A Phase I/II Open-Label, Single-Arm Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Delamanid in Combination with Optimized Multidrug Background Regimen (OBR) for Multidrug-Resistant Tuberculosis (MDR-TB) in HIV-Infected and HIV-Uninfected Children with MDR-TB

Manual of Procedures

FINAL Version 2.0
8 April 2020
Table of Contents

1.0 Study Overview ............................................................................................................. 6
2.0 Preparing for the Study .................................................................................................. 6
   2.1 Investigator Responsibilities ...................................................................................... 7
   2.2 Drug Regulatory Authority and Institutional Review Board/Ethics Committee Oversight... 7
   2.3 Protocol Registration ............................................................................................... 8
   2.4 Site-Specific Study Activation ................................................................................. 8
3.0 Study Resources ............................................................................................................ 9
   3.1 Study-Related Information and Communications .................................................... 9
   3.2 Data Management Center (DMC) IMPAACT Portal .................................................. 13
   3.3 Study Web Page ..................................................................................................... 14
   3.4 Source Documentation and Essential Documents .................................................... 14
4.0 Informed Consent and Assent Considerations ............................................................ 15
   4.1 Study-specific Informed Consent and Assent Processes ........................................... 15
   4.2 Assessment of Understanding .............................................................................. 15
   4.3 Documentation Requirements ................................................................................ 16
   4.4 Considerations Regarding Death of a Guardian ...................................................... 16
5.0 Protocol Implementation ............................................................................................... 16
   5.1 Overview ................................................................................................................ 16
   5.2 Site-Specific Accrual and Retention ...................................................................... 17
   5.3 Recruitment .......................................................................................................... 17
   5.4 Screening and Enrollment ..................................................................................... 17
   5.5 Enrolling Eligible Participants ............................................................................. 19
6.0 Study Visits and Procedures ....................................................................................... 19
   6.1 PK Visit Considerations ......................................................................................... 20
   6.2 Protocol Deviations .............................................................................................. 20
7.0 Laboratory Considerations ......................................................................................... 21
   7.1 Introduction and Overview ...................................................................................... 21
   7.2 Infection Control/Biosafety .................................................................................... 21
   7.3 Specimen Chain of Custody .................................................................................. 22
   7.4 Labeling Specimens .............................................................................................. 22
   7.5 Laboratory Data Management System (LDMS) ..................................................... 22
   7.6 Sample/Specimen Collection and Processing Prior to Shipment to the Laboratory ...... 23
   7.7 Biomarker Specimen Collection .......................................................................... 23
8.0 Pharmacy Considerations .......................................................................................... 25
   8.1 DLM Dosing ........................................................................................................... 25
   8.2 DLM Dispensing and Administration ..................................................................... 25
   8.3 Adherence .............................................................................................................. 25
   8.4 Concomitant Medications ..................................................................................... 26
9.0 Expedited Adverse Event Reporting to DAIDS .......................................................... 26
   9.1 Selected Definitions ............................................................................................... 26
   9.2 EAE Reporting Requirements .............................................................................. 27
   9.3 AE Relationship Assessment .................................................................................. 28
   9.4 EAE Reporting Procedures .................................................................................... 29
   9.5 Reporting Protocol-Specified Events to the CMC .................................................. 30
10.0 Clinical Management Considerations ...................................................................... 30
   10.1 Karnofsky/Lansky Performance Status ................................................................. 30
   10.2 Cardiac Safety Monitoring ................................................................................... 30
10.3 Contraception and Pregnancy ................................................................. 31
10.4 TB Monitoring and Treatment Outcome ............................................. 32

APPENDIX I: Delamanid Oral Suspension Preparation Instructions ............. 37

APPENDIX IA: Delamanid Oral Suspension Preparation (Medication Cup) for 25 mg Dose ........ 37
APPENDIX IB: Delamanid Oral Suspension Preparation (Syringe) for 25 mg Dose ............... 39
APPENDIX IC: Delamanid Oral Suspension Preparation (Medication Cup) for 10 mg Dose ...... 41
APPENDIX ID: Delamanid Oral Suspension Preparation (Syringe) for 10 mg Dose .......... 43
APPENDIX IE: Delamanid Oral Suspension Preparation (Medication Cup) for 5 mg Dose .... 45
APPENDIX IF: Delamanid Oral Suspension Preparation (Syringe) for 5 mg Dose .......... 47
APPENDIX II: Suggestions for the Caregiver and DOTS Supporter for Using DLM in Children . 49

APPENDIX III: Digital Photographs of Chest X-Rays ........................................ 50
APPENDIX IV: Assessment of Karnofsky/Lansky Performance Status .......... 54
APPENDIX V: Sample Informed Consent Coversheet for IMPAACT 2005 ......... 56
<table>
<thead>
<tr>
<th>Section</th>
<th>Current Version</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Section 1 Study Overview        | 2.0 8 April 2020| • Updated Table 1-1 to align with Protocol Version 2.0  
• Minor clarifications and revisions throughout |
| Section 2 Preparing for the Study | 2.0 8 April 2020| • Updated website links to DAIDS documents and added link to the IMPAACT Network Manual of Procedures (MOP)  
• Added clarification and guidance regarding site investigator responsibilities  
• Minor clarifications and revisions throughout |
| Section 3 Study Resources       | 2.0 8 April 2020| • Added clarifications for study related communications  
• Minor clarifications and revisions throughout |
| Section 4 Informed Consent and Assent Considerations | 2.0 8 April 2020| • Removed information on informed consent, assent and other human subjects considerations that is specified in the Network MOP  
• Added further guidance on informed consent and assent requirements for sites and procedures for participants who meet IRB/EC criteria for providing consent or assent after enrollment |
| Section 5 Protocol Implementation | 2.0 8 April 2020| • Updated to provide further guidance on participant accrual, screening and enrollment procedures based on study implementation to date and for consistency with Protocol Version 2.0  
• Minor clarifications and revisions throughout |
| Section 6 Study Visits and Procedures | 2.0 8 April 2020| • New section added to provide guidance on key considerations for study visits and procedures |
| Section 7 Laboratory Considerations | 2.0 8 April 2020| • Updated website links as appropriate  
• Update section for consistency with protocol Version 2.0  
• Added further guidance for collection and processing of pharmacokinetic (PK) samples  
• Minor clarifications and revisions throughout |
| Section 8 Pharmacy Considerations | 2.0 8 April 2020| • Updated section to align with Delamanid (DLM) dosing specified in protocol Version 2.0.  
• Added Section 8.4 to provide guidance on concomitant medications per the protocol  
• Minor clarifications and revisions throughout |
| Section 9 Expedited Adverse Event Reporting to DAIDS | 2.0 8 April 2020| • Updated website links as appropriate  
• Added Figure 9-3 to describe relationship assessment categories for Expedited Adverse Event (EAE) reporting  
• Minor clarifications and revisions throughout |
| Section 10 Clinical Considerations | 2.0 8 April 2020| • Updated section to align with protocol Version 2.0 and the most current version of the DLM Investigator’s Brochure  
• Updated website links as appropriate  
• Minor clarifications and revisions throughout |
<table>
<thead>
<tr>
<th>Section</th>
<th>Current Version</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendix I Delamanid Oral Suspension Preparation Instructions</td>
<td>2.0</td>
<td>• No changes from Version 1.1</td>
</tr>
<tr>
<td>Appendix II Suggestions for the Caregiver and DOTS Supporter for Using DLM in Children</td>
<td>2.0</td>
<td>• No changes from Version 1.1</td>
</tr>
<tr>
<td>Appendix III Digital Photographs of Chest X-Rays</td>
<td>2.0</td>
<td>• Minor clarifications and revisions throughout</td>
</tr>
<tr>
<td>Appendix IV Assessment of Karnofsky/Lansky Performance Status</td>
<td>2.0</td>
<td>• No changes from Version 1.1</td>
</tr>
<tr>
<td>APPENDIX V: Sample Informed Consent Coversheet for IMPAACT 2005</td>
<td>2.0</td>
<td>• New appendix added for reference</td>
</tr>
</tbody>
</table>
1.0 Study Overview

IMPAACT 2005 is a Phase I/II, open-label, single arm, multi-site study to evaluate the pharmacokinetics (PK), safety and tolerability of delamanid (DLM) in combination with optimized multidrug background regimen (OBR) for multidrug-resistant tuberculosis (MDR-TB) in HIV-infected and HIV-uninfected children with MDR-TB disease.

Up to 48 participants (12 per age cohort) may be enrolled to achieve 36 evaluable (9-12 per age cohort). The study will enroll HIV-infected and HIV-uninfected infants, children, and adolescents less than 18 years of age with confirmed or probable MDR-TB who have received 2-8 weeks of routine MDR-TB treatment prior to enrollment. This study will take place in seven sites across Botswana, India, South Africa and Tanzania.

All participants will receive DLM in combination with an optimized background TB treatment regimen (OBR) for 24 weeks. For HIV-infected participants, DLM will also be given in combination with an acceptable antiretroviral (ARV) therapy regimen initiated at least two weeks prior to enrollment. Participants will be stratified by age at screening into one of four cohorts as shown in Table 1-1. Within each cohort, at least six participants with HIV-infection will be enrolled. Each participant will be followed for approximately 96 weeks.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Age in Years</th>
<th>DLM Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12 to &lt;18</td>
<td>≥40 kg: 100 mg twice daily (adult formulation)</td>
</tr>
<tr>
<td>2</td>
<td>6 to &lt;12</td>
<td>30 to &lt;40 kg: 50 mg twice daily (adult formulation)</td>
</tr>
<tr>
<td>3</td>
<td>3 to &lt;6</td>
<td>15 to &lt;30 kg: 25 mg twice daily (pediatric formulation)</td>
</tr>
<tr>
<td>4</td>
<td>0 to &lt;3</td>
<td>&lt;15 kg: 15 mg twice daily (pediatric formulation)</td>
</tr>
</tbody>
</table>

2.0 Preparing for the Study

Note: Refer to Section 11 of the IMPAACT Manual of Procedures for comprehensive information on Study-Specific Pre-Implementation Activities. The IMPAACT Manual of Procedures is available on the Resources page of the IMPAACT website: https://impaactnetwork.org/resources/policies-procedures.htm

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 site selection materials. A copy of the approved site selection materials should be maintained in each site’s study-specific essential document files.

| CRS 5118 | Kilimanjaro Christian Medical Centre (KCMC), Moshi, Tanzania |
| CRS 12701 | Gaborone Prevention/Treatment Trials CRS, Gaborone, Botswana |
| CRS 12702 | Molepolole Prevention/Treatment Trials CRS Molepolole, Botswana |
| CRS 31441 | Byramjee Jeejeebhoy Medical College (BJMC), Pune, Maharashtra, India |
| CRS 31790 | Desmond Tutu TB Centre, Cape Town, South Africa |
| CRS 31929 | Sizwe Tropical Disease Hospital, Johannesburg, South Africa |
| CRS 31976 | PHRU Matlosana, Klerksdorp, South Africa |
2.1 Investigator Responsibilities

IMPAACT 2005 must be conducted in accordance with the US Code of Federal Regulations (45 CFR 46; 21 CFR 11, 50, 54, 56, and 312) and the International Council for Harmonization (ICH) Guideline 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 2005: https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations

IMPAACT 2005 also must be conducted in accordance with the IMPAACT Manual of Procedures and all site-specific regulations, policies, and guidelines applicable to human subjects research in general and the conduct of study procedures in particular. Copies of all applicable regulations, policies, and guidelines should be maintained in on-site essential document files.

The Investigator of Record (IoR) at each site must sign the IMPAACT 2005 Protocol Signature Page to formally document his or her agreement to conduct the study in accordance with the study protocol and all applicable protocol-related documents and in compliance with applicable US regulations; the ICH Guideline for GCP; institutional review board/ethics committee (IRB/EC) determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements and institutional policies.

The Investigator of Record (IoR) at each site must sign an FDA form 1572 to formally indicate his or her agreement to conduct the study in accordance with the protocol and to personally conduct or supervise the study at his or her site. The obligations and responsibilities assumed by the IoR when signing the Form FDA 1572 are listed on the form, which is available at: https://rsc.niaid.nih.gov/clinical-research-sites/protocol-registration-forms

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.

2.2 Drug Regulatory Authority and Institutional Review Board/Ethics Committee Oversight

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 and the ICH GCP guidance, as well as on the website of the U.S. 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 2005 involves pediatric participants, IRBs/ECs must consider the potential benefits, risks, and discomforts of the study to children 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 children in the following categories:

§46.404 Research not involving greater than minimal risk

§46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects

§46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition

§46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children

The risk category assessed by the IRBs/ECs then determines the informed consent requirements for participation of children in the study. Specifically, per 45 CFR 46.408 (b), “the IRB may find that the permission of one parent is sufficient for research to be conducted under §46.404 or §46.405. Where research is covered by §46.406 and §46.407 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.”

IRBs/ECs should document their risk determination, and study sites should adapt the signature pages of their informed consent forms as needed to accommodate the parental consent requirements associated with the IRBs/ECs’ determination. In the absence of a clearly documented determination from the IRBs/ECs, the most conservative approach specified in the regulations should be followed.

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.

### 2.3 Protocol Registration

The IMPAACT Operations Center will notify the DAIDS Protocol Registration Office (PRO) that DAIDS-approved sites selected by the Protocol Team for participation are permitted to submit for protocol registration for the study. After all required DRA and IRB/EC approvals are obtained, the IoR (or designee) at each site are then responsible for submitting documentation of the approvals and other required documentation to the PRO. Further information on the protocol registration process can be found in the DAIDS Protocol Registration Manual, which is available at: https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations

Upon confirming receipt of all required documentation, the PRO will issue a registration notification that indicates successful completion of the process. The IoR is responsible for maintaining documentation of all submissions for the study, along with all associated approvals/notifications and other correspondence from the PRO.

### 2.4 Site-Specific Study Activation

Prior to conducting any study procedures, each site must obtain all required approvals and complete study-specific activation procedures specified by the Protocol Team. To help ensure site readiness for study initiation, the Protocol Team has specified a set of study activation requirements that must be met to obtain approval to begin study implementation. These requirements are listed on the IMPAACT 2005 Site-Specific Study Activation Checklist, which is provided to each of the
participating sites. They include sign-off on laboratory, pharmacy, and data management readiness and completion of study-specific training, including the acquisition of and training on study-provided ECG machines. In addition, sites are also required to prepare site protocol-specific standard operating procedures (SOPs) on Participant Recruitment, Participant Retention, Study Drug Adherence/Directly Observed Therapy (DOT), and Audiology Testing (pediatric and adolescents/adults).

As noted in the IMPAACT 2005 Protocol Team Update on Implementation Materials for IMPAACT 2005, Protocol Version 2.0, dated 26 September 2019, sent to sites on 23 January 2010, prior to implementing Protocol Version 2.0, sites must receive all IRB/EC and regulatory entity approvals and receive an Implementation Notice from the IMPAACT Operations Center confirming that all operational requirements for implementing the amendment at the Network level have been completed.

Any questions related to the study activation process should be directed to the Operations Center Clinical Trials Specialists. On a site-by-site basis, when all activation requirements have been met, the Clinical Trials Specialists (CTSs) 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

3.1 Study-Related Information and Communications

This section specifies the resources available to IMPAACT 2005 study site staff, including study-related communication and informational resources, the Data Management Center IMPAACT Portal, and other essential documents.

All IMPAACT 2005 visits and procedures must be conducted in accordance with the study protocol. The purpose of this Manual of Procedures (MOP) 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 CTS 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 Protocol Team, a response from the appropriate team member can generally be expected within 24 hours.

- **General questions**: Questions related to protocol interpretation or study implementation, including administrative, ethical, regulatory, counseling, data, and laboratory operations should be emailed to the IMPAACT 2005 Protocol Team as listed in Figure 3-1. Any questions that are not answered by the protocol or this document should also be emailed to the IMPAACT 2005 Protocol Team.

- **Clinical and toxicity management questions and notifications**: Questions concerning clinical management of study participants and adverse experiences should be emailed to the IMPAACT 2005 Clinical Management Committee (CMC) as listed in Figure 3-1. Figure 3-3 provides a listing of issues for which consultation with the CMC is required per protocol. When submitting questions and notifications to the CMC, to help ensure that CMC members have adequate information to respond in a timely manner, please address each of the points listed in Figure 3-2. Replies can generally be expected within 24 hours. When it may not be possible to provide a complete response within 24 hours, the person who submitted the question or notification will be provided with an interim response and informed that more time is needed to provide a complete response. Always retain a copy or correspondence with the CMC in the relevant participant’s study chart.
• **Study implementation questions**: Questions related to participant eligibility, co-enrollment, potential enrollment of an ineligible participant, and/or deviation from other protocol requirements for screening and enrollment should also be directed to the IMPAACT 2005 CMC as listed in **Figure 3-1**.

• **Other types of questions** should be managed as listed in **Figure 3-1**.

To ensure receipt of important information about study implementation and conduct, sites should email user.support@fstrf.org to have relevant site personnel added to the protocol email group ([IMPAACT.prot2005@fstrf.org](mailto:IMPAACT.prot2005@fstrf.org)).

Site staff should avoid sending messages to the protocol team email group ([IMPAACT.prot2005@fstrf.org](mailto:IMPAACT.prot2005@fstrf.org)) as this group is used for broadcast distribution to all Protocol Team members and study sites. The group is comprised of many individuals and is not intended to receive site-specific or participant-specific queries.
### Figure 3-1
IMPAACT 2005 Study-Related Communications

<table>
<thead>
<tr>
<th>Topic</th>
<th>Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adding site staff to Protocol Team email group: <strong><a href="mailto:IMPAACT.prot2005@fstrf.org">IMPAACT.prot2005@fstrf.org</a></strong></td>
<td><strong>User Support</strong>&lt;br&gt;<strong><a href="mailto:user.support@fstrf.org">user.support@fstrf.org</a></strong>&lt;br&gt;include “IMPAACT 2005” in the subject line of the message</td>
</tr>
<tr>
<td>Any aspect of protocol interpretation or study implementation not listed below</td>
<td><strong>IMPAACT 2005 Protocol Team</strong>&lt;br&gt;<strong><a href="mailto:IMPAACT.TEAM2005@fstrf.org">IMPAACT.TEAM2005@fstrf.org</a></strong> for triage to other team members as needed</td>
</tr>
<tr>
<td>Clinical management issues, audiology questions, and PK sample collection and shipping notification</td>
<td><strong>IMPAACT 2005 CMC</strong>&lt;br&gt;<strong><a href="mailto:IMPAACT.2005CMC@fstrf.org">IMPAACT.2005CMC@fstrf.org</a></strong>&lt;br&gt;<em>For cardiology management issues, including questions regarding eligibility:</em>&lt;br&gt;<strong>IMPAACT 2005 Core Cardio Team</strong>&lt;br&gt;<strong><a href="mailto:IMPAACT.2005corecardio@fstrf.org">IMPAACT.2005corecardio@fstrf.org</a></strong></td>
</tr>
<tr>
<td>Participant eligibility, potential enrollment of an ineligible participant, and/or deviation from protocol requirements for eligibility determination and/or enrollment</td>
<td><strong>IMPAACT 2005 CMC</strong>&lt;br&gt;<strong><a href="mailto:IMPAACT.2005CMC@fstrf.org">IMPAACT.2005CMC@fstrf.org</a></strong></td>
</tr>
<tr>
<td>Co-enrollment</td>
<td><strong>IMPAACT 2005 CMC</strong>&lt;br&gt;<strong><a href="mailto:IMPAACT.2005CMC@fstrf.org">IMPAACT.2005CMC@fstrf.org</a></strong></td>
</tr>
<tr>
<td>Frontier Science DMC Portal and Medidata Rave study access</td>
<td><strong>User Support (Frontier Science)</strong>&lt;br&gt;<strong><a href="mailto:user.support@fstrf.org">user.support@fstrf.org</a></strong>&lt;br&gt;or by phone: +716-834-0900 x7302</td>
</tr>
<tr>
<td>Subject Enrollment System</td>
<td><strong>DMC Randomization Support Office</strong>&lt;br&gt;<strong><a href="mailto:rando.support@fstrf.org">rando.support@fstrf.org</a></strong>&lt;br&gt;or by phone: +716-834-0900 x7301</td>
</tr>
<tr>
<td>Study drug (other than study drug orders)</td>
<td><strong>Protocol Pharmacists</strong>&lt;br&gt;Justine Beck, PharmD, BCPS, RPh&lt;br&gt;<strong><a href="mailto:Justine.beck@nih.gov">Justine.beck@nih.gov</a></strong>&lt;br&gt;Oladapo Alli, PharmD&lt;br&gt;<strong><a href="mailto:oladapo.alli@nih.gov">oladapo.alli@nih.gov</a></strong>&lt;br&gt;or by phone: 301-761-5288</td>
</tr>
<tr>
<td>Study drug orders</td>
<td><strong><a href="mailto:BIO.CRPMC.Ph@Thermofisher.com">BIO.CRPMC.Ph@Thermofisher.com</a></strong>&lt;br&gt;(Phone contact: +301-294-0741)</td>
</tr>
<tr>
<td>Expedited Adverse Event (EAE) Reporting</td>
<td><strong>DAIDS RSC Safety Office</strong>&lt;br&gt;<strong><a href="mailto:DAIDSRSCSafetyOffice@tech-res.com">DAIDSRSCSafetyOffice@tech-res.com</a></strong>&lt;br&gt;or by phone: 800-537-9979 or +301-897-1709&lt;br&gt;or by fax: 800-275-7619 or +301-8977-1710</td>
</tr>
<tr>
<td>DAIDS Adverse Experience Reporting System (DAERS)</td>
<td><strong>NIAID Clinical Research Management System</strong>&lt;br&gt;<strong><a href="mailto:CRMSSupport@niaid.nih.gov">CRMSSupport@niaid.nih.gov</a></strong>&lt;br&gt;(questions also may be submitted from within the DAERS application)</td>
</tr>
</tbody>
</table>
# Questions for IMPAACT 2005 CMC

Please copy and paste this listing into the body of your email message to IMPAACT.2005CMC@fstrf.org to help ensure that all required information is included. Include the protocol number and PID in the subject line of your email.

For questions regarding an ECG-determined or clinical cardiac toxicity, please send email to IMPAACT.2005corecardio@fstrf.org and include “Cardiac Safety” in the subject line of your email.

<table>
<thead>
<tr>
<th>Question</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Site name and number:</td>
<td></td>
</tr>
<tr>
<td>2. Name of person submitting query:</td>
<td></td>
</tr>
<tr>
<td>3. PID(s):</td>
<td></td>
</tr>
<tr>
<td>4. Query is for consultation on (choose one):</td>
<td></td>
</tr>
<tr>
<td>a. Eligibility or enrollment (describe in case description)</td>
<td></td>
</tr>
<tr>
<td>b. AE or toxicity management (specify severity grade in case description)</td>
<td></td>
</tr>
<tr>
<td>c. Optimized background TB treatment regimen (OBR) management (describe in case description)</td>
<td></td>
</tr>
<tr>
<td>d. ARV regimen management (describe in case description)</td>
<td></td>
</tr>
<tr>
<td>e. Other (specify in case description)</td>
<td></td>
</tr>
<tr>
<td>5. Cohort: 1, 2, 3, or 4</td>
<td></td>
</tr>
<tr>
<td>6. Age of participant:</td>
<td></td>
</tr>
<tr>
<td>7. Current week on study:</td>
<td></td>
</tr>
<tr>
<td>8. Current optimized background TB treatment regimen (OBR):</td>
<td></td>
</tr>
<tr>
<td>9. HIV status of participant</td>
<td></td>
</tr>
<tr>
<td>a. Current ARV regimen (drug names and current dose of each), if applicable:</td>
<td></td>
</tr>
<tr>
<td>10. Case description and question or notification for CMC:</td>
<td></td>
</tr>
</tbody>
</table>
Figure 3-3
Requirements for Consultation with the IMPAACT 2005 CMC

For details on toxicity management, refer to the following appendices in the protocol:
- Appendix IX: Toxicity Table for ECG-Determined or Clinical Cardiac Toxicity
- Appendix IX: Toxicity Management of Specific Toxicities
- Appendix X: Toxicity Management of General Toxicities

Study Implementation
- Requests for co-enrollment in other studies.
- A participant is administered any precautionary or prohibited medications as described in protocol Sections 5.6.1 and 5.6.2, respectively.
- Investigator or designee determines continued participation in the study would be unsafe or otherwise not in the best interest of the participant.
- Initial reports of pregnancy in a study participant.

