Institute (SCRI) Lab,** whether it is a direct shipment to SCRI, or if specimens will be sent to BRI first and then on to SCRI in real time. Please contact the team with any questions (impaact.teamp1090@fstrf.org)

Site Name & Number: _____

Site Contact Name & Phone Number: _____

Subject PID	Date of Specimen Collection	Study Visit	Plasma HIV Viral Load* (c/mL)	Laboratory Testing Required	
				Genotyping (Screening)	Genotyping (Virologic failure)
Example: 123456J	*March 1, 2011*	*Screening*	*45,000*	*X*	

*If viral load data is not available on specimen's ship date, please forward viral load by email to sheila.styrchak@seattlechildrens.org or ingrid.beck@seattlechildrens.org as soon as possible. Specimens will not be processed until viral loads are received.