

IMPAACT 2001 Version 1.0 Frequently Asked Questions

SCREENING AND ELIGIBILITY CONSIDERATIONS

When a potential participant is identified for IMPAACT 2001, what is the next step to begin the screening process?

After written informed consent is obtained, a Screening Identification Number (SID) must be obtained for the potential participant by completing the PS2001 IMPAACT Screening Checklist in the Subject Enrollment System (SES) on the FSTRF portal. To proceed with obtaining a SID in the SES, enter “2001” in Q0002 for the study number.

Note: A Screening Failure and Non-Enrollment Results (SCR0053) case report form (CRF) must be completed for each woman who provides informed consent but does not enroll in the study for any reason.

For the index case of the potential participant that is a household contact, is confirmation of smear/Xpert/culture positive test result necessary or is proof of TB treatment sufficient?

A smear/Gene Xpert/culture is only required for potential participants with TB symptoms to confirm probable active TB, which is exclusionary for this study (per exclusion criterion 4.2.1). The protocol does not require test results or proof of TB treatment for the index TB case, particularly as consent from the index TB case will not be obtained; potential participants (both HIV-infected and uninfected) may be eligible if they report they are a household contact of a known active pulmonary TB patient as defined in inclusion criterion 4.1.3 per Letter of Amendment (LoA) #2.

Can the administrative enrollment procedures at the Entry visit (i.e. final eligibility determination, review consent and enrollment in SES) be done the night before starting study drugs?

Per Clarification Memorandum (CM) #1, administration of study drug and intensive PK sampling should be performed on the day of enrollment. To facilitate swift enrollment in the SES on the first day of the Entry visit, sites may review the potential participant’s eligibility and consent the day prior to enrollment. However, final eligibility determination and confirmation will need to be completed on the day of enrollment. Sites may also prepare any source documents, CRFs, collection materials and intensive PK supplies needed for the Entry visit the day prior to alleviate delays in beginning PK sampling as soon as possible after the potential participant is enrolled.

Is IGRA or TST required for both HIV-infected and HIV-uninfected participants if not available in medical records?

IGRA or TST is only required for HIV-infected potential participants if not available in medical records and they are not a household contact of a known active pulmonary TB patient (i.e. only one of the risk factors for TB in inclusion criterion 4.1.3 is required for HIV-infected women).

HIV-uninfected potential participants may be eligible only if they are a household contact of a known active pulmonary TB patient (see LoA #2 definition of household contact).

Is sputum microscopy, Gene Xpert, and shielded CXR only required at Screening for potential participants with clinical symptoms or suspected TB?

Yes, at least one of these tests should be performed *and* the WHO symptom screen to confirm eligibility at screening per exclusion criterion 4.2.1.

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Would an HIV-uninfected woman who has uncertain history of being a household contact with an active pulmonary TB patient, but has documented positive TST or IGRA, be eligible to participate in IMPAACT 2001?

No, HIV-uninfected women are only eligible for the study if they are a known household contact with an active pulmonary TB patient per eligibility criterion 4.1.3.

SCHEDULE OF EVALUATIONS

When should infant coagulation samples be collected?

Coagulation specimen collection for infants should be done at the Newborn visit only if the mother is still on the study drug regimen, and during infant monthly visits *if clinically indicated* (i.e. not related to timeline of mother's recent dose).

For participants who deliver after completing the study drug regimen, are monthly visits scheduled beginning from labor and delivery or the last weekly visit?

Following completion of the study drug regimen, monthly visits (every 4 weeks) are scheduled independent of labor and delivery, beginning from the last weekly visit (ideally week 11). Per LoA #1, women who complete the study drug regimen prior to delivery should also have a Postpartum visit within 3 days of delivery.

LABORATORY CONSIDERATIONS

Documentation of HIV-1 infection status:

a. Can two positive rapid tests be used for Sample #1 followed by another positive rapid test for Sample #2?

If Sample #2 is tested with a rapid antibody test, in combination with two rapid tests for Sample #1, at least one of the three rapid tests must be FDA-approved and the third rapid test must be from a third manufacturer or based on a third principle or epitope. All sites should follow their algorithm for HIV testing approved by the IMPAACT Laboratory Center.

b. Do any of the tests need to be FDA approved?

All test methods should be FDA-approved if available. If FDA-approved methods are not available, test methods should be verified according to GCLP and approved by the IMPAACT Laboratory Center.

c. Is one negative rapid test sufficient to confirm HIV-uninfection?

HIV-1-uninfected status must be confirmed per Sample #1 requirements, which requires two rapid tests from different manufacturers or based on different principles and epitopes.

d. Does a result slip that indicates "Reactive" with a date of the result meet the Sample #1 requirements for documentation of HIV-1 infection?