General adverse events
- Any Grade 3 or 4 toxicity

ECG-determined or clinical cardiac toxicity
- Grade 3 or 4 ECG-Determined or Clinical Cardiac Toxicity

Hepatoxicity Management (bilirubin, AST, ALT)
- Any events that meet Hy’s law
- Confirmed ≥ Grade 3 event regardless of relatedness

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 electronic Case Report Forms (eCRFs), data collection form schedules, participant calendar, Subject Enrollment System (SES) and study-specific messages. The IMPAACT Portal can be accessed from the Frontier Science Foundation webpage at https://www.frontierscience.org/.

Site staff members apply for access to the Portal by submitting a registration form located on the Frontier Science Foundation home page. All requests for Portal access are subject to review and verification by User Support before processing. The site leader or site coordinator will be contacted by the DMC to ensure legitimate affiliation of the applicant. To request DMC IMPAACT Portal access complete the form located at: https://www.frontierscience.org/apps/cfmx/apps/common/register/index.cfm

Click on the IMPAACT project link to enter the project website. A log-in screen appears. Enter your username (format: lastname.firstname) and the password that you set up when you registered for DMC web access.

For clinical user support, send an email message to impaact.support@fstrf.org or call +1 (716) 834-0900 x 7302 (x7200 if outside U.S. hours). If you experience problems, or have questions about the IMPAACT portal on the Frontier Science website, please contact the Webmaster at webmaster@fstrf.org and include a detailed description of your question or the problem you encountered.
3.2.1 Electronic Case Report Form (eCRF) Completion and Data Entry

The DMC has developed a Forms Manual to assist site staff in the accurate completion of electronic Case Report Forms (eCRFs) 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 reporting data, understanding forms, forms components and conventions, submitting data, data collection formats and participant status categories.

For reporting clinical diagnoses, including TB diagnosis, sites should refer to Appendix 100 (“DIAGNOSES APPENDIX CRITERIA FOR CLINICAL AND OTHER EVENTS”) for the diagnoses definitions. To obtain the most current version of the CRF appendix, please refer to the IMPAACT Portal of the DMC website, and select “CRF Appendix Codes” under the category “Case Report Forms.”

3.2.2 Obtaining eCRFs and other related materials

eCRFs and other related materials can be accessed through the Medidata RAVE system. The eCRFs may be used as a guide for source documentation purposes. The IMPAACT 2005 eCRF Completion Guide and IMPAACT 2005 Print Matrix (blank eCRFs) are located in the DMC IMPAACT Portal under Site Support, Medidata Rave Resources.

3.3 Study Web Page

A variety of IMPAACT 2005 study-related materials and information can be found on the study-specific webpage: http://www.impaactnetwork.org/studies/IMPAACT2005.asp

Resources available on this site include:

- Protocol documents
- Study contacts
- Study implementation materials, including this manual and the Laboratory Processing Chart (LPC)
- Study training materials
- Application and examples for import permit for biological substances for UCT PK samples
- Financial Disclosure Form

3.4 Source Documentation and Essential Documents

All sites must comply with the DAIDS policies on Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials and Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. Refer to the detailed operational guidance provided in Appendix I of these policies. Both the policies and the appendices can be found via the “Site Implementation and Operations” page of the DAIDS Clinical Research Policies and Standard Procedures Documents website: https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures

Links directly to the documents are as follows:

Source Documentation Requirements:
4.0 Informed Consent and Assent Considerations

This section contains operational guidance for obtaining informed consent and assent for IMPAACT 2005. This guidance complements but does not duplicate the comprehensive information on informed consent, assent, and other human subjects considerations provided in Section 8 of the Network MOP. Please refer to the Network MOP as needed. Also refer to protocol Section 13.3, Section 4.8 of the ICH Guideline for GCP, and the informed consent section of the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials as needed.

Consistent with inclusion criterion 4.1.1, this study requires that written informed consent be obtained from each participating child’s parent or legal guardian. In addition, when applicable per IRB/EC policies and procedures, assent must be obtained from the participating child. Each site must have on file a SOP for obtaining informed consent/assent that addresses all aspects of the process consistent with all applicable local laws and regulations, as well as institutional and DAIDS policies and procedures pertaining to the informed consent process. The SOP must address vulnerable populations such as children and those who are illiterate. All sites must follow their SOPs consistently for all IMPAACT 2005 informed consent processes. All site staff involved in obtaining informed consent must be designated on the study-specific delegation of duties log and listed on the Form FDA 1572 for the study. These staff must be qualified by education, experience, training, and knowledge of the study, as determined by the IoR, and appropriate training documentation must be available to support the IoR’s delegation to these staff.

4.1 Study-specific Informed Consent and Assent Processes

Informed consent for study participation must be obtained before any study-specific screening or study procedures are performed. As indicated on the sample signature page in protocol Appendix II A, this informed consent form must be signed or marked by the consenting parent or guardian to formally document his or her consent. When applicable per site IRB/EC policies and procedures (e.g., based on participant age), assent for study participation must be obtained before any study-specific screening or study procedures are performed.

For participants who do not meet IRB/EC criteria for providing consent or assent at the time of screening and enrollment, if such criteria are subsequently met during follow-up, consent or assent should be obtained as soon as possible and prior to conducting the next study visit when the criteria are met. For example, if the IRB/EC requires that assent be obtained from children seven years of age and older, a child who is six-and-a-half years of age at the time of screening and enrollment would not be expected to provide assent prior to enrollment but would be expected to provide assent at the first study visit following his or her seventh birthday. Assent signature requirements should comply with site IRB/EC policies and procedures.

4.2 Assessment of Understanding

The IoR or designee is responsible for providing participants, parents, and guardians with all information relevant to their informed consent and assent decisions in a manner that is understandable to the participant/parent/guardian. The participant/parent/guardian should not be asked to make an informed consent or assent decision or to sign or mark an informed consent or assent form until he or she fully understands the study. The IoR or designee is therefore responsible for ensuring that each participant/parent/guardian understands all aspects of study participation before signing or marking an informed consent or assent form.
A variety of approaches can be taken to assess understanding. Regardless of the method used to assess understanding, if the assessment indicates misunderstanding of aspects of the study, the IoR or designee should review those aspects again until the participant/parent/guardian fully understands them. If after additional review and discussion the participant/parent/guardian is not able to demonstrate adequate understanding, he or she should not be asked to sign or mark the informed consent or assent form. Similarly, if the participant/parent/guardian has concerns about possible adverse impacts if he or she were to provide informed consent or assent, or if the participant/parent/guardian indicates that he or she may have difficulty adhering to the study requirements, he or she should not be asked to sign or mark the informed consent or assent form unless or until such issues can be resolved to the satisfaction of the participant/parent/guardian and the IoR or designee.

4.3 Documentation Requirements

Please refer to Section 8 of the Network MOP and the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials for detailed guidance on documentation requirements. The DAIDS policy includes requirements and suggestions; study sites must comply with all requirements and are encouraged to comply with all suggestions. To assist with compliance, sites may choose to use informed consent coversheets similar to the example provided in Appendix V below. 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 and assent process. All informed consent and assent documentation must be maintained on file in participant study records.

In addition to completing required entries on informed consent and assent forms, each informed consent and assent process should be documented in a signed and dated chart note. For the study informed consent and assent processes, the note should document that informed consent and assent when applicable were obtained before any study procedures were performed. 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 information recorded on the coversheet into the chart note. Informed consent and assent decisions should also be entered in appropriate eCRFs.

4.4 Considerations Regarding Death of a Guardian

The expectation is that permission for participation in IMPAACT 2005 will be sought either directly from the child – if above the age of legal consent (per country) – or from the child’s parent/legal guardian. Given that this is a study to establish safety of DLM in a pediatric population, it is important that children may continue follow-up in the study even in the event of the death of the guardian. Sites are therefore, encouraged to identify and document the individual(s) who would assume legal guardianship of the participant in the event of death of the parent/guardian who initially signed the consent.

5.0 Protocol Implementation

5.1 Overview

The study aims to enroll up to 48 participants to achieve a minimum of 36 evaluable participants (9-12 in each cohort) within a minimum of six HIV-infected participants per cohort. In all cohorts, the number of participants will be stratified by age and weight at enrollment, as per protocol Section 5.1. Participants with confirmed or probable intra-thoracic (pulmonary) and/or selected forms of extrathoracic MDR-TB will be considered evaluable if they have completed PK visits up to Week 8 and have PK data sufficient to estimate drug exposures using a model-based approach.
The study opened to accrual on 30 January 2018. Initially, under protocol Version 1.0 (dated 9 March 2017) enrollment was limited to participants in Cohorts 1 and 2, with Cohorts 3 and 4 to open following review of safety data from the Otsuka 232/233 trials. In October 2018, a directive to restrict enrollment to participants in Cohorts 1 or 2 weighing ≥40kg was issued to participating sites at the request of the IMPAACT Study Monitoring Committee (SMC). This restriction was warranted following review and pharmacokinetic analysis of data from adult DLM trials and the Otsuka 232/233 pediatric trials, which suggested a revised dosing regimen for all four study age cohorts in order to achieve the protocol-defined PK targets; these modifications necessitated a full version protocol amendment. Protocol Version 2.0 was released to participating sites on 4 October 2019. Under protocol Version 2.0, enrollment into Cohorts 1-4 will occur simultaneously, with dosing dependent on the weight of the participant. Each cohort will remain open after the minimum of nine evaluable participants has been enrolled until one of the following occurs: 1) The study has enrolled at least eight evaluable children across all the age cohorts who are taking EFV-based ART and eight evaluable children who are taking PI-based ART; or, 2) 12 participants have enrolled into the cohort.

Sites were required to provide projected enrollment into each of the cohorts as an element of site selection. Accrual to this study will be monitored by the protocol team and IMPAACT leadership in accordance with the Network MOP and the Study Progress, Data, Safety Monitoring Plan.

5.2 Site-Specific Accrual and Retention

The study accrual plan is based on site-specific accrual projections established during the site selection process. 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 a condition for study activation, each site will establish SOPs as described in Section 2.4. All sites are responsible for following these SOPs, and for updating them as needed throughout study implementation.

The Statistical and Data Management Center (SDMC) will routinely report the number of participants screened and enrolled at each site — by weight band and by month and cumulatively — to the protocol team. The team will monitor all available data in relation to site-specific accrual projections to determine whether accrual targets should be adjusted across sites to achieve the study objectives most efficiently. Participant retention will also be closely monitored by the study team. If accrual or retention rates fall below targets, team members will work with study sites to identify operational issues or problems and to take appropriate action to address below-target rates.

5.3 Recruitment

Refer to protocol Section 4.5 for an overview of participant recruitment, screening, and enrollment processes for this study. It is expected that sites will identify potentially eligible participants from healthcare centers where children with MDR-TB routinely receive care, including the following:

- In-patient treatment at a TB or other hospital
- Ambulatory care at community-based TB clinic or hospital
- Through household contact tracing of an MDR-TB source case

Selected operational considerations related to the recruitment, screening, and enrollment processes are provided in the remainder of this section.

5.4 Screening and Enrollment

Per the DAIDS policy on Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials, 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 participant is defined as having signed the study consent.
Logs should include the following information:

- Initials of all patients screened for each study
- PID
- Date screened

Additional information is provided at: https://www.niaid.nih.gov/research/dails-clinical-site-implementation-operations

5.4.1 Assigning Participant Identification Numbers Obtaining a Screening Number

A Participant Identification Number (PID) must be assigned to each potential participant for whom informed consent (and assent if applicable) for study participation is obtained. The only exception to this requirement applies when a participant has previously been assigned a PID for another IMPAACT study. In that case, the previously-assigned PID would be used for IMPAACT 2005. Study site staff should assign PIDs from lists provided by the DMC. Contact the protocol Data Managers with any questions related to use of PID lists.

5.4.2 Screening for Eligibility

The study eligibility criteria are provided in protocol Sections 4.1 and 4.2; procedural eligibility screening requirements are described in protocol Sections 6.1 (Screening Visit) and 6.2 (Enrollment Visit). Contact the CMC with any questions related to participant eligibility. Note, consultation with the CMC is not required prior to initiating screening; however, sites are encouraged to seek input, as needed. All participating sites will have access to enrollment availability in real-time via the Phase/Accrual report, which is available on the DMC website under “Reports.” This report provides target vs. actual accrual for each cohort and for the study overall, enrollment status of each cohort, and accrual by HIV status.

A PID will be assigned to all potential participants for whom informed consent (and assent if applicable) for study participation is obtained. In addition, a study-specific screening number will be obtained for each potential participant using the PS2001 IMPAACT Screening Checklist, located in the DMC’s SES. Sites are encouraged to perform screening procedures that are least burdensome and/or most likely to identify ineligibility first. Following site SOPs for eligibility determination, eligibility assessment for potential participants should be completed by the site IoR or designee.

It is the responsibility of the IoR and other designated study staff to ensure that all required screening procedures are performed and adequately documented, and that only participants who meet the study eligibility criteria are enrolled. Each site must have on file a study-specific SOP for eligibility determination that describes how study staff will fulfill this responsibility; all sites must follow their SOPs when assessing eligibility for all potential participants. In the event that study staff identify that an ineligible participant has been enrolled, the CMC must be consulted as soon as possible and within 24 hours per the communication procedures described in Section 3 of this manual.

5.4.3 Screening Failures

For potential participants who provide informed consent but are ineligible, or who do not enroll in the study for any reason, an IMPAACT 2005 Screening Failure and Non-Enrollment Results eCRF (SCR0061) must be completed and keyed in the study database. The reason(s) for screening failure, should be documented appropriately in the source documentation. In some cases, if the reason for screen failure changes, the patient may be rescreened in the future, using the original PID number. Potential participants identified as ineligible should be referred for non-study care as needed.
5.5 Enrolling Eligible Participants

Participants will be considered enrolled in IMPAACT 2005 upon successful entry of the eligibility checklist data into the SES, which will result in generation of a Study Identification Number (SID). Refer to protocol Section 6.2 for Entry visit requirements, including requirements related to the timing and ordering of Entry visit procedures, which should be taken into consideration when planning for logistical and staffing needs for the visit.

For potential participants who are determined to be eligible and enrolled in the study, all pre-existing conditions (i.e. identified signs, symptoms, and/or diagnoses) and concomitant medications should be entered into eCRFs, consistent with protocol specifications and applicable form instructions.

6.0 Study Visits and Procedures

Protocol Section 6 and Appendix I, Schedule of Evaluations (SoE), provide comprehensive information on procedural requirements for conducting study visits. Each site should establish SOPs for providing all relevant information and reminders to participants and their parents or caregivers to optimize compliance with protocol requirements.

Clinical evaluations and laboratory tests that comply with the requirements specified in protocol Section 6.27.2 and performed as part of clinical care within the Screening visit window may be abstracted from the participant’s medical record to meet the Screening 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 potential participants who are not confirmed to be eligible, when possible.

In preparation for each study visit, site staff should review protocol specifications for study drug dosing, list of concomitant medications, and food intake prior to the visit and provide timely reminders to participants and their caregivers of these specifications. Visit reminders may include reminding participants and their caregivers of the need to note doses of DLM, OBR and ARVs in the days preceding the visit, and to bring their remaining study drug and concomitant medications list to the visit. Site staff may also want to contact the participant and their caregiver to discuss visit expectations and duration (particularly for the intensive PK visits), and any need for arranging transportation or hospital admission if required. Further key points regarding study follow-up visits for participants are as follows:

- Target visit dates are counted from the day of study entry; day of entry = Day 0.
- Each visit should ideally be conducted on the target date but may be conducted on any day within the protocol-specified visit window.
- Every effort should be made to conduct all study visits within the protocol-specified visit window. Some visit windows overlap by a period of several days; during this overlap, completion of the earlier of the two visits should be prioritized, when applicable. Failure to conduct any study-specific procedures within the protocol-specified visit window is a deviation from the protocol and should be documented as such. See Section 6.2 for further guidance on protocol deviations.
- Site-specific procedures should be established among clinic and laboratory staff to ensure that all laboratory results are reviewed in a timely manner for participant safety monitoring and entry of results in appropriate eCRFs per protocol Section 7.2. This includes procedures and management for critical laboratory results that require additional follow-up per the protocol and Figure 3-3.
- In preparation for each visit, sites should review the protocol required evaluations for the visit and any laboratory tests from the prior visit.
- For all Cohorts, DLM dosing is twice daily, initiated at enrollment and should continue through the Week 24 visit.
- Reflex fT4 testing should be done if TSH is elevated.
• If a participant discontinues DLM prior to the Week 24 visit, an Early DLM Discontinuation visit should be done with evaluations conducted per the SoE “Early DLM D/C only or Early DLM & Study D/C” column and protocol Section 6.21. The participant’s follow-up visit schedule should be determined based on the time of DLM discontinuation.

6.1 PK Visit Considerations

PK sampling procedures and information for participants are provided in protocol Sections 6 and 10. Further operational instructions for study visits with PK collections are provided below.

• Prior to each PK visit, ensure availability and access to required supplies, including specimen collection materials, study drug supplies, source documents, eCRFs and meals as appropriate.
• DLM administration will be directly administered by study staff on the day of PK sampling.
• Doses, including administration date and time of DLM, OBR and ARVs for the two days preceding PK sampling should be obtained and recorded on eCRFs.
• Sparse PK (pre-dose) samples should be collected prior to directly observed administration of DLM at Weeks 4, 12, 16, 24, and 28.
  - For children less than six months of age, real-time PK assays will be performed at Week 2 (to include samples from Day 0 and Week 2) and Week 8 (to include samples from Week 4 and Week 8) for both DLM and DM-6705 (rather than waiting for samples to be batched with other samples and run at a later timepoint), to determine whether they need a dose adjustment. For those children < 6 months of age who do require an individual dose adjustment (refer to protocol Section 10.4.3), the semi-intensive PK collection following the dose adjustment should ideally be collected at the Dose Adjustment Visit (refer to protocol Section 6.20) but may also be collected at any point from two weeks after the dose adjustment until the date of the last DLM dose (refer to protocol Section 10.4.3).

6.2 Protocol Deviations

Any non-compliance with the IRB/EC approved protocol is a protocol deviation. Refer to protocol Section 14.4, Section 12 of the Network MOP, and DAIDS SOPs for source and essential documentation as needed for comprehensive information and requirements for protocol deviations.

All protocol deviations should be adequately documented in study records consistent with DAIDS SOPs for Essential Documents at Clinical Research Sites. This documentation should include a description of the deviation, the reasons why it occurred, and corrective and preventive actions taken in response.

Protocol deviations that meet the criteria for network level reporting, as specified in Section 12.4.2 of the Network MOP, should be entered in the IMPAACT 2005 study database. Specifically, a protocol deviation eCRF (DEV0001) should be completed and entered in the study database as soon as possible and within ten working days of site awareness. A copy of the completed eCRF should also be emailed to IMPAACT.deviation@fstrf.org, along with any supplemental documents. Of note, the site IoR retains responsibility for the final determination of reportability. Consultation with the CMC and Operations Center on reportability is available as needed.

If a reportable deviation involves more than one participant, one protocol deviation eCRF should be completed for each participant. If more than 25 participants are involved, or if the deviation does not involve specific participants, the deviation should be reported via email only to IMPAACT.deviation@fstrf.org.
7.0 Laboratory Considerations

7.1 Introduction and Overview

This section contains instructions related to collection and processing of IMPAACT 2005 specimens. For detailed information on tests and specimens required for each visit, please refer to protocol Section and Schedule of Evaluations (Appendix I) and the IMPAACT 2005 Laboratory Processing Chart (LPC). Please also refer to Section 17 of the Network MOP as needed. Information on specimen shipping and processing are available in the LPC available here: http://impaactnetwork.org/studies/IMPAACT2005.asp

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 specimen collection and/or 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.

Key elements of specimen management include collection, transport, storage and shipping. Also essential for clinical trials is a Chain of Custody, as described in Section 7.3, which refers to the tracking of specimens and results. Specimens must be transported within the 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.

7.2 Infection Control/Biosafety

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 U.S. Centers for Disease Control and Prevention (CDC). Respiratory infections like *M. tb* 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 CDC: http://www.cdc.gov/niosh/topics/bbp/universal.html

Site guidelines / SOPs should be used for infection control and prevention, with specific consideration of TB as an airborne disease. Guidance on preventing the transmission of *M. tb* is available as follows:

- WHO Guidelines on Tuberculosis Infection Prevention and Control, 2019 Update: https://apps.who.int/iris/bitstream/handle/10665/311259/9789241550512-eng.pdf?ua=1&ua=1
- CDC MMWR Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health-Care Settings, 2005. http://www.cdc.gov/mmwr/pdf/rr/rr5417.pdf and the accompanying slide set is found at: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5417a1.htm?s_cid=rr5417a1_e
7.3 Specimen Chain of Custody

All IMPAACT sites must have an 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. Participant names or initials may NOT be used on research samples or the accompanying tracking forms.

7.4 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 LIMS or LDMS system, if available, and aliquots must be labeled using standard LDMS-generated barcode labels.

7.5 Laboratory Data Management System (LDMS)

The LDMS is to be used at all sites to track the collection, storage, and shipment of the laboratory specimens. There will be some IMPAACT 2005 sites that do not have ready LDMS access; they will be relying on their designated contract laboratory to enter the information for them into LDMS. IMPAACT 2005 includes testing which requires processing to begin at the clinical site, immediately following sample collection (e.g. the PK specimens). For these samples, it is essential that all protocol specific processing information is transferred from the clinical site to the contract laboratory, where it may be entered into the LDMS as needed.

All sites should upgrade to the most current version of the LDMS as soon as possible. Detailed instructions for use of the LDMS are available at: https://www.ldms.org/

For supported label and printer options, refer to the product listing documents located on the LDMS Client Reference Guides page on the FSTRF Portal:

https://www.frontierscience.org/apps/cfmx/apps/common/Portal/index.cfm

Contact LDMS user support for further information. Questions about LDMS, shipping and storage for IMPAACT 2005 should be directed to the protocol Laboratory Data Managers:

Kyle Whitson, FSTRF
Phone: +1 (716) 834-0900, extension 7273
Email: whitson@fstrf.org

Mark Lojacono, FSTRF
Phone: +1 (716) 834-0900, extension 7346
Email: lojacono@fstrf.org

7.5.1.1 LDMS User Support

Regular business hours for LDMS user support are 12 AM - 6:00 PM Eastern Time in the U.S. (ET) Monday through Friday. During business hours, please contact LDMS User support as follows:

Email: Ldmshelp@fstrf.org
Phone: +1 (716) 834-0900, extension 7311
Fax: +1 (716) 898-7711
7.5.1.2 Off-Hours Contact Information

If site staff are locked out of your LDMS or are experiencing errors that prevent completion of LDMS lab work after business hours, LDMS User Support may be accessed using the LDMS Web Pager utility or by e-mailing the paging system directly at ldmspager1@fstrf.org. Please allow at least 15 minutes to get a response.

7.6 Sample/Specimen Collection and Processing Prior to Shipment to the Laboratory

Important details regarding specimen management are included in the LPC. Particularly for the PK and biomarkers, all of which require some element of specimen processing within one hour following collection as well as special collection procedures, the clinical staff will need to be familiar with procedures in the LPC.

7.6.1 PK Specimen Collection and Processing

Venous blood specimens for DLM PK are collected at the following visits:

- Semi-Intensive PK: Week 0, 2*, 8 and the Dose Adjustment Visit
- Sparse PK: Week 4, 12, 16, 24, 28 and at early D/C

*Note: The Week 2 Semi-Intensive PK visit has four collection timepoints, all other semi-intensive PK visits have three collection timepoints.

Semi-intensive PK sampling is performed at the Entry, Weeks 2, 8 and Dose Adjustment Visits. Semi-intensive PK sampling at Entry, Week 8 and the Dose Adjustment Visit should be collected prior to DLM administration (pre-dose) and 4 and 8 hours post-dose. Semi-intensive PK sampling at Week 2 should be drawn pre-dose, and 2, 4 and 8 hours post-dose. Sparse PK sampling at Weeks 4, 12, 16, 24 should be collected prior to DLM administration (pre-dose). Sparse PK sampling at Week 28 may be drawn at any time during the visit. If a participant prematurely discontinues DLM or the study, the participant should return for an Early DLM Discontinuation (D/C) or Early Study D/C visit, respectively, and sparse PK sampling performed at any time during this visit, ensuring that the date and time of last dose and the time of sampling is collected.

Prior to sampling, prepare the blood sampling tubes by covering each tube in foil to protect the analyte from light. As the tubes are drawn, invert 8-10 times gently. Place the collection tubes in crushed ice immediately after collection. Process and store two aliquots of equal volume of plasma in amber cryovials at -70°C or lower. Protect the plasma from light at all times. Maintain cold chain at all stages, if possible; room temperature for centrifugation is acceptable, if necessary, but there should be no delay in processing the plasma.

PK specimens should be stored at sites as specified in the LPC until requested to ship by the protocol team to the testing laboratory. A site-specific shipping request will be issued by the protocol Laboratory Data Manager when PK samples should be shipped; no specimens can be shipped without this request. Further details on PK specimen management and shipping are available in the LPC.

7.7 Biomarker Specimen Collection

Biomarkers (serum and urine) are collected for all participants at Entry, Week 24 and Week 72 visits. As these specimens must be processed rapidly, it is important that clinic staff are familiar with the LPC specimen management procedures.
For collection of urine for TB biomarkers:

- Precautions must be taken to reduce cellular and microbial contamination that could prevent optimal results.
- Urine should be collected with the same care as when collecting a urine to diagnose bacterial urinary tract infections (UTIs), i.e. midstream collection after cleansing. However, for young children, invasive collection methods such as catheterization or suprapubic aspiration which are used to diagnose bacterial UTIs would not be acceptable in the context of TB biomarker research and should not be used.
- If midstream specimens after cleansing cannot be obtained in young children, collecting the urine using a sterile urine bag, although not recommended for the diagnosis of UTIs, will therefore be allowed for TB biomarker research specimens.
- Disinfectants used as cleansers (benzalkonium or hexachlorophene) can interfere with the growth of some organisms causing a false negative result. Most references recommend liquid soap cleansers, rather than disinfectants, which do not significantly affect the common organisms causing UTI. Similarly, for TB biomarkers, disinfectants should not be used. Instead, use soap and water to clean the area before midstream collection or applying urine collection bag. Let the area dry after.
- Cotton wool balls, gauze and sanitary towels should not be used.
- The urine SOP used at the Desmond Tutu TB Centre is available here as an example: https://www.dropbox.com/sh/tbdrcl7jw9boofc/AADZYIIIVX4uBtTM4BWOSr6pV?dl=0

7.7.1 Specimens for TB Testing

For IMPAACT 2005, the type of respiratory specimens collected can be expectorated sputum, induced sputum, and/or gastric aspirate. The choice of procedure will be according to local practice with the same technique used for each participant for the duration of the study. Ideally, the collection of early morning sputum (expectorated or induced) or overnight gastric aspirate after fasting (at least six hours, nil per mouth) should be encouraged as much as possible.


Note, this SOP is typically more useful in older children (>6 years of age) who are able to expectorate sputum, with or without assistance.

An additional video tutorial is available at: Respiratory Specimen Collection for TB Investigation. *Enter password "IMPAACT2017" in Vimeo to watch.

Key elements for collection of expectorated sputum, induced sputum and gastric aspirate, as well as additional specimen collection references are available in the Mycobacteriology Laboratory Sourcebook for Harmonization and Support of Tuberculosis (TB) Clinical Trials (Sourcebook) at: https://www.hanc.info/labs/labresources/procedures/Pages/TB-Sourcebook.aspx

8.0 Pharmacy Considerations

For detailed information on study drug considerations refer to protocol Section 5.

8.1 DLM Dosing

DLM twice daily dosing is initiated at enrollment and should continue through the Week 24 visit. Refer to protocol Section 5.1 for DLM dosing for Cohorts 1 – 4.

Participants who enrolled in the study weighing less than 30 kg (Cohorts 3 or 4) and gain weight to be ≥ 30 kg during the 24 weeks of DLM dosing should be transitioned from the pediatric to adult formulation. This change should be made in accordance with protocol Section 5.1 and recorded in the participant’s study file and eCRFs.

In addition, per protocol Sections 10.4.3, 10.4.4, and Appendix XI, individual dose adjustments may be considered for participants less than six months of age and/or weighing <12kg. Individual dose adjustments should also be recorded in source documentation and eCRFs.

8.2 DLM Dispensing and Administration

To comply with US Federal Regulations, all study products must be dispensed in child-resistant packaging. The DLM blister packs are not certified as child-resistant; therefore, DLM will be dispensed in a child-resistant pouch. Child resistant pouches can be obtained directly from the CRPMC.

For participants who are able to do so, delamanid (DLM) should be taken with high-fat food. The pediatric dispersible tablet formulation of DLM may be swallowed, chewed or dispersed into water as per protocol Section 5.1.1. Refer to protocol Section 5.2.2 and Appendix I for detailed instructions regarding study drug preparation for the pediatric formulation.

There should be at least one hour between the DLM dose and the administration of OBR (with or without ARVs). If a participant misses a dose of DLM, they should make up the missed dose (i.e. take another dose when it is remembered) if it is within 6-8 hours of the time the dose is usually taken. If it is more than 8 hours after the time the dose is usually taken, the dose should be skipped, and the next dose should be taken as scheduled. The study team should be made aware of any missed doses.

On intensive PK days a study-specific meal will be provided to the child. The study-specific meals should consist of a meal typical for the child’s age group, and should be expected to provide roughly 25% or more of its calories from fat.

Food intake prior to the DLM dosing on intensive PK sampling days should be documented on the PK eCRF; details documented include the start time of the meal and the type (full meal or snack). Meals on PK sampling days should be standardized as much as possible per site.

The ideal order of giving DLM is as follows: meal, followed by DLM administered within 30 minutes of starting the meal. Thereafter a waiting period of at least one hour, followed by OBR (with or without ARVs).

8.3 Adherence

Sites should work closely with participants and/or parents/guardians and with hospital personnel to ensure adherence and provide them with resources to document dosing of DLM, OBR and ARVs, as appropriate. Directly observed therapy (DOT) is the expectation throughout the study, per local guidelines. The exact time of doses on the two days prior to each study visit will be recorded on
eCRFs. Study drug will be directly administered by the research team on the day of PK sampling. As an element of activation, each site is required to prepare an SOP on ensuring adherence and DOT.

8.4 Concomitant Medications.

All TB medications and ARVs, if applicable, should be recorded in eCRFs. A log of all concomitant medications, including non-TB and non-ARV medications, should be documented in each participant’s study file and entered into eCRFs consistent with protocol specifications and applicable form instructions. Refer to protocol Section 5.6 for guidance on prohibited and precautionary medications in IMPAACT 2005.

Based on the potential risks of DLM, all sites should closely monitor participants taking concomitant medications that are potentially QTcF prolonging and consult the Core Cardio Team regarding the clinical management of any such participants. For reference, a list of drugs with the potential for mild to moderate QT prolonging effects will be posted on the study-specific webpage; sites should limit the use of these medications when possible.

9.0 Expedited Adverse Event Reporting to DAIDS

Refer to protocol Section 7 and the following resources to guide expedited adverse event (EAE) reporting for IMPAACT 2005:

- DAIDS Table for Grading Adult and Pediatric Adverse Events (DAIDS Toxicity Table), Corrected Version 2.1, dated July 2017: https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables
- Investigator’s Brochure for Delamanid

Note: It is the responsibility of the IoR and designated study staff to review and be informed of the Investigator’s Brochure for DLM and any updates during the study.

9.1 Selected Definitions

Key definitions associated with expedited adverse event reporting in IMPAACT 2005 are provided below. Refer to the Manual for Expedited Reporting of Adverse Events to DAIDS for additional terms and definitions.

*Adverse event (AE)* The AE definition specified in protocol Section 7 applies to infants, children and adolescents enrolled in IMPAACT 2005 beginning at entry into the study. Medical conditions, illnesses, problems, signs, symptoms, and findings identified before entry are considered pre-existing conditions. If a pre-existing condition worsens (increases in severity or frequency) after entry into the study, the worsened condition is considered an AE. If a pre-existing condition resolves after entry into the study but then recurs at a later date, the recurrence is considered an AE.

All AEs occurring among participants enrolled in IMPAACT 2005 must be source documented in participant study files, including the severity of the AE and its relationship to DLM assessed by the IoR or their designee.
**Serious AE (SAE)**

Medical and scientific judgment should be exercised in deciding whether other AEs not listed in the definition of SAEs in protocol Section 7.3.2 should be considered serious. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the outcomes listed above should usually be considered serious (ICH E6 and E2A).

**SUSAR**

Suspicious unexpected serious adverse drug reaction

SUSARs are SAEs that are assessed as both suspected and unexpected:
- **Suspected** = related \( \Rightarrow \) there is a reasonable possibility that an AE may be related to an investigational agent

As indicated in the definitions above, and as shown in Figure 9-1, SAEs are a subset of all AEs, and SUSARs are a subset of all SAEs.

**Figure 9-1**

Adverse Event, Serious Adverse Event, and SUSAR Subsets

**Expedited AE (EAE)**

An AE that meets protocol criteria for reporting in an expedited manner to the DAIDS Regulatory Support Center Safety Office

**9.2 EAE Reporting Requirements**

For infants, children, and adolescents enrolled in IMPAACT 2005, SAEs as defined in Version 2.0 of the DAIDS EAE Manual, should be reported as EAEs per protocol Section 7.3.

The EAE reporting period for this study is the entire study duration of follow-up for an individual participant (from study enrollment until study completion or discontinuation of the participant from study participation for any reason). SAEs as defined in Version 2.0 of the DAIDS EAE Manual must be reported as EAEs.
Note: The severity of all AEs identified in this study — except QT interval grading and grading of cardiac symptoms related to cardiac conduction abnormalities (see protocol Appendices VII and VIII) — will be graded according to the Corrected Version 2.1 of the DAIDS Toxicity Table, dated July 2017.

After the above-specified period, only suspected, unexpected, serious adverse reactions (SUSARs) as defined in Version 2.0 of the EAE Manual, will be reported if the study staff become aware of the events on a passive basis (from publicly available information).

9.3 AE Relationship Assessment

For purposes of toxicity management — as specified in protocol Section 8.1 — the IoR or designee must assess the relationship of all AEs identified in enrolled participants to DLM according to the categories shown in Figure 9-2. The categories are also used when recording AEs on eCRFs.

### Figure 9-2

**Relationship Assessment Categories for Toxicity Management**

<table>
<thead>
<tr>
<th>Relationship Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely related</td>
<td>The event and administration of the medication are related in time, and a direct association can be demonstrated.</td>
</tr>
<tr>
<td>Probably related</td>
<td>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.</td>
</tr>
<tr>
<td>Possibly related</td>
<td>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.</td>
</tr>
<tr>
<td>Probably not related</td>
<td>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.</td>
</tr>
<tr>
<td>Not related</td>
<td>The event is clearly explained by another cause not related to the medication.</td>
</tr>
</tbody>
</table>

For purposes of EAE reporting the IoR or designee must report the relationship of EAEs to the investigational dose of DLM according to the categories shown in Figure 9-3 (see protocol Section 7.3.4).

### Figure 9-3

**Relationship Assessment Categories for EAE Reporting**

<table>
<thead>
<tr>
<th>Relationship Category</th>
<th>Definition</th>
</tr>
</thead>
</table>
| Related               | There is a reasonable possibility that the EAE may be related to study-supplied DLM. 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 study-supplied study drug. 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 DLM  
  • A plausible biologic mechanism for the DLM to cause the EAE  
  • Previous reports of similar events associated with DLM  
  • Resolution of the event after de-challenge (hold/discontinuation of DLM)  
  • Recurrence of the event after re-challenge (resumption of DLM 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 study-supplied DLM. |
| Not related           | There is not a reasonable possibility that the EAE may be related to DLM. |
Figure 9-4 shows how the five relationship categories used for toxicity management should be mapped to the two relationship categories used for EAE report.

### Figure 9-4
Mapping of Relationship Categories for Toxicity Management to Relationship Categories for EAE Reporting

<table>
<thead>
<tr>
<th>Relationship Category for Toxicity Management</th>
<th>Maps To</th>
<th>Relationship Category for EAE Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely related</td>
<td></td>
<td>Related</td>
</tr>
<tr>
<td>Probably related</td>
<td></td>
<td>Related</td>
</tr>
<tr>
<td>Possibly related</td>
<td></td>
<td>Related</td>
</tr>
<tr>
<td>Probably not related</td>
<td></td>
<td>Not related</td>
</tr>
<tr>
<td>Not related</td>
<td></td>
<td>Not related</td>
</tr>
</tbody>
</table>

#### 9.4 EAE Reporting Procedures

All EAEs should be reported to the DAIDS RSC Safety Office using the internet-based DAIDS Adverse Experience Reporting System (DAERS), per instructions provided in the DAERS Reference Guide for Site Enrollment Users: [https://rsc.niaid.nih.gov/clinical-research-sites/daers-reference-guide-site-enrollment-users](https://rsc.niaid.nih.gov/clinical-research-sites/daers-reference-guide-site-enrollment-users)

More information on DAERS Expediting Reporting is also available in the Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0, January 2010.

The process of EAE reporting via DAERS involves a designated “Study Reporter” creating an electronic EAE report and a designated “Study Physician” reviewing the EAE report, signing the EAE report with an electronic signature, and submitting the EAE report to the DAIDS RSC Safety Office. If an EAE report is not completed and submitted within three reporting days of site awareness that an event meets EAE reporting criteria, an explanation must be entered in DAERS before the report can be submitted (see the Manual for Expedited Reporting of Adverse Events to DAIDS for the definition of reporting days). DAERS also may be used to withdraw an EAE report that was submitted in error and to modify or update a previously submitted EAE report.

For all submitted EAE reports, updates must be submitted to report the final or stable outcome of the EAE, unless the original report provided a final or stable outcome. Updates also should be submitted if significant additional information becomes available after an EAE report is first submitted. Significant additional information may include, for example, an updated severity grade or relationship assessment, information on participant status after resumption of one or more study drugs, and/or newly available information on cause of death.

*When updated EAE reports are submitted, it is NOT necessary to complete and submit another Event Evaluation eCRF to the DMC. Only one Event Evaluation eCRF should be completed and submitted for each event.*

DAERS incorporates a report printing function that should be used to print all EAE reports — including modifications and updates — for filing in participant study records. Automated email messages confirming submission of EAE reports also should be printed and filed with the print-out of the associated EAE report.

For questions about DAERS, email DAIDS-ESSupport@niaid.nih.gov. Questions also may be submitted from within the DAERS application itself.

In the event that DAERS cannot be accessed (e.g., due to poor internet connectivity), paper-based EAE reporting should be used, per instructions provided in the Manual for Expedited Reporting of Adverse Events to DAIDS. Completed paper EAE Forms may be faxed or digitally scanned and...
emailed to the DAIDS RSC Safety Office. The EAE Form and form completion instructions are available on the DAIDS RSC website; contact details for submission of EAE Forms are provided in the Manual for Expedited Reporting of Adverse Events to DAIDS, which is also available on the DAIDS RSC website.

9.5 Reporting Protocol-Specified Events to the CMC

Adverse events, pregnancies and laboratory abnormalities meeting pre-defined criteria will be reported promptly to the CMC by the investigator who determines that the event meets the protocol definition for that event. In addition, site requirements for reporting to local regulatory authorities and IRBs need to be followed.

10.0 Clinical Management Considerations

10.1 Karnofsky/Lansky Performance Status

In IMPAACT 2005, the Karnofsky/Lansky Performance scale will be used to determine the functional status of study participants at Screening. The Karnofsky Scale is designed for recipients age > 16 years and the Lansky Scale is designed for recipients age < 16 years. Refer to Appendix IV for instructions on how to complete these assessments. Additional information can also be found using the following resources:

- http://www.hospicepatients.org/karnofsky.html

10.2 Cardiac Safety Monitoring

As QT prolongation and/or potential QT interval effects can be caused by DLM alone and together with the use of other drugs used in the treatment of MDR-TB (e.g. levofloxacin and clofazimine), cardiac safety will be carefully monitored throughout in IMPAACT 2005. Consultation with the protocol cardiologist is available and encouraged for any abnormal or equivocal ECG findings and/or questions related to cardiac toxicities and assessment.

A pre-tested ECG machine and accessories are provided to all sites from IQVIA. Further details on the study ECG machines and materials provided are available in the following documents:

- Investigator Manual: Provides guidance on implementation of the ECG machine, the ECG transmission process, accessing the IQVIA Web Portal (https://infosario.quintiles.com), and site staff responsibilities for IMPAACT 2005.
- Visit Code Poster: Provides a list of visit codes to use while obtaining ECGs.
- Quick Reference Guide: Highlights important reminders to conduct ECGs throughout the study.

A training CD-ROM is also included in the materials shipped with the ECG machine from IQVIA. All site staff who are conducting and/or transmitting participant ECGs in IMPAACT 2005 are required to complete the training and print a certificate documenting completion of the training, which should be filed in site essential document files for IMPAACT 2005. After completion of the training, which includes the successful transmission of a test ECG, sites should notify the Operations Center, as this is a required element of study activation. In addition, each site will be required to complete the cardiac safety training included as part of the IMPAACT 2005 study-specific training for study activation.
For any questions or problems with the IQVIA Web Portal, ECG machine and materials, sites may contact the IQVIA Helpdesk via email: ecg.helpdesk@quintiles.com

Details on obtaining ECGs are provided in the IQVIA Investigator’s Manual and Visit Code Poster. Please refer to protocol Appendices VII and IX for details on grading and management of ECG and clinical cardiac toxicities. Study-specific pediatric ECG training is also available on the IMPAACT 2005 study webpage.

**10.2.1 ECG Monitoring and Clinical Management**

Due to the inherent challenges in obtaining an accurate ECG reading in a pediatric population, ECGs in IMPAACT 2005 are conducted in triplicate, ideally by the same member of the study team at each time point specified in protocol Appendix I. Triplicate ECGs should be completed consecutively with a minimal time (seconds to minutes) between each; however, there is no specific required time in between ECGs. A recommended approach would be to allow one minute in between each of the ECGs (i.e. the third ECG should be completed within approximately five minutes of the first).

All potentially eligible participants for IMPAACT 2005 will have an ECG performed at the Screening and Entry visits. ECGs conducted at these visits should be performed in triplicate and a mean value of the QT interval manually calculated using the Frederica correction to confirm eligibility per exclusion criterion 4.24. Sites are encouraged to review the IQVIA final reading of the screening ECGs to confirm eligibility; however, this determination ultimately lies with the Site Investigator(s).

The site IoR or designee – in consultation with a site pediatric cardiologist, if available – will review ECGs in real-time in order to identify potential safety concerns that would require urgent attention, and move forward with appropriate clinical management as per local standard of care and protocol-specific requirements (see protocol Appendices VII and IX for grading and management of ECG and clinical abnormalities). For any abnormal or equivocal ECG findings, the site clinical team should notify the IMPAACT 2005 Core Cardio Team by sending the tracings by email to IMPAACT2005corecardio@fstrf.org. The subject line of the email should be: “IMPAACT 2005 CRS # ___ PID ___ Study ECG.” The Protocol Cardiologist will respond to the site by email; this email should be printed and included in the participant’s study records.

For each participant time point, three ECGs will be uploaded for review by IQVIA. The Medical IQVIA Cardiac Team will review the electronic data and verify significant ECG findings based on study-specific ECG abnormality criteria (Appendix V of the protocol). The IQVIA interpretation will be available within 72 hours, posted to the study-specific IQVIA Web Portal, and sent to the site. ECG reports transmitted to IQVIA will also be reviewed by the protocol cardiologist.

If the site identifies a cardiac abnormality warranting clinical action, the site staff should manage appropriately as per the site interpretation and contact the IMPAACT 2005 Core Cardio Team (IMPAACT2005corecardio@fstrf.org) as per MOP Section 3.1 and protocol Appendices VII and IX. Sites should not hold back from appropriate clinical management or notification of the team pending the IQVIA interpretation.

**10.3 Contraception and Pregnancy**

As per the DLM (trade name, Deltyba) Investigator’s Brochure (IB), 15th Edition:

> Fetal development studies performed in rats and rabbits did not suggest teratogenicity at the maximal feasible doses due to DLM. No clinical trials have been conducted on the use of DLM during pregnancy or breastfeeding. As the toxicity profile of delamanid in pregnant or lactating women has not yet been determined, if it is determined during treatment that a participant has become pregnant during follow-up, study drug treatment must be discontinued immediately.
Therefore, any participant of reproductive potential must agree to maintain contraceptive use throughout the first 28 weeks on study to be eligible for the study per inclusion criteria 4.1.11 - 4.1.13. Refer to protocol Section 8.8 for further guidance on contraception and pregnancy in IMPAACT 2005.

10.3.1 Contraceptive Counseling

Contraceptive counseling for participants will be provided according to local standards of care. Note that appropriate counseling should be provided to all participants of reproductive age (i.e. both male and female participants). To supplement local SOPs on provision of contraceptive counseling, sites are encouraged to download the following publications from the WHO Selected Practice Recommendations for Contraceptive Use, Third edition, 2016: http://www.who.int/reproductivehealth/publications/family_planning/SPR-3/en/

If an adolescent participant undergoes postpartum surgical sterilization (e.g., hysterectomy, bilateral oophorectomy, tubal ligation, salpingectomy; or vasectomy) she/he does not require the use of a contraceptive method to prevent pregnancy; however, these participants should continue to be reminded to use condoms to prevent acquisition/transmission of sexually transmitted diseases.

10.3.2 Pregnancy

Female adolescent participants of reproductive potential and who have not undergone surgical sterilization (e.g., hysterectomy, bilateral oophorectomy, tubal ligation, salpingectomy) should have a pregnancy test administered per protocol Appendix I and when pregnancy is suspected or considered clinically indicated during study follow-up. If a participant becomes pregnant during the study, DLM should be discontinued and the participant will continue follow-up per the protocol. If the outcome of the pregnancy is not known at the time the participant exits the study, study staff should continue to contact the participant until that information is available; refer to protocol Section 6.18.

Because the potential effects of DLM on sperm are not known, pregnancies in partners of male participants will be reported per protocol Section 8.8 Male participants of reproductive potential should be queried as part of standard contraceptive counseling about whether a sexual partner has become pregnant during the study. If the outcome of the pregnancy is not known at the time the participant exits the study, study staff should continue to contact the participant until that information is available.

10.4 TB Monitoring and Treatment Outcome

10.4.1 Centralized Chest X-Ray

Chest X-rays (CXR) are performed for all participants at Screening and at the Weeks 24, 48 and 72 visits. CXRs should be uploaded to the Frontier Science Foundation File Exchange Utility, as outlined in Figure 10-1 for centralized review.
Figure 10-1
Uploading a CXR to the Frontier Science Foundation File Exchange Utility

Sites should upload all CXRs collected for each participant, starting with images from the Screening Visit. All images should be uploaded on a regular basis, soon after the visit.

1. To prepare the CXR for uploading:
   a. Redact any personal identifying information (name, date of birth, hospital number) from the image.
   b. Save the image files (either the digital CXR from your imaging department or a digital photograph of the X-ray, prepared as per instructions in Appendix V) as a .jpg format with a maximum file size of 2048 KB.
   c. Save the file on the computer used to access the exchange utility.
   d. Save each image file you plan to upload using the following naming conventions:

**IMPAACT 2005_PID_dateofCXR_view**
- PID= participant ID
- dateofCXR= date the x-ray was taken (this same date is recorded on the eCRF)
- view= use AP for antero-posterior view, LAT for lateral view, PA for posterior-anterior view.
All of these must match the eCRF

2. Refer to the Frontier Science Portal to upload image files: [https://www.frontierscience.org](https://www.frontierscience.org).

3. Make sure you are signed into the Frontier Science portal – click on “Sign in.” Enter your full email address along with your password. If you do not have an account, email usersprt@fstrf.org. If you do have an account but you experience a problem signing in, email usersprt@fstrf.org.

   IMPAACT Home > File Exchange Utility

   **File Exchange Utility**

   Enter a study, select whether you would like to view, download, upload, or manage files, and click Submit.

   ![File Exchange Utility interface](image)

   **Study:** 2005
   **Action:**
   - View files
   - Upload files
   - Manage files
   - Download files
   Submit Reset

5. Upload as many images files as needed for a given PID using the “Browse” button to search for files on your computer. Follow the instructions in the application.

6. Once you have successfully submitted your files, you will see a successful submission confirmation message. If you do not receive this confirmation message, contact email usersprt@fstrf.org
10.4.2 TB Treatment Outcome

TB treatment outcomes in participants, specified in the protocol Section 8.5, will be defined as bacteriological cure, probable cure, treatment failure, TB recurrence, death, and loss to follow-up. Attainment of clinical and radiological improvement will be taken to mean significant improvement in clinical signs and symptoms (such as resolution or substantial improvement in cough, fever, activity level, anthropometry, abnormal physical exam findings such as lung crepitations, lymph node swelling, etc.) in the judgment of the site investigator or designee. Attainment of radiological improvement will be taken to mean significant improvement in radiographic findings in children with intrathoracic TB, in the judgment of the investigator or designee. Further details of these classifications are given in Table 10-1 and Table 10-2.
### Table 10-1
Classification of Treatment Outcomes for Children with Bacteriologically Confirmed MDR-TB*

<table>
<thead>
<tr>
<th>Bacteriological outcome</th>
<th>And vs. Or</th>
<th>Clinical/radiological outcome</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three consecutive negative cultures(^1) at least four weeks apart with no positive culture after first negative culture, with ≥1 negative culture in the last 48 weeks of treatment after treatment initiation</td>
<td>AND</td>
<td>Completion of treatment with clinical/radiological improvement in the assessment of site investigators by 24 weeks, not meeting criteria for treatment failure AND no recrudescence of clinical/radiological criteria for TB (prior to 72 weeks)</td>
<td>Cure</td>
</tr>
<tr>
<td>Criterion as written above is not met (for those with confirmed MDR-TB at baseline(^6)), but not meeting criteria below for treatment failure</td>
<td>AND</td>
<td>Completion of treatment with clinical/radiological improvement in the assessment of site investigators by 24 weeks AND no recrudescence of clinical/radiological criteria for TB prior to 72 weeks</td>
<td>Probable cure</td>
</tr>
<tr>
<td>Culture positivity (+ culture at 24 weeks and beyond after starting treatment) but prior to completing treatment</td>
<td>OR</td>
<td>Insufficient clinical/radiological improvement after 24 weeks or more on treatment or recrudescence of clinical/radiological criteria for TB while on treatment</td>
<td>Treatment failure</td>
</tr>
<tr>
<td>Three consecutive cultures negative at least four weeks apart with no positive culture after first negative culture, with ≥1 negative culture in the last 48 weeks of treatment after treatment initiation OR Criterion as written above is not met (for those with confirmed MDR-TB at baseline), but not meeting bacteriological criteria for treatment failure</td>
<td>AND</td>
<td>Completion of treatment with clinical/radiological improvement in the assessment of site investigators by 24 weeks AND no recrudescence of clinical/radiological criteria for TB prior to 72 weeks AND recurrence of clinical/radiological signs/symptoms consistent with TB or new positive cultures - AFTER treatment is completed and before 72 weeks</td>
<td>TB Recurrence</td>
</tr>
<tr>
<td>Any bacteriological outcome</td>
<td>AND</td>
<td>Death for any reason while on DR-TB treatment or at any point prior to 72 weeks after start of study regimen</td>
<td>Death</td>
</tr>
</tbody>
</table>

* Children who at one time were actively participating in the trial but are lost to follow-up, as well as those who do not complete study regimen, will not be classified according to these tables but will be tabulated and reported separately. Loss to Follow-Up is defined as becoming unfindable by the study team at any point prior to 72 weeks and not having evaluable data to assess treatment outcome at 72 weeks.

\(^1\)Contaminated samples or indeterminate results will not be counted in determining whether negative results are consecutive (e.g., if two consecutive culture results are both negative, followed by a contaminated result and subsequently a negative result, then the participant meets this criterion).

\(^6\)Baseline indicates screening or entry.
## Table 10-2

**Classification of Treatment Outcomes for Children with Probable, Clinically diagnosed MDR-TB***

<table>
<thead>
<tr>
<th>Clinical/ radiological outcome</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completion of treatment with clinical/radiological improvement in the assessment of site investigators by 24 weeks AND no recrudescence of clinical/radiological criteria for TB prior to 72 weeks</td>
<td>Probable cure</td>
</tr>
<tr>
<td>Insufficient clinical/radiological improvement after 24 weeks or more on treatment or recrudescence of clinical/radiological criteria for TB while on treatment</td>
<td>Treatment failure</td>
</tr>
<tr>
<td>Completion of treatment with clinical/radiological improvement in the assessment of site investigators by 24 weeks AND no recrudescence of clinical/radiological criteria for TB prior to 72 weeks AND recurrence of clinical/radiological signs/symptoms consistent with TB or new positive cultures - AFTER treatment is completed and before 72 weeks</td>
<td>TB Recurrence</td>
</tr>
<tr>
<td>Death for any reason while on DR-TB treatment or at any point prior to 72 weeks after initiation of study regimen</td>
<td>Death</td>
</tr>
</tbody>
</table>

*Children whose cultures are initially negative whose cultures become positive at some later point in the trial will then need to be classified per Table 10-1. Children who at one time were actively participating in the trial but are lost to follow-up, as well as those who do not complete study regimen, will not be classified according to these tables, but will be tabulated and reported separately. Loss to Follow-Up is defined as becoming unfindable by the study team at any point prior to 72 weeks and not having evaluable data to assess treatment outcome at 72 weeks.

*Notes: Clarifications on the criteria may be included in the IMPAACT 2005 TB Treatment Outcome Endpoint Review Process Document.*
### APPENDIX I: Delamanid Oral Suspension Preparation Instructions

#### APPENDIX IA: Delamanid Oral Suspension Preparation (Medication Cup) for 25 mg Dose

<table>
<thead>
<tr>
<th>#</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Put 1 tablet (25 mg x 1) of delamanid pediatric formulation into the medication cup. Pour 15 mL of water into the cup, and let stand for 30 seconds. Gently swirl to make a uniform suspension. [Caution] Be careful.</td>
</tr>
<tr>
<td>2</td>
<td>Administer suspension to the patient.</td>
</tr>
<tr>
<td>#</td>
<td>Procedure</td>
</tr>
<tr>
<td>----</td>
<td>-----------</td>
</tr>
</tbody>
</table>
| 4  |       ![Image of a cup](image1.png) **Pour another 15 mL of water into the cup and gently swirl in order to capture any remaining drug.**  
    ![Image of a cup](image2.png) **[Caution] Be careful not to spill the suspension.** |
<p>| 5  | <strong>Administer suspension to the patient.</strong> |</p>
<table>
<thead>
<tr>
<th>#</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Disassemble the oral syringe into three parts: cap, barrel and plunger.</td>
</tr>
<tr>
<td>2</td>
<td>Put one tablet (25 mg x 1) of delamanid pediatric formulation into the barrel of the syringe.</td>
</tr>
<tr>
<td>3</td>
<td>Place the plunger in the barrel of the syringe, and then adjust the plunger seal to align with the 5 mL mark as shown in the picture above.</td>
</tr>
<tr>
<td>4</td>
<td>Place the tip of the syringe in a container of water and pull the plunger until the plunger seal aligns with the 20 mL mark as shown in order to collect 15 mL of water.</td>
</tr>
<tr>
<td>#</td>
<td>Procedure</td>
</tr>
<tr>
<td>----</td>
<td>-----------</td>
</tr>
</tbody>
</table>
| 5  | Cap the syringe and shake five times to suspend the tablets.  
    Note: If the syringe does not have the cap, please wear a glove and use the tip of your index finger as a stopper to avoid spillage of suspension. |
| 6  | Confirm the suspension is the same throughout (as shown in the above picture). If necessary, shake the syringe a few more times in order to suspend the tablets evenly. |
| 7  | Remove the cap, and then administer the entire suspension into the mouth of the patient.  
    [Caution] In order to avoid ejecting the suspension inadvertently, pull back a little on the plunger before removing the cap. |
<p>| 8  | Draw up another 15 mL of water in order to capture any residual drug in the syringe and administer to the patient. |</p>
<table>
<thead>
<tr>
<th>#</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Put 2 tablets (5 mg x 2) of delamanid pediatric formulation into the medication cup. Pour 4 mL of water into the cup, and let stand for 30 seconds.</td>
</tr>
<tr>
<td>2</td>
<td>Gently swirl to make a uniform suspension. [Caution] Be careful not to spill the suspension.</td>
</tr>
<tr>
<td>3</td>
<td>Administer suspension to the patient.</td>
</tr>
<tr>
<td>#</td>
<td>Procedure</td>
</tr>
<tr>
<td>----</td>
<td>-----------</td>
</tr>
</tbody>
</table>
| 4  | ![Image of a cup](image1)  
**Pour another 4 mL of water into the cup and gently swirl in order to capture any remaining drug.**  
**[Caution] Be careful not to spill the suspension.** |
| 5  | ![Image of a person drinking](image2)  
**Administer suspension to the patient.** |
# APPENDIX ID: Delamanid Oral Suspension Preparation (Syringe) for 10 mg Dose

<table>
<thead>
<tr>
<th>#</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Disassemble the oral syringe into three parts: cap, barrel and plunger.</td>
</tr>
<tr>
<td>2</td>
<td>Put two tablets (5 mg x 2) of delamanid pediatric formulation into the barrel of the syringe.</td>
</tr>
<tr>
<td>3</td>
<td>Place the plunger in the barrel of the syringe, and then adjust the plunger seal to align with the 1 mL mark as shown in the picture above.</td>
</tr>
<tr>
<td>4</td>
<td>Place the tip of the syringe in a container of water and pull the plunger until the plunger seal aligns with the 5 mL mark as shown in order to collect 4 mL of water.</td>
</tr>
<tr>
<td>#</td>
<td>Procedure</td>
</tr>
<tr>
<td>----</td>
<td>-----------</td>
</tr>
<tr>
<td>5</td>
<td>Cap the syringe and shake for 30 seconds to suspend the tablets.</td>
</tr>
<tr>
<td>6</td>
<td>Shake the syringe a few more times to ensure that the material in the tablets is suspended evenly in the syringe.</td>
</tr>
<tr>
<td>7</td>
<td>Remove the cap, and then administer the entire suspension into the mouth of the patient. [Caution] In order to avoid ejecting the suspension inadvertently, pull back a little on the plunger before removing the cap.</td>
</tr>
<tr>
<td>8</td>
<td>Draw up another 4 mL of water in order to capture any residual drug in the syringe and administer to the patient.</td>
</tr>
</tbody>
</table>
## APPENDIX IE: Delamanid Oral Suspension Preparation (Medication Cup) for 5 mg Dose

<table>
<thead>
<tr>
<th>#</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>Procedure</strong>&lt;br&gt;Put 1 tablet (5 mg x 1) of delamanid pediatric formulation into the medication cup.&lt;br&gt;Pour 4 mL of water into the cup, and let stand for 30 seconds.</td>
</tr>
<tr>
<td>2</td>
<td><strong>Procedure</strong>&lt;br&gt;Gently swirl to make a uniform suspension.&lt;br&gt;[Caution] Be careful not to spill the suspension.</td>
</tr>
<tr>
<td>3</td>
<td><strong>Procedure</strong>&lt;br&gt;Administer suspension to the patient.</td>
</tr>
<tr>
<td>4</td>
<td><strong>Procedure</strong>&lt;br&gt;Pour another 4 mL of water into the cup and gently swirl in order to capture any remaining drug.&lt;br&gt;[Caution] Be careful not to spill the suspension.</td>
</tr>
<tr>
<td>#</td>
<td>Procedure</td>
</tr>
<tr>
<td>---</td>
<td>-----------</td>
</tr>
<tr>
<td>5</td>
<td>Administer suspension to the patient.</td>
</tr>
</tbody>
</table>
## APPENDIX IF: Delamanid Oral Suspension Preparation (Syringe) for 5 mg Dose

<table>
<thead>
<tr>
<th>#</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Disassemble the oral syringe into three parts: cap, barrel and plunger.</td>
</tr>
<tr>
<td>2</td>
<td>Put one tablet (5 mg x 1) of delamanid pediatric formulation into the barrel of the syringe.</td>
</tr>
<tr>
<td>3</td>
<td>Place the plunger in the barrel of the syringe, and then adjust the plunger seal to align with the 1 mL mark as shown in the picture above.</td>
</tr>
<tr>
<td>4</td>
<td>Place the tip of the syringe in a container of water and pull the plunger until the plunger seal aligns with the 5 mL mark as shown in order to collect 4 mL of water.</td>
</tr>
<tr>
<td>#</td>
<td>Procedure</td>
</tr>
<tr>
<td>----</td>
<td>-----------</td>
</tr>
<tr>
<td>5</td>
<td>Cap the syringe and shake for 30 seconds to suspend the tablets.</td>
</tr>
<tr>
<td>6</td>
<td>Shake the syringe a few more times to ensure that the material in the tablets is suspended evenly in the syringe.</td>
</tr>
</tbody>
</table>
| 7  | Remove the cap, and then administer the entire suspension into the mouth of the patient.  
[Caution] In order to avoid ejecting the suspension inadvertently, pull back a little on the plunger before removing the cap. |
| 8  | Draw up another 4 mL of water in order to capture any residual drug in the syringe and administer to the patient. |
APPENDIX II: Suggestions for the Caregiver and DOTS Supporter for Using DLM in Children

1. General Instructions and Safety Information
   • The total number of weeks your child will be on DLM is 24 weeks.
   • It is important that the DLM, and all medications, be stored away from children so that they do not accidentally take medication that is not meant for them or so that they do not take an overdose.
   • If parents or caregivers have any questions or instructions about these instructions, please talk to the study staff, who can help.

2. Should my child eat before taking the DLM medication?
   • Your child should take the DLM study medication with a meal, ideally one in which there is a good amount of fat-containing foods, such as eggs, full cream milk, butter, etc.
   • Your child should not take DLM on an empty stomach.
   • The recommended sequence would be food first, DLM within 30 minutes of starting the meal, then wait at least one hour after the DLM before taking other medicines.

3. DLM can be taken with any of the following beverages (drinks):
   • Water that is clean and safe to drink.
   • Note: Warm or fizzy drinks (for example: soda, hot tea etc.) MUST NOT be used to take the DLM study drug.

4. Oral syringe cleaning instructions:
   1. After each use, wash the syringe with clean, warm or hot water, to remove any leftover powder or particles.
   2. Draw up at least 20mL water, preferably warm, clean water, to rinse.
   3. Allow to dry with the plunger out and take the cap off.

5. What should I do if my child misses their usual dose of DLM study medication?
   If your child misses a dose of DLM study medication, your child should make up the missed dose (i.e. take another dose when it is remembered) if it is within six to eight hours of the time the dose is usually taken. If it is more than eight hours after the time the dose is usually taken, the dose should be skipped, and the next dose should be taken as scheduled. The study team should be made aware of any missed doses.

6. What should I do if my child vomits after taking his/her DLM medication?
   • If your child vomits within 15 minutes of taking the DLM, you should try to give your child another full dose.
   • If your child vomits more than 15 minutes after taking the DLM, you should NOT try to give your child another dose. Instead, be sure to write it down on the TB treatment card, let the study team know and wait to give your child his/her next dose as usual.

7. Do the DLM tablets need to be refrigerated?
   No. The DLM tablets should be kept at room temperature which is 15°C to 30°C (59°F to 86°F). The tablets should not be kept in the refrigerator. The tablets must also be kept only in the blister pack that the pharmacist gave them to you. The DLM study medicine must be kept away from places that might get too hot (like a cabinet next to an oven, in direct sunlight, in a hot vehicle etc.).
APPENDIX III: Digital Photographs of Chest X-Rays

Instructions for preparation of digital photographs of Chest X-rays (CXRs) is provided below. Given variation in technical facilities across study sites, this procedure will be adapted to describe the process followed by each site to record CXR images.

**Equipment**

1. Light box – for viewing X-rays
2. Digital camera or tablet Connector
3. Battery charger for camera/tablet
4. Small tripod
5. Data/memory card

**Procedure**

1. Setting up the radiograph
   a. Correct patient? Left and R sides labelled correctly? Date?
   b. The CXR should be placed on the light box and the light switched on.
   c. Outside light entering the room should be minimized by drawing the curtain or switching off the overhead lighting. (Note the room does not need to be completely dark)
   d. Complete a card with the:
      - Patient’s study number and PID
      - Date that the CXR was performed
      - Whether film is AP/PA/lateral
   e. Verify that the details match the CXR
   f. Place this card below the CXR so as not to obscure any part of the CXR.
   g. Cover the patient’s identifying details where they are printed on the CXR using a card or paper.
   h. Ensure that the labelling or cover do not obstruct the radiograph at all.

2. Setting up the camera or tablet
   a. Switch the camera/tablet on and ensure it contains a memory card.
   b. Check the settings
   c. Turn off the flash function.
   d. Attach the camera firmly to the tripod

3. Positioning the camera
   a. Place the tripod and camera approximately 1 meter from the radiograph
   b. The camera should be lined up with the center of the CXR from left to right and from top to bottom. You might need to place the tripod on a book or box for this.
   c. Use the zoom function so the image is central and occupies the most space possible in the viewfinder without any of the CXR or label being ‘cut-off’.
   d. Make sure you can see the patient study ID label and the entire radiograph.
   e. Make sure all identifying labels are covered (e.g. patient name)
Figure V-1
Camera Set up

4. Capture the image by pushing the shutter down fully.
5. Check the quality of the image on the viewfinder and or after uploading it onto a computer. Check that
   a. The image is centered
   b. The image is in focus
   c. That you can see the full radiograph
   d. If you are not happy with the quality of the image, re-take the picture.
6. Uploading the image into exchange utility can be done with the camera’s own memory and cable or card reader, or with any other digital medium such as a memory stick or a CD. Keep a copy in the designated file on the computer too. Check the clarity of the captured images.
**GOOD QUALITY X-RAY**

![Good Quality X-ray Example]

**POOR QUALITY X-RAY**

<table>
<thead>
<tr>
<th>Film on an angle</th>
<th>Patient details showing</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Poor Quality X-ray Example" /></td>
<td><img src="image2" alt="Poor Quality X-ray Example" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Too small</th>
<th>Over-exposed film</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image3" alt="Too Small Example" /></td>
<td><img src="image4" alt="Over-exposed Film Example" /></td>
</tr>
</tbody>
</table>
Recommendations for taking digital photos with a camera:

1. Camera recommendations:
   a) Should have CPU of at least 3 million megapixels with a 24 colour depth
   b) Should have a remote activation of the shutter
   c) Should be able to save the photos in the jpeg and tiff formats
   d) Should have a tripod. Camera at the level of the lightbox.
   e) Autofocus should be used throughout.
   f) The exposure compensation should be set to 1.3 mv.
   g) White balance and ISO set to auto.
   h) Picture quality set to fine.
   i) Camera should be at approximately 1 meter from the light box
   j) Camera zoom used to ensure the CXR fills the viewfinder
   k) Camera flash should be turned off when taking the photo

2. Room and light box specifications
   a) The room should be able to turn the lights down
   b) The CXR image box should be a standard box with 2 light panels of approximately 15-20 watt fluorescent lights
   c) Only one light panel should be turned on
   d) The image can be improved by having a cardboard with a hole the size of the CXR
   e) Ensure the patient identification/case number is visible

3. Compression protocol
   a) The image should be saved as a jpeg file. The reason is that the image is equivalent to the analog image and is of a convenient size (800k) while tiff images are approximately 9 meg making then difficult to transmit.

4. Reading the digital images.
   a) The quality of the computer screen does not affect the result.

5. Using a smart phone to take images:
   a) Should only be used if other equipment not available and only for acute clinical problems.
   b) Use the original CXR
   c) Position the smart phone perpendicular to the CXR and at arm’s length.
   d) Use the zoom function to ensure the image is as large as possible.
   e) Compare the original CXR to the smart phone image before sending it and ensure that it is the correct image.
### APPENDIX IV: Assessment of Karnofsky/Lansky Performance Status

#### Karnofsky Performance Status scale

<table>
<thead>
<tr>
<th>Value</th>
<th>Level of functional capacity</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Normal, no complaints, no evidence of disease</td>
<td>Able to carry on normal activity and to work; no special care needed</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity, minor signs or symptoms of disease</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort, some signs or symptoms of disease</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>Cares for self, unable to carry on normal activity or to do active work</td>
<td>Unable to work; able to live at home and care for most personal needs; various degrees of assistance needed</td>
</tr>
<tr>
<td>60</td>
<td>Requires occasional assistance but is able to care for most needs</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent medical care</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>Disabled, requires special care and assistance</td>
<td>Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled, hospitalization is indicated although death is not imminent</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Hospitalization is necessary, very sick, active supportive treatment necessary</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Moribund, fatal processes progressing rapidly</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Dead</td>
<td></td>
</tr>
</tbody>
</table>
Read the following statement to the child’s parent/caregiver:

“On this form are a series of descriptions. Each description has a number beside it. Think about your child's play and activity over the past week. Think about both good days and bad days. Average out this period. Now read the descriptions and pick the one that best describes your child's play during the past week.”

Circle the one option that best describes the child’s play during the last week.

<table>
<thead>
<tr>
<th>Lansky Play Performance Scale (Lansky et al., 1987)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Score</strong></td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>100</td>
</tr>
<tr>
<td>90</td>
</tr>
<tr>
<td>80</td>
</tr>
<tr>
<td>70</td>
</tr>
<tr>
<td>60</td>
</tr>
<tr>
<td>50</td>
</tr>
<tr>
<td>40</td>
</tr>
<tr>
<td>30</td>
</tr>
<tr>
<td>20</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

## APPENDIX V: Sample Informed Consent Coversheet for IMPAACT 2005

<table>
<thead>
<tr>
<th>Participant’s identifier</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