IMPAACT 2007

Phase I Safety and Pharmacokinetic Study of Maraviroc in HIV-1-Exposed Infants at Risk of Acquiring HIV-1 Infection

Manual of Procedures

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IMPAACT 2007 Manual of Procedures

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1.0 Study Overview

IMPAACT 2007 is a Phase I, multi-center, open label, intensive PK study to evaluate the safety and PK of maraviroc solution when administered with a single or combination ARV regimen for prevention of perinatal HIV transmission to HIV-1 exposed infants at risk of infection. The aim of the study is to determine an appropriate dose of maraviroc solution during the first six weeks of life for infants born to HIV-1 infected mothers.

The study involves two sequential dosing cohorts. Cohort 1 will be stratified by in utero exposure to maternal EFV and Cohort 2 will be stratified by exposure to maternal EFV during breastfeeding, as follows:

Cohort 1: Infant *in utero* exposure to maternal EFV	
Stratum 1A:	Infants without in utero exposure to maternal EFV (no EFV exposure during the eight weeks immediately prior to delivery) (n= 6-18)
Stratum 1B:	Infants with in utero exposure to maternal EFV (EFV exposure for a minimum of two weeks immediately prior to delivery) (n= 6-18)

Cohort 2: Infant exposure to maternal EFV after birth	
Stratum 2A:	Infants without any exposure to maternal EFV either *in utero* (no EFV exposure during the eight weeks immediately prior to delivery) and if breastfeeding while breastfeeding. (n= 12-18)
Stratum 2B:	Infants with exposure to maternal EFV both *in utero* and after birth while breastfeeding (EFV exposure for a minimum of two weeks immediately prior to delivery and while breastfeeding). (n= 12-18)

Breastfeeding and formula feeding infants are eligible for Strata 1A, 1B and 2A; only breastfeeding infants are eligible for Stratum 2B. Up to 72 mother-infant pairs are expected to be enrolled to achieve 36 evaluable infants receiving the final recommended dose of maraviroc. Accrual is expected to require approximately 24 months and enrolled infants will be followed for four months.

2.0 Preparing for the Study

This study will be conducted at the following IMPAACT clinical research sites (CRSs), which were selected by the Protocol Team based on review and approval of a Site Application and Site Implementation Plan (SIP):

CRS 4001	Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, United States
CRS 4601	University of California at San Diego, CRS, San Diego, United States
CRS 5011	Boston Medical Center CRS, Boston, United States
CRS 5048	University of Southern California CRS, Los Angeles, United States
CRS 5052	University of Colorado Denver CRS, Aurora, United States
CRS 5083	Rush University Cook County Hospital Chicago CRS, Chicago, United States
CRS 5115	Siriraj Hospital Mahidol University CRS, Bangkok, Thailand
CRS 5121	Kenya Medical Research Institute - Walter Reed Project CRS, Kericho, Kenya
CRS 6501	St. Jude Children's Research Hospital, Memphis, United States
CRS 8052	Perinatal HIV Research Unit CRS, Johannesburg, South Africa
CRS 30293	Makerere University - Johns Hopkins University CRS, Kampala, Uganda
CRS 30300	CAPRISA Umlazi CRS, Durban, South Africa

A copy of the approved Site Application and SIP should be maintained in each site's study-specific essential document files.

2.1 Investigator Responsibilities

At each site, this study must be conducted in accordance with the United States (US) Code of Federal Regulations (CFR) and the International Conference on Harmonization (ICH) Consolidated Guidance for Good Clinical Practice (GCP). The Division of AIDS (DAIDS) policies on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* and *Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials* are useful for interpreting and operationalizing the regulations and guidelines in accordance with DAIDS expectations. These policies are available at the following website and must be followed throughout implementation of IMPAACT 2007:

https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures

This study also must be conducted in accordance with all site-specific regulations, policies, and guidelines applicable to human subjects research in general and/or the conduct of study procedures in particular. Copies of all of the above-listed regulations, policies, and guidelines should be maintained in on-site essential document files.

The Investigator of Record (IoR) at each site must sign a US Food and Drug Administration (FDA) 1572 Form to formally indicate his or her agreement to conduct the study in accordance with the protocol and all applicable regulations, policies, and guidelines. The obligations and responsibilities assumed by the IoR when signing this form are listed on the form, which is available on the DAIDS Regulatory Support Center (RSC) website:

http://rsc.tech-res.com/clinical-research-sites/protocol-registration

IoRs may delegate their obligations and responsibilities for conducting this study to other study staff; however, delegation does not relieve the IoR of his or her ultimate responsibility for all study procedures performed and all study data collected. Delegation of IoR responsibilities must be formally documented throughout the period of study implementation.

Additionally, IoRs and all sub-investigators as designated on the FDA 1572 form must complete a ViiV Healthcare Statement of Investigator Financial Interest, Forms A and B. Form A should be completed and submitted to the protocol CTS at the Operations Center prior to study implementation, and Form B should be completed at the end of study participant. Form B should also be used if the investigator needs to self-report due to a change in their financial interest during their participation in the study, and up to one year after ending their participation in the study.

Consistent with the regulations, guidelines, and policies cited above, the IoR at each site must obtain all applicable drug regulatory and ethical review approvals prior to study initiation; the IoR must also maintain these approvals in good standing throughout the period of study implementation. With regard to drug regulatory authorities (DRAs), the IoR must complete initial and continuing submissions in accordance with DRA policies. With regard to institutional review boards and ethics committees (IRBs/ECs), further guidance on initial and continuing review requirements is available in 45 CFR 46, 21 CFR 56 and the ICH GCP guidance, as well as on the website of the US Office for Human Research Protections (OHRP):

http://www.hhs.gov/ohrp/

All sites are encouraged to request an acknowledgement of receipt for all documents submitted to their DRAs and IRBs/ECs and to request that DRAs and IRBs/ECs note the effective and expiry dates of all approvals. Because IMPAACT 2007 involves maternal and pediatric participants, IRBs/ECs must consider the potential benefits, risks, and discomforts of the study to maternal and infant participants and assess the justification for their inclusion in the study (see protocol Section 13.2). As part of this assessment, IRB/ECs must assess the level of risk to participants as described in protocol Section 13.2.

Complete documentation of all correspondence to and from all responsible DRAs and IRBs/ECs (i.e., complete copies of all submissions, responses, and approvals) must be maintained in on-site essential document files. All submission letters should list the date of the submission, the contents of the submission, and the version number and/or version date of each document submitted.