"Reactive" does not meet the criteria for adequate documentation for Sample #1. Further information is needed to indicate what "Reactive" means, such as Name/Identifier, Sample/Test Date, Name of Tests Performed and the Results.

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- e. **We have had participants with samples tested by non-study public or PEPFAR programs with a positive/reactive result and assay date, but no documentation of the assay used. Should the actual assays from the public programs be made available to the study prior to enrolling the participant with a results slip indicating that they are HIV-1 infected?**

For Sample #1: If the participant presents with documentation for Sample #1 from the “Non-study/PEPFAR/Other” program, the tests/methods do not have to be FDA-approved. The documentation should include: Name/Identifier, Sample/Test Date, Name of Tests Performed and the Results. Please note that Sample #2 cannot be performed by an outside lab, and must be tested at a laboratory that operates according to GCLP guidelines and participates in appropriate external quality assurance program.

- For sites that are not performing coagulation testing locally, how often should coagulation specimens be shipped for testing?**

Per the Laboratory Processing Chart (LPC), both the maternal screening visit and infant newborn visit coagulation specimens should be batch shipped every three months to the appropriate testing lab, beginning from the time the first mother-infant pair is enrolled at the site (or upon request by the Protocol Team). Specimens should be processed and frozen as indicated in Section 9.7 of the Manual of Procedures (MOP).

Coagulation samples collected at one weekly visit for women who are ≥ 34 weeks gestational age and taking the study drug regimen, and *only if clinically indicated* at the maternal postpartum visit, maternal monthly visits, and infant monthly visits should be shipped in real-time for participant safety monitoring.

- For breastmilk PK sampling collection, is a sterile conical tube or plastic container required?**

The PK testing laboratory, University of Cape Town, has indicated that a sterile container or tube is preferred, particularly given that the lab cannot control for the effects of growth on the analytes. If a site is unable to procure sterile containers for the study, please contact the IMPAACT Laboratory Center (impaact.qaqc@fstrf.org) for assistance.

DATA COLLECTION AND CASE REPORT FORM CONSIDERATIONS

- When should the WHO staging form be completed (CRF PE0043)?**

The WHO staging form should only be completed for HIV-infected mothers at screening.

- Should cases of common HIV, pregnancy and pediatric conditions – such as acute GE, URTI, otitis media, rash – be recorded on diagnoses CRFs?**

Appendix 100 has been adopted by IMPAACT and applies to IMPAACT 2001. Therefore, conditions listed on the “Do Not Record” list do not need to be recorded on CRFs.

- Does the form week reset at labor and delivery or do we continue counting weeks on study?**

No, maternal form week begins at entry and does not reset at labor and delivery.

- Does the infant form week begin at birth or maternal study entry?**

The infant form week begins at birth.

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The SES requires an absolute number for the total bilirubin level to proceed. How should this be entered if a participant has a value below the limit of detection?

Values below the limit of detection should be recorded as the limit of detection. So, if the result was < 5, the result would be recorded as 5.

For sites that do not perform coagulation testing locally, how should the PE6813 CRF be completed?

The PE6813 CRF should be completed with Question 2 answered as 'No' when the coagulation sample is collected. When the Prothrombin Time results become available, the form should be updated by changing the answer in Question 2 to 'Yes', entering the date the specimen was obtained in Question 2a, and then completing Question 2e with the result information. Per protocol Section 6.8.1, only Prothrombin Time (PT) is required to be recorded on CRFs. However, other coagulation profile results *can* be reported if obtained and if clinically relevant or requested by the Protocol Team.

Given that screening procedures may be conducted on different days, how should the CRF MAW0016 (Obstetrical ultrasound) be completed for the following scenarios:

a. On the CRF header, the date of the participant visit must be entered. Should the date entered be the date of the participant's first visit day or the day the ultrasound was performed?

If the ultrasound is performed at the first screening visit: the date of the participant visit should be the date of the screening visit.

If the ultrasound is performed *after* the first screening visit: the date of the participant visit should be the date when the ultrasound was performed (to avoid entering a future date in Question 1a).

b. For question #1 ("was the ultrasound performed? Y/N"), should an answer be submitted on the day of consent and again when the ultrasound is conducted, or should the answer be submitted only when the ultrasound is conducted?

Only one CRF should be submitted during screening. If screening procedures are completed on multiple days (e.g. consent and the ultrasound are completed on separate days), complete one form with the date entered per the outlined scenarios in (a) above.

c. For question 1a, ("If No, Stop. If Yes== Date ultrasound performed?"), if the answer entered for the CRF header is a date different from the date an ultrasound was performed, should the answer submitted for 1a be based on the date of the initial visit or the date the ultrasound was conducted?

The date entered for 1a should be the date the ultrasound was performed. The date entered on the CRF header is determined by when the ultrasound was performed in relation to the date of the initial screening visit. See answer to (a) above.

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CLINICAL AND STUDY PROCEDURES CONSIDERATIONS

What is the guidance for a participant who vomits study drugs on the day of the Intensive PK visit and/or weekly DOT?

In the event that a participant vomits within 30 minutes of dosing, they may be re-dosed once to replace the dose. The PK sampling may then proceed if the participant does not vomit the re-dose. For IMPAACT 2001, we do not anticipate that this will be a problem in women enrolled in their second and third trimesters, so please contact the Core Team (impaact.core2001@fstf.org) for clinical management if the participant vomits the re-dose.

In the event of in utero fetal demise, is an event evaluation form required for the infant?

No, an Event Evaluation CRF (PE6866) is not required. However, the Off Study CRF (F1601) should be used as the infant is enrolled at the same time as the mother. The reason for off study will be “44 – fetal demise” for the infant.

OPERATIONAL CONSIDERATIONS

If a potential participant initially suspected for active TB with a positive WHO TB symptom screen is later determined to be negative for TB upon further testing, does the re-screening process include re-consenting, if the participant has already consented to participate in the study?

If re-evaluation of active TB disease is completed within 14 days prior to Entry, and a screening failure form has not been entered in the study database, the potential participant does not need to be re-consented as evaluations to confirm eligibility may be repeated within the Screening visit window. The potential participant’s initial and follow-up TB assessments and any results should be documented in their chart.

If consent was obtained more than 14 days prior to Entry, a Screening Failure and Non-Enrollment Results CRF (SCR0053) for the initial screening process should be completed and a new screening number will need to be obtained to re-screen for IMPAACT 2001. The potential participant should provide written informed consent for the study prior to any study-specific screening procedures are performed per protocol Section 6.1.

As CBC and ALT are not drawn at the Entry visit, will the CBC and ALT values obtained at Screening visit serve as the baseline values for these laboratory tests?

Yes, CBC and ALT values collected at Screening should be used as the baseline values.

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Can study visits be conducted outside of the visit window?

Every effort should be made to conduct all study visits within the protocol-specified visit window. Failure to conduct any study-specific procedures within the protocol-specified visit window is a deviation from the protocol. The visit should be documented as a protocol deviation and the reason for performing the visit outside of the protocol-specified visit window in the participant's chart. This type of deviation is not generally expected to require entry into a deviation eCRF or reporting at the IMPAACT network level; however, the site Investigator of Record retains responsibility for final determination of reportability (see Section 12 of the [IMPAACT MOP](#) for further guidance related to this). This type of deviation should be reported to site IRBs/ECs per their policies and procedures (for example, the IRBs/ECs may require reporting in real time or at the time of your next continuing review). Other corrective and preventive actions, such as discussing the importance of the study visit schedule with the participant or parent/guardian, scheduling visits on dates that are most appropriate, and providing visit reminders, should also be documented. Note that protocol teams cannot grant permission to conduct a visit outside of the protocol-specified window.

For PK collection, CRF PKW0392 specifies a 15-minute allowable window for the collection time. Should PK sampling be collected if the 15-minute window has passed?

Acknowledging that it may be challenging to perform a PK blood draw at the exact collection time point, PK specimens may be collected within an allowable window of +/- 15 minutes of the PK time point. If it is not possible to collect a PK sample within the collection window for the sampling time points specified in protocol Section 6.3, the PK sample should be collected as soon as possible and the time the specimen is obtained recorded on the CRF. The reasons why the sample was collected outside of the window should also be documented in the participant's file and on the PK CRF.

ADVERSE EVENTS AND EAE CONSIDERATIONS

Please clarify if 'toxicity' refers only to AEs that are deemed related to study drug?

An adverse event is any untoward medical occurrence in a clinical research participant administered an investigational product, which does not necessarily have a causal relationship with the investigational product. All adverse events should be assessed, source documented, and graded as listed in the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, dated November 2014, except for complications during pregnancy. Complications during pregnancy should be graded per the Complications of Pregnancy Section of the Female Genital Grading Table for Use in Microbicide Studies (Version 1.0, dated November 2007). Both grading tables are available on the RSC website at <http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables>. Management of adverse experiences will be according to the best clinical practice and the judgement of the site investigator. Further guidance on study drug management and frequency of repeat assessments is provided in protocol Section 8.1 (see LoA #2 for modifications to Section 8.1.7, Asymptomatic Elevations in ALT and Total bilirubin).