2.2 Protocol Registration

The IMPAACT Operations Center will notify the DAIDS Protocol Registration Office (PRO) that sites with SIPs and Site Applications approved by the Protocol Team are permitted to submit for protocol registration for the study. After all required DRA and IRB/EC approvals are obtained, site staff are then responsible for submitting documentation of the approvals and other required documentation to the PRO as described in protocol Section 14.2.

2.3 Site-Specific Study Activation

Prior to conducting any study procedures, each site must obtain all required approvals as described in Section 2.2 above. Each site must also complete study-specific activation requirements specified by the Protocol Team to obtain approval to begin study implementation. These requirements are listed on the IMPAACT 2007 Site-Specific Study Activation Checklist, which is available from the IMPAACT Operations Center.

Any questions related to the study activation process should be directed to the IMPAACT Operations Center. On a site-by-site basis, when all activation requirements have been met, the Operations Center will issue a site-specific study activation notice. At each site, no study procedures may be performed prior to receipt of the activation notice.

3.0 Study Resources

This section specifies the resources available to IMPAACT 2007 study site staff, including contact information, an overview of study-related informational resources, the Data Management Center (DMC) IMPAACT Portal, and other essential documents.

3.1 Study-Related Information and Communications

All IMPAACT 2007 visits and procedures must be conducted in accordance with the study protocol. The purpose of this manual is to supplement the protocol, not to replace or substitute for it. If this manual is inconsistent with the protocol, the specifications of the protocol take precedence. Please notify the IMPAACT Operations Center of any such inconsistencies.

The Protocol Team has developed study-specific contacts for various types of issues and questions, as summarized below, with further details provided in Figure 3-1. For issues and questions directed to the study team, a response from the appropriate team member can generally be expected within 24 hours.

Figure 3-1
IMPAACT 2007 Study-Related Communications

Topic	Contact
Clinical user support and adding site staff to protocol email group (IMPAACT.prot2007@fstrf.org)	**User Support** **user.support@fstrf.org** *(include the protocol number in the subject line of your email message)*
Any aspect of protocol interpretation or study implementation not listed below	**IMPAACT 2007 Protocol Team** **impaact.team2007@fstrf.org** *for triage to other team members as needed*
Clinical and toxicity management issues	**IMPAACT 2007 Core Team** **impaact.core2007@fstrf.org**
Participant eligibility, potential enrollment of an ineligible participant, and/or deviation from protocol requirements for eligibility determination and/or enrollment	**IMPAACT 2007 Core Team** **impaact.core2007@fstrf.org**
Co-enrollment	**IMPAACT 2007 Core Team** **impaact.core2007@fstrf.org**
Data management computer and screen problems	**User Support (FSTRF)** **user.support@fstrf.org** *or by phone: +716-834-0900 x7302*
Subject Enrollment System	**DMC Randomization Support Office** **rando.support@fstrf.org** *or by phone: +716-834-0900 x7301*
Study drugs (other than study drug orders)	**Protocol Pharmacist** Bijal Patel, Pharm. D, BCPS **bijal.patel@nih.gov** *or by phone: 250-421-8445*
Study drug orders	**Clinical Research Products Management Center** **BIO.CRPMC.Ph@Thermofisher.com** *(or by phone: +301-294-0741)*
Expedited Adverse Event (EAE) Reporting	**DAIDS RSC Safety Office** **DAIDSRSCSafetyOffice@tech-res.com** *or by phone: 800-537-9979 or +301-897-1709* *or by fax: 800-275-7619 or +301-8977-1710*
DAIDS Adverse Experience Reporting System (DAERS)	**NIAID Clinical Research Management System** **CRMSSupport@niaid.nih.gov** *or by phone: 1-240-778-2517* *(questions also may be submitted from within the DAERS application)*

The IMPAACT 2007 Core Team is composed of study team members who have been designated to receive and reply to clinical management questions and notifications. When submitting clinical management questions to the IMPAACT 2007 Core Team, please address each of the points listed in Figure 3-2 to help ensure that Core Team members have adequate information to respond in a timely manner. The responding Core Team member will reply to your question or notification by return email.

Figure 3-2
IMPAACT 2007 Core Team Communications

Questions for IMPAACT 2007 Core Team: Please copy and paste this listing into the body of your email message to impaact.core2007@fstrf.org to help ensure that all required information is included. Include the protocol number and PID in the subject line of your email.

1. Site name and number:
2. Name of person submitting query:
3. PID(s):
4. Date enrolled:
5. Query is for consultation on (choose one):
   a. Eligibility or enrollment (describe in case description)
   b. Adverse event (AE) or toxicity management (specify diagnoses or symptoms, severity grade, and relationship assessment in case description)
   c. Study drug management (describe in case description)
   d. Other (specify in case description)
6. Stratum: 1A, 1B, 2A, or 2B
7. Age (days) of participant:
8. Current week on study:
9. Current day/week of study drug (maraviroc) dosing (include number of doses received and doses of ARVs, if applicable):
10. Case description and question or notification for Core Team:

Print and file a copy of the email exchange in the participant's study chart.

The IMPAACT 2007 protocol also details the circumstances in which Investigators of Record (IoRs) should consult with the Core Team. For ease of reference, a summary of issues requiring consultation with the IMPAACT 2007 Core Team is provided below in Figure 3-3. IoRs are also encouraged to contact Core Team with any other issues, questions, or concerns related to study drug.

Figure 3-3
Requirements for Consultation with the IMPAACT 2007 Core Team

Issues Requiring Consultation with the Core Team

Study Implementation

- A participant requires any of the disallowed medications listed in protocol Section 5.11.
- Investigator or designee determines continued participation in the study would be unsafe or otherwise not in the best interest of the participant.

Cohort 1 Toxicity Management

- Management of infants with confirmed Grade 1 ALT, any ≥ Grade 2 ALT or AST, and any ≥ Grade 3 laboratory and clinical events, regardless of relationship to maraviroc, as soon as possible and within 3 business days of site awareness
- Prior to administering the second dose of maraviroc in infants following:
  - Confirmed Grade 2 ALT
  - Confirmed Grade 3 ALT or AST
  - Confirmed Grade 4 laboratory values or clinical events assessed as not related, probably not related, or possibly related

Cohort 2 Toxicity Management

- Management of infants with initial and confirmed Grade 1 ALT, any ≥ Grade 2 ALT or AST, and any ≥ Grade 3 laboratory and clinical events, regardless of relationship to maraviroc, as soon as possible and within 3 business days of site awareness
- Prior to resuming dosing of maraviroc in infants following:
  - Confirmed Grade 2 ALT
  - Confirmed Grade 3 ALT or AST
  - Confirmed Grade 4 laboratory values or clinical events assessed as not related, probably not related, or possibly related

Issues for which Consultation with the Core Team is Available But Not Required

- Management of infants that experience non-maraviroc antiretroviral drug-related toxicities

3.2 Data Management Center (DMC) IMPAACT Portal

The IMPAACT Portal of the DMC website provides information, documents and tools to assist site staff with the data management aspect of conducting IMPAACT studies, including Case Report Forms (CRFs), data collection forms schedules, Participant Calendar, Subject Enrollment System and study-specific messages. The IMPAACT Portal can be accessed from the Frontier Science and Technology Research Foundation (FSTRF) webpage at **https://www.frontierscience.org/**

3.3 Case Report Form (CRF) Completion and Data Entry

The DMC has developed a Forms Manual to assist site staff in the accurate completion of CRFs used for DAIDS-sponsored Clinical Trials. The Forms Manual is located in the DMC IMPAACT Portal under the Case Report Forms heading.

The manual outlines standards and guidelines which when followed, will result in fewer queries, shorter delinquency lists, and most important, straightforward and timely analyses. The manual includes sections that cover topics such as the CRF notebook, reporting data, understanding forms, forms components and conventions, submitting data, data collection formats and participant status categories.

3.4 Study Web Page

IMPAACT 2007 study-related materials and information can be found on the study webpage of the IMPAACT website: **www.impaactnetwork.org/studies/IMPAACT2007.asp**

Resources available on this site include:

- Current version of the protocol
- Current study implementation materials, including the Laboratory Processing Chart
- Study training materials

4.0 Participant Accrual

The study aims to enroll up to 36 mother-infant pairs in each cohort to achieve a target of 12 evaluable infants for Cohort 1 (six in each stratum) and 24 evaluable infants for Cohort 2 (12 in each stratum). Accrual is expected to be completed within 24 months, beginning from the date the first participant is enrolled. Each study site should have a standard operating procedure (SOP) for participant accrual on file. All sites are responsible for following these SOPs and for updating them if needed to meet site-specific accrual projections throughout the study accrual period.

Study sites may enroll participants in Cohort 1, Cohort 2, or both. For each site, accrual will begin after all required approvals are obtained and a site-specific study activation notice is issued by the IMPAACT Operations Center, as described in Section 2.3, above. Once accrual is initiated, the SDMC will report the number of mother-infant pairs enrolled in each cohort to the Protocol Team at least monthly.

Throughout the accrual period, the Protocol Team will review accrual from each site to determine whether accrual targets should be adjusted across sites to achieve the study objectives most efficiently. Findings and recommendations from these reviews will be communicated to all sites, and all sites will adjust their accrual efforts accordingly. Similar adjustments may be made after the IMPAACT Study Monitoring Committee (SMC) reviews of the study, which are expected at least once annually.

5.0 Recruitment, Screening and Enrollment

Refer to protocol Section 4.4 for an overview of participant recruitment, screening, and enrollment processes for this study. For both cohorts, when a potentially eligible participant is identified, the mother of the infant will be informed about the study and asked to provide written informed consent for herself and her infant for the study per protocol Section 13.3. Study-specific procedures may not be performed before written informed consent is obtained. Refer to Appendix I of this manual for an overview of general considerations for obtaining informed consent.

For all mothers and infants, informed consent is also requested for storage and future research use of blood specimens collected during the study. Consent for storage and future research use of specimens may be declined, with no impact on study participation. Refer to Appendix II of this manual for an overview of general considerations for obtaining informed consent for specimen storage and future use.

Informed consent will also be documented on study case report forms (CRFs). Main study consent decisions will be recorded on the Visit Status Report CRF (ADM0040), and consent decisions for storage and future research use of blood specimens will be recorded on the Specimen Consent/Deconsent Tracking for Non-Protocol Defined Testing CRF (TRK0103).

After written informed consent for the study is obtained, and consent for storage and future research use of specimens (if applicable), study sites should obtain a screening number by completing the PS2001 IMPAACT Screening Checklist in the Subject Enrollment System (SES) on the DMC Portal. Study sites can then assign PIDs to the mother and infant and proceed with screening visit procedures to determine eligibility for the study. Refer to protocol Section 6.3 and Appendices IB-IC for infant Screening Visit requirements; maternal Screening Visit requirements are provided in protocol Section 6.1 and Appendix IA. Sites are encouraged to perform procedures that are least burdensome and/or most likely to identify ineligibility first.

Mother-infant pairs identified as ineligible for the study should be referred for non-study care and treatment as needed. *An IMPAACT 2007 Screening Failure Reasons CRF (SCR0054) must be completed for each mother-infant pair who provides informed consent but does not enroll in the study for any reason.* Study sites should complete and key enter these CRFs as soon as possible after ineligibility is determined so that reasons for non-enrollment can be carefully tracked by the Protocol Team.

For mother-infant pairs identified as potentially eligible at their screening visits, a study Entry visit will be scheduled pending receipt of screening laboratory test results. Mothers and infants who are confirmed to meet the eligibility criteria specified in protocol Sections 4.1 and 4.2 should be enrolled as a pair in the study using the SES. Following successful completion of the enrollment process, study drug may be prescribed and dispensed to the infant and all other Entry visit procedures may be performed. As described in protocol Section 6.2, mothers are considered "off study" upon completion of the Entry visit.

It is the responsibility of the IoR and other designated study staff to ensure that all required screening evaluations are performed and adequately documented, and that only participants who meet the study eligibility criteria are enrolled. Each study site should have an SOP for eligibility determination on file that describes how study staff will fulfill this responsibility; all sites must follow their SOPs when assessing eligibility for all potential participants. Any questions related to eligibility should be emailed to the IMPAACT 2007 Core Team. The Core Team should also be notified if study staff identify an ineligible participant has been enrolled, per the communication procedures described in Section 3.0 of this manual.

6.0 Study Visits and Procedures

Protocol Section 6 and Appendices IA-IC, the Schedule of Evaluations (SoEs), provide comprehensive information on procedural requirements for conducting study visits. Each site should establish SOPs for providing all relevant information and reminders to the parent or caregiver to optimize compliance with protocol requirements. Infants enrolled into the study will be followed through Week 16 of life. Figures 6-1 and 6-2 provide an illustration of the study visit schedule for an infant that enrolls in Cohort 1 and Cohort 2, respectively. For all infants, target visit dates are counted from the infant's date of birth; Day 0 = date of birth. Visits highlighted in yellow involve intensive PK evaluations; visits highlighted in green involve population PK evaluations.

For all infants, the Screening and Entry visit procedures specified in protocol Section 6 and the SoEs must be performed within three days of birth. All procedures may be performed on the same day or over multiple days within three days of birth. The study informed consent form presents the procedures required at Screening and Entry separately, but this organization of information is not intended to preclude performing all procedures on the same day. However, all screening laboratory test results required for eligibility determination must be available prior to enrollment.

Laboratory tests that comply with the requirements specified in protocol Section 6.15 and performed as part of clinical care, during the first 3 days of life, may be abstracted from the participant's medical record to meet the Screening laboratory requirements and do not need to be repeated. Operationally, specimen collection for required evaluations should be managed by the site investigator or designee to minimize needle sticks and avoid specimen collection for infants who are not confirmed to be eligible, when possible.

Figure 6-1: Cohort 1 Follow-up Visit Schedule

Visit	Target Visit Day	Visit Window	
		Window Opens	Window Closes
Screen/Entry[1]	-	Day 0[2]	Day 3
Week 1	Day 7	Day 7	Day 14
7 Days Post Dose Safety	7 days after receiving last dose of study drug	7 days after Week 1 visit – 3 days	7 days after Week 1 visit + 3 days
Week 6	Day 35	Day 35	Day 42
Week 16 or Early Study Discontinuation	Day 112	Day 112	Day 140

[1] Intensive PK sampling should be initiated after enrollment and on the same day as the first dose of maraviroc.
[2] Day 0 = date of birth.

Figure 6-2: Cohort 2 Follow-up Visit Schedule

Cohort 2: Follow-up Visit Schedule			
Visit	Target Visit Day	Visit Window	
		Window Opens	Window Closes
Screen/Entry	-	Day 0[1]	Day 3
Week 1	Day 7	Day 7	Day 14
Week 4	Day 28	Day 21	Day 31
Week 6	Day 35	Day 35	Day 42
Week 12	Day 84	Day 77	Day 91
Week 16 or Early Study Discontinuation	Day 112	Day 112	Day 140

[1] Day 0 = date of birth.

Further key points regarding the follow-up visit schedule are as follows:

- For infants in Cohort 2, provide instructions and adherence counseling for home administration of the study drug at the Screen/Entry visit.

- The Week 16 visit procedures specified in the SoE should be performed for infants that discontinue the study early prior to completing follow-up at Week 16.

7.0 Pharmacokinetic Considerations

Pharmacokinetic (PK) sampling procedures and information for infants enrolled in Cohort 1 and Cohort 2 are provided in Sections 6 and 10. Per protocol Appendices IB and IC, a 0.5 mL sample should be drawn for each time point for the intensive, limited and population PK sampling. Operational tips and reminders intended to assist sites in following all such requirements are provided below.

7.1 Cohort 1 Infant Entry Visit (within 3 days of birth)

Intensive PK sampling for Cohort 1 (Stratum 1A and Stratum 1B) will be done at the Entry Visit and conducted over the course of up to 72 hrs. The Entry Visit should be conducted within 3 days of birth with Day 0 defined as the infant's date of birth.

PK sampling timepoints and guidelines for Cohort 1 intensive PK sampling are as follows:

Cohort 1: Entry - Intensive PK Sampling						
Time Points	Pre-dose < 1 hr before dosing	1 – 2 hrs post-dose	4 – 8 hrs post-dose	11 – 13 hrs post-dose	20 – 24 hrs post-dose	48 – 72 hrs post-dose
	Stratum 1B only: Collect single sample for EFV level at any time <u>on the same day</u> as the first dose of maraviroc					

hr(s)=hour(s)

- PK sampling must be initiated on the <u>same day</u> as the first dose of maraviroc.
- The first single dose of maraviroc (within 3 days of birth) will be prepared by the site pharmacist and administered orally by study staff.
- If the infant vomits most or all of the dose within 30 minutes of administration, the dose should not be repeated. The PK sampling collection should then not be completed at Entry or at the

Week 1 visit per protocol Section 5.5. The infant should continue to be followed for toxicity per the Schedule of Evaluations.

- For infants in *Stratum 1B only*, a single additional 0.5 mL sample should be collected at any time on the same day as the first dose of maraviroc for analysis of EFV levels.
- Depending on site capacity, infants and their parent or caregiver may stay at the clinical research facility overnight for the PK sampling.

7.2 Cohort 1 Infant Week 1 Visit (Day 7 – 14)

Limited PK sampling for Cohort 1 (Stratum 1A and Stratum 1B) will be done at the Week 1 visit and conducted over the course of up to 26 hours. The Week 1 visit is targeted to take place on Day 7, with an allowable visit window through Day 14.

PK sampling timepoints and guidelines for Cohort 1 limited PK sampling are as follows:

Cohort 1: Week 1 - Limited PK sampling			
Time Points	Pre-dose < 48 hrs before dosing	1 – 2 hrs post-dose	22 – 26 hrs post-dose
	Stratum 1B only: Collect single sample for EFV level at any time during PK sampling		

hr(s)=hour(s)

- The second dose of maraviroc should not be administered until the Week 1 AST and ALT results are reviewed per Letter of Amendment (LoA) #1. (Note: The Week 1 pre-dose sample can be collected at any time within 48 hours prior to dosing to allow flexibility when collecting samples for the required chemistry tests.)
- The second single dose of maraviroc administered at the Week 1 visit (Day 7 – 14) of life will be prepared by the site pharmacist and administered orally by study staff.
- Post-dose PK sampling must be initiated on the same day as the second dose of maraviroc.
- If the infant vomits most or all of the dose within the first 30 minutes after administration, the dose should not be repeated. The PK sampling should not be completed, and the infant should be followed for toxicity.
- For infants in *Stratum 1B only*, a single additional 0.5 mL sample for analysis of EFV levels should also be drawn at any time during the PK sampling at the Week 1 visit.
- Depending on site capacity, infants and their parent or caregiver may stay at the clinical research facility overnight for the PK sampling.

7.3 Cohort 2 Infant Week 1 Visit (Day 7 – 14) and Week 4 Visit (Day 21 – 31)

Intensive PK sampling for Cohort 2 (Stratum 2A and Stratum 2B) will be done at the Week 1 and Week 4 visits. The intensive PK sampling timepoints for each stratum in Cohort 2 are dependent on the frequency of daily dosing determined from the corresponding stratum in Cohort 1. Infants in each stratum will be administered maraviroc either once daily or twice daily as communicated to study sites via a protocol Clarification Memorandum.

7.3.1 Cohort 2 Intensive PK with Once Daily Dosing

PK sampling timepoints and guidelines for intensive PK sampling for Cohort 2 *once daily* dosing are as follows:

Cohort 2: Weeks 1 and 4 - Intensive PK Sampling with Once Daily Dosing					
Time Points	Pre-dose < 1 hr before dosing	1 – 2 hrs post-dose	4 – 8 hrs post-dose	11 – 13 hrs post-dose	20 – 24 hrs post-dose
	Stratum 2B only: Collect single sample for EFV level at any time during PK sampling				

hr(s)=hour(s)

- PK sampling should be scheduled so that the observed dosing of maraviroc is as close as possible to 24 hours (generally 22-26 hours) after the previous dosing.
- Infants should take maraviroc for 3 days (i.e., be fully adherent) prior to the intensive PK visit; the dose and time of the three maraviroc doses administered by the parent or caregiver should be source documented and entered into CRFs. If a missed dose is reported within this period, the intensive PK visit should be rescheduled.
- Prior to this visit, the site should remind the parent or caregiver not to administer the dose of maraviroc in the home on the day of the PK sampling visit.
- The dose of maraviroc on the day of PK sampling will be directly observed by study staff in the clinic and administered orally by the parent or caregiver or study staff.
- PK sampling must be initiated on the same day as the observed dose of maraviroc
- If the infant vomits within 30 minutes after administration on the PK sampling day, the PK sampling should be rescheduled within 1-2 days when the infant can receive another maraviroc dose.
- For infants in *Stratum 2B only*, a single additional 0.5 mL sample for analysis of EFV levels should also be drawn at any time during the PK sampling at the Week 1 and 4 visits.
- Depending on site capacity, infants and their parent or caregiver may stay at the clinical research facility overnight for the PK sampling.

7.3.2 Cohort 2 Intensive PK with Twice Daily Dosing

PK sampling timepoints and guidelines for intensive PK sampling for Cohort 2 *twice daily* dosing are as follows:

Cohort 2: Weeks 1 and 4 - Intensive PK Sampling with Twice Daily Dosing					
Time Points	Pre-dose < 1 hr before dosing	1 – 2 hrs post-dose	3 – 5 hrs post-dose	6 – 8 hrs post-dose	11 – 13 hrs post-dose
	Stratum 2B only: Collect single sample for EFV level at any time during PK sampling				

hr(s)=hour(s)

- PK sampling should be scheduled so that the observed dosing of maraviroc is as close as possible to 12 hours (generally 11-13 hours) after the previous dosing.
- Infants should take maraviroc for 3 days (i.e., be fully adherent) prior to the intensive PK visit; the dose and time of the three most recent maraviroc doses administered by the parent or caregiver should be source documented and entered into CRFs. If a missed dose is reported within this period, the scheduled PK evaluation should be rescheduled.

- Prior to this visit, the site should remind the parent or caregiver not to administer the dose of maraviroc in the home on the day of the PK sampling visit.
- The dose of maraviroc on the day of PK sampling will be directly observed by study staff in the clinic and administered orally by the parent or caregiver or study staff.
- PK sampling must be initiated on the same day as the observed dose of maraviroc
- If the infant vomits within 30 minutes after administration on the PK sampling day, PK sampling should be rescheduled within 1-2 days when the infant can receive another maraviroc dose.
- For infants in *Stratum 2B only*, a single additional 0.5 mL sample for analysis of EFV levels should also be drawn at any time during the PK sampling at the Week 1 and 4 visits.

7.4 Cohort 2 Infant Week 6 Visit (Day 35 – 42)

A single 0.5 mL population PK sample for infants enrolled in Cohort 2 (Stratum 2A and Stratum 2B) will be done at the Week 6 visit. This sample may be drawn at any time. For infants in *Stratum 2B only*, an additional 0.5 mL sample for analysis of EFV levels should also be drawn at any time during this visit.

8.0 Pharmacy and Study Drug Considerations

For Cohort 1, The first single dose administered within 3 days of birth and the second single dose administered at Week 1 of life (Day 7-14), will be prepared by the site pharmacist in an appropriate size syringe and administered orally by study staff.

For Cohort 2, the first dose administered within 3 days of birth, will be prepared by the site pharmacist and administered orally by the study staff. The Week 1 and Week 4 doses will be administered orally by the parent or caregiver or study staff and directly observed in the clinic as described in the protocol Sections 6 and 10 (the parent or caregiver will be instructed not to administer the dose in the home on the days of the PK visits). The parent or caregiver will administer all other doses orally.

Please see protocol Section 5 for any additional information regarding study product considerations.

8.1 Supplies Available from the CRPMC for Study Product Preparation and Administration

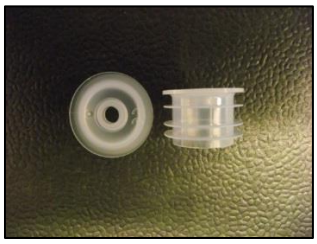
Clinical research site (CRS) pharmacists can order the following supplies from the CRPMC by following the instructions in Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks. Product may be ordered as soon as the site is protocol registered.

- Maraviroc 20mg/ mL oral solution bottles
- Press in bottle adapters (PIBA)
- Comar 1ml oral syringes
- Comar 5ml oral syringes
  Polypropylene (PP) syringe caps

8.2 Instructions for the Site Pharmacist for Preparing Maraviroc Oral Solution Bottle

1. Clean the work area, wash your hands and ensure that materials necessary are present.
2. Open bottle, set cap aside. Retain the cap.
3. The PIBA has three fins plus the top lip that acts as the stop (see Figure 8-1). Place the PIBA into the bottle opening, with the top lip or 'stop' uppermost.

Figure 8-1: Press in Bottle Adaptor (PIBA)



4. Using gentle pressure, push the PIBA down into the neck of the bottle (so that all three fins are completely inserted into the bottle) leaving only the single top lip (stop) of the PIBA outside of the bottle (Figure 8-2).

Figure 8-2: Insertion of PIBA

5. The stop should be flush with the top of the bottle (Figure 8-3). Once inserted, the PIBA should not be removed. If withdrawing solution for dose administration follow the instructions provided for preparation and administration. If dosing is not required return the cap to the bottle and securely close the bottle utilizing the original cap.

Figure 8-3: PIBA Fully Inserted

8.3 Product Labeling Instructions

Dosing syringes should be labeled with the following and any additional information required at the site:

IMPAACT 2007 Maraviroc 20mg/ml Oral Solution
PID__
Dose: _____ml
Exp:____@___: ____
Initials:_____/____

The syringe carrier bag should be labeled with a participant-specific label containing the following and any other information required at the site:

- Date dispensed
- Participant Name or Identifiers (per site's SOP)
- Directions: Administer by mouth
- IMPAACT 2007 Maraviroc 20mg/ml Oral Solution
- Expiration Date____time____in 24 hr
- Initials of pharmacy preparer and Authorized prescriber's name

The syringe carrier bag should be labeled with an auxiliary label stating:

"FOR ORAL ADMINISTRATION ONLY"

8.3.1 Product Labeling Prior to Dispensing the Maraviroc Oral Solution Bottle to the Caregiver

Sites should supply sufficient supply of syringes, syringe caps and the study product to last until the next scheduled visit.

The study product bottle should be labeled with a participant-specific label containing the following and any other information required at the site:

- Date dispensed
- Participant Name or Identifiers (per site's SOP)
- Directions: Administer by mouth (include dose in ml and frequency)
- IMPAACT 2007 Maraviroc 20mg/ml Oral Solution
- Expiration Date _____
- Initials of pharmacy preparer and Authorized prescriber's name

The bottle should be labeled with an auxiliary label stating:

"FOR ORAL ADMINISTRATION ONLY"

8.4 Caregiver Instructions for Preparation and Administration of Maraviroc Oral Solution Dose

1. Parent or caregiver should be given adequate oral dosing syringes of the correct size.
2. A clean dry syringe or syringes should be used for each dose
3. Completely depress the plunger on the dosing syringe. Remove the cap from the bottle and insert the dosing syringe tip into the PIBA.
4. Invert the bottle and syringe.

5. Pull back on the plunger of the oral dosing syringe to the appropriate graduation mark on the oral dosing syringe barrel, being careful not to remove the syringe from the PIBA (Figure 8-4). When pulling back, check for air bubbles in the syringe. If an air bubble is present, depress the plunger to expel the air and continue to pull back to obtain the full dose.

Figure 8-4: Dose Extraction

6. Measure the dose by aligning the rib on the plunger to the appropriate marking on the barrel.
7. Return the bottle to the upright position, and then remove the oral dosing syringe from the PIBA. Cap the dosing syringe if not administering immediately.
8. Place the oral dosing syringe down onto a clean surface and securely close the bottle.
9. If multiple syringes are need to deliver the required dose; repeat steps 1 to 8.
10. Appropriate syringes should be selected for optimum dose accuracy.

    *Note: Use the size syringe and amount of study medicine that the doctor has prescribed. Administer the study medicine into the baby's mouth. Use the markings on the side of syringe as a guide. Once the study medicine is withdrawn in a syringe, it should be given to the baby as soon as possible. If the baby spits up most or all the dose in the first 30 minutes after administration, the dose should be repeated.

11. After each use do the following:
    - Clean the syringe(s) by removing the plunger and rinsing the barrel and plunger with water.
    - Allow the barrel and plunger to air dry or use a clean paper towel or clean cloth to dry.
    - When dry, push the plunger back into the syringe barrel.

9.0 Specimen Collection and Laboratory Considerations

The SoEs and Laboratory Processing Chart (LPC) are the primary sources of information on specimen collection, processing, testing, and storage, and shipping for this study; refer to these documents for further operational guidance as needed.

NIH recommendations for maximum pediatric and adult blood draw volumes must be followed in this study. For mothers, the volume of blood drawn shall not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight-week period. ***For infants, the volume of blood drawn at any visit must not exceed 5 mL/kg in a single day and 9.5 mL/kg over any eight-week period.*** At each visit, the infant's weight should be measured, the total volume of blood collected over the past eight weeks should be tabulated, and the maximum blood draw for that day should be determined prior to phlebotomy. In the event that the calculation performed at any given visit indicates that the full blood draw volume specified in the SoE cannot be collected, refer to protocol Section 6.15.1 to determine how the volume of blood that is permitted to be collected should be prioritized. An example of this type of determination is shown below.

Sample Case 1: An infant in Cohort 1, Stratum 1B, who weighs 3.8 kg at Week 6 and whose blood draw volume in the past six weeks was generally consistent with the SoE:

Screen/Entry	8.0 mL
Week 1	3.5 mL
7 Days Post Dose Safety	1.5 mL
Total	13.0 mL

For this infant, on the day of the Week 6 visit:

- The "single day" maximum blood draw volume = (3.8 kg*5 mL/kg) = **19.0 mL**
- The "last 8 weeks" maximum blood draw volume = (3.8 kg*9.5 mL/kg) – 13.0 = **23.1 mL**

Based on these calculations, up to **23.1 mL** could be drawn at Week 6. This volume (23.1 mL) is greater than the volume specified in the SoE for the Week 6 visit (3.5 mL). Therefore, volume specified in the SoE should be drawn at the Week 6 visit.

It is important that blood draw volumes are documented at each visit and are easily accessible for calculating maximum draw volumes at each visit. At any visit when the full volume specified in the SoE cannot be collected, this should be documented in the participant study chart, along with the reason for the less-than-full draw.

10.0 Expedited Adverse Event (EAE) Reporting to DAIDS

Refer to Section 7 of the IMPAACT 2007 protocol and the following resources to guide EAE reporting for this study:

- DAIDS Table for Grading Adult and Pediatric Adverse Events (DAIDS Toxicity Table), Version 2.0, dated November 2014
- Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0, dated January 2010
- DAIDS Adverse Experience Reporting System (DAERS) Reference Guide for Site Reporters and Study Physicians
- Package insert and Investigator's Brochure for maraviroc

10.1 EAE Reporting Requirements

EAE reporting is required in this study only for infants. The EAE reporting period begins at the time of administering the first dose of study drug to the infant and continues through the protocol-specified end of follow-up. Serious adverse events (SAEs) as defined in Version 2.0 of the DAIDS EAE Manual must be reported as EAEs.

Note: The severity of all adverse events identified in this study — except malnutrition — will be graded according to Version 2.0 of the DAIDS Toxicity Table. For grading of infant malnutrition, refer to protocol Section 7.3.3.

10.2 AE Relationship Assessment

For purposes of ***toxicity management*** — as specified in protocol Section 8 — the IoR or designee must assess the relationship of all AEs identified in enrolled infants to study drug according to the categories shown in Figure 10-1. The categories are also used when recording AEs on CRFs.

Figure 10-1
Relationship Assessment Categories for Toxicity Management

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 (i.e., the possibility cannot be excluded), but the event is most likely explained by causes other than the medication.
Not related	The event is clearly explained by another cause not related to the medication.

For purposes of ***EAE reporting***, the IoR or designee must report the relationship of EAEs to the investigational dose of maraviroc according to the categories shown in Figure 10-2.

Figure 10-2
Relationship Assessment Categories for EAE Reporting

Relationship Category	Definition
Related	There is a **reasonable possibility** that the EAE may be related to the investigational dose of maraviroc. Consistent with ICH guidance, the term "reasonable possibility" is intended to convey that there are facts, evidence, or arguments to suggest a causal relationship between the EAE and the investigational dose of maraviroc. Facts, evidence, and arguments that may support a reasonable possibility of a causal relationship include: • A temporal relationship between the EAE and use of the drug • A plausible biologic mechanism for the drug to cause the EAE • Previous reports of similar events associated with the drug (or drugs of the same class) • Resolution of the event after de-challenge (hold/discontinuation of drug) • Recurrence of the event after re-challenge (resumption of drug after a hold) Other potential causes of the EAE (e.g., past medical history, concurrent illness, concomitant medications) should also be considered when assessing whether there is a reasonable possibility that an EAE may be related to the investigational dose of maraviroc.
Not related	There is **not** a reasonable possibility that the EAE may be related to the investigational dose of maraviroc.

Figure 10-3 presents how the five relationship categories used for toxicity management should be mapped to the two relationship categories used for EAE reporting.

Figure 10-3
Mapping of Relationship Categories for Toxicity Management to Relationship Categories for EAE Reporting

Relationship Category for Toxicity Management	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

Appendix I: Informed Consent Considerations

Informed consent is a process by which an individual voluntarily expresses his or her willingness to participate in research after having been informed of all aspects of the research that are relevant to the decision. Informed consent is rooted in the ethical principle of respect for persons. It is not merely a form or a signature, but a process involving information exchange, comprehension, voluntariness, and documentation. Each of these aspects of the informed consent process is described in greater detail below. Please also refer to Section 4.8 of the International Conference on Harmonization (ICH) *Consolidated Guidance for Good Clinical Practice* (GCP) and the informed consent section of the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* for further information.

US regulations (45 CFR 46 and 21 CFR 56) specify the elements of informed consent that must be conveyed to consenters through the informed consent process. It is the responsibility of the IoR, and by delegation of all study staff involved in the informed consent process, to deliver all required information to consenters.

Based on the reviews completed as part of the IMPAACT 2007 protocol development and study activation processes, there is adequate assurance that once a site-specific study activation notice has been issued, a site's informed consent forms (ICFs) include all information required by the regulations. However, responsibility for informed consent does not end with preparation of an adequate ICF. It also is the responsibility of the IoR and designated study staff to:

- Deliver all required information in a manner that is understandable to the consenter
- Assure that informed consent is obtained in a setting free of coercion and undue influence
- Confirm that the consenter comprehends the information
- Document the process

Further guidance related to each of these requirements is provided below. Each site must have on file a study-specific SOP for obtaining informed consent that addresses all aspects of the informed consent process consistent with all applicable regulations, DAIDS policies and procedures, and protocol specifications. All sites must follow their SOPs consistently for all IMPAACT 2007 informed consent processes.

Deliver all Required Information in a Manner that is Understandable to the Consenter

The informed consent process should be conducted in the consenter's preferred language and should reflect whether the consenter is determined to be literate per site SOPs. It is important that the consenter must not be asked to agree to take part in the study, or to sign or make her mark on the ICF, until she fully understands the study. Study staff are responsible for ensuring that each consenter understands all aspects of study participation before signing or marking the ICF.

If the consenter is literate, begin the informed consent process by providing the consenter with a copy of the ICF to read. Also, provide her with any other informational materials developed to complement the ICF. If the consenter is not literate, read the materials to her. After the consenter has read the materials (or had them read to her), verbally review the information provided. A checklist or the ICF itself may serve as a useful guide for this. For example, site staff may note the main points described in each paragraph of the ICF and ask if the consenter has questions or concerns about each point. Listen carefully to the questions and/or concerns expressed by the consenter, and discuss these thoroughly. Take as much time as needed to address each question or concern.

If the consenter is not literate, an impartial literate witness must be present during the entire informed consent process. As part of the documentation steps detailed below, the witness will be asked to sign and date the ICF to attest that the information in the ICF was accurately explained to, and apparently understood by, the consenter, and that informed consent was freely given by the consenter. ICH-E6 identifies an "impartial" witness as a person who is independent of the study, who cannot be unfairly influenced by people involved with the study. The IMPAACT Operations Center has previously received guidance from the US Food and Drug Administration's GCP office stating that the witness need not be "totally unaffiliated with the study. It may be possible, for example, to designate a "subject advocate" who would be available at each site …" Sites with questions about who may serve as an impartial witness are encouraged to consult with their IRBs/ECs on possible options.

Please see the end of this appendix for a summary of considerations for obtaining informed consent from illiterate consenters.

Assure that Informed Consent is Obtained in a Setting Free of Coercion and Undue Influence

During informed consent discussions, take care to not overstate the possible benefits of the study, nor to understate the risks. Also, describe the alternatives to study participation and emphasize that the availability of medical care and other services routinely obtained from the study site institution will not be affected by the consenter's decision whether or not to take part in the study. Encourage the consenter to take as much time as needed, and to talk about study participation with others if she chooses, before making a decision. Acknowledging potential challenges regarding the protocol-specified timeframe for enrollment, sufficient time should be provided for an adequate informed consent process to be conducted.

When a witness is present during the informed consent process, care should be taken to minimize the perception of coercion due to the presence of the witness. For example, the purpose of having the witness present should be clearly explained to the consenter, with emphasis on the fact that the witness is there as a protection for the consenter, not as an agent of the study per se.

Document the Process

US regulations require that informed consent be documented by a written informed consent form approved by the IRB/EC and signed and dated by the consenter or the consenter's legally authorized representative at the time of consent.

To fulfill this requirement, all signature and date blocks on the ICF should be completed in ink. Legal names should be used. Fabricated/falsified names should not be used. Initials may not be used in place of a consenter's full surname, and it is strongly recommended that initials not be used in place of a consenter's full first name. However, if a consenter commonly signs her name using an initial for her first name, the initial may be used, provided this practice is acceptable per the policies of the study site institution(s).

If the consenter is not literate, the witness who was present during the informed consent process must sign and date the ICF to attest that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the consenter, and that informed consent was freely given by the consenter. The consenter's printed name, signature, and signature date blocks on the ICF should be completed.

The DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* lists detailed requirements and suggestions for documenting the informed consent process. Study sites must comply with all requirements and are encouraged to comply with all suggestions. To assist with compliance, study staff may use informed consent coversheets similar to the examples provided in Appendix II. Sites choosing to use coversheets should identify the coversheets as source documents in their study-specific SOPs for source documentation and should use the coversheets consistently to document each informed consent process conducted with each consenter. All informed consent documentation must be maintained on file in participant study records.

In addition to completing the documentation requirements of the ICF itself, each informed consent process should be documented in a signed and dated chart note. The note should document that informed consent was obtained before conducting any study procedures. The note also should document adherence to the requirements of the informed consent section of the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials*. However, if an informed consent coversheet is used, it is not necessary to transcribe or otherwise duplicate information recorded on the coversheet into the chart note.

Regulations require that consenters be given a signed copy of their ICF. If a consenter opts not to receive a copy, this should be documented and the consenter should be offered an alternate form of study contact information (e.g., a contact card or appointment card) in lieu of the full ICF.

Summary of Considerations for Obtaining Informed Consent from Illiterate Consenters

- Each site must specify procedures for obtaining and documenting informed consent from illiterate persons in its SOP for obtaining informed consent. These procedures must be consistent with the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* and must be followed each time informed consent is obtained from an illiterate consenter. It is recommended that each site seek IRB/EC review and approval of these procedures.

- An impartial witness must be present during the entire informed consent process with an illiterate consenter. The witness must sign and date the informed consent form to attest that the information in the consent form was accurately explained to, and apparently understood by, the consenter, and that informed consent was freely given by the consenter.

- The site SOP for obtaining informed consent should define who may serve as the witness to the informed consent process.

- Take care to minimize the perception of coercion due to the presence of the witness.

- Unless other conventions that have been endorsed by DAIDS are specified in site SOPs, the study staff member who completes the informed consent process with the consenter should print the consenter's name below the consenter's printed name line on the informed consent form, together with a signed and dated note documenting the name of the person who made the entry and the date of the entry.

- The consenter should make her mark on the consenter's signature line.

- Unless other conventions that have been endorsed by DAIDS are specified in site SOPs, the study staff member who completes the informed consent process with the consenter should enter the date upon which the consenter made her mark on the informed consent form below the consenter's signature date line, together with a signed and dated note documenting the name of the person who made the entry and the date of the entry.

- For more information, see Section 4.8 of the ICH GCP guidance and the informed consent section of the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials*.

Appendix II: Informed Consent for Specimen Storage and Future Use

Mothers and infants will have biological specimens collected throughout their participation. Some of these specimens will be tested immediately. Others will be stored for later protocol-specified testing (performed either during the study or after the study has been completed). Any specimens that are leftover after all protocol-specified testing has been done may be useful for other research testing in the future. In order to use the leftover specimens for future research testing, including future genetic testing, informed consent must be obtained. As such, for each mother and infant pair enrolled in IMPAACT 2007, informed consent for specimen storage and future use will be requested.

Each mother must be asked to provide informed consent for storage and future use of her leftover specimens, specifically indicating whether genetic testing may be performed.

Separately for infants, mothers must be asked to provide informed consent for storage and future use of the infant's leftover specimens, specifically indicating whether genetic testing may be performed.

While it is required that the informed consent process for specimen storage and future use be conducted, providing consent for specimen storage and future use is optional. That is, mothers and infants can take part in IMPAACT 2007 regardless of whether consent for specimen storage and future use is provided or declined. For those participants for whom informed consent is provided, the consent is applicable to all leftover specimens from both cohorts.

The study protocol permits the specimen storage informed consent process to be conducted at any time after study entry (including on the day of the study entry visit) but note that the process should ideally be conducted within a few weeks of study entry.

As indicated on the signature pages of the sample ICFs included in the study protocols, separate informed consent decisions for maternal and infant specimens must be documented on each ICF. In particular, signatures are required on the signature page for all maternal and infant participants, regardless of whether consent is provided or declined. Notations are also required on each form to indicate whether consent for genetic testing is provided or declined, separately for mothers and infants.

Note: All study sites must inform the Data Management Center of all mothers and infants for whom informed consent for specimen storage and future use is declined and/or for whom genetic testing is declined.

Sample Informed Consent Coversheet for IMPAACT 2007 Participants

Mother's identifier	
Infant's identifier	
Can the mother read?	☐ Yes ☐ No ⇒ *A literate impartial witness should be present during the entire IC process. Record name and relationship/role of witness below.*
Language of IC process	☐ [Language A] ☐ [Language B]
Version number and version date of informed consent form used during IC process	
Was the IC process conducted per site SOPs?	☐ Yes ☐ No ⇒ *Record and explain departures from site SOPs below.*
Was all information required to make an informed decision provided in a language understandable to the mother?	☐ Yes ☐ No ⇒ *Explain below.*
Were all of the mother's questions answered?	☐ Yes ☐ No ⇒ *Explain below.*
Did the mother comprehend all information required to make an informed decision?	☐ Yes ☐ No ⇒ *Explain below.*
Was the mother given adequate time and opportunity to consider all options, in a setting free of coercion and undue influence, before making an informed decision?	☐ Yes ☐ No ⇒ *Explain below.*
Did the mother choose to provide IC?	☐ Yes ☐ No ⇒ *STOP.*
Date and time at which the mother signed or marked the informed consent form	☐ NA (consent declined, form not signed or marked) **Date:** **Time:**
Did the mother accept a copy of the IC form?	☐ NA (mother chose not to provide informed consent) ☐ Yes ☐ No ⇒ *Offer alternate form of study contact information.*
Notes/Comments	
Signature of study staff person completing informed consent process (and this coversheet)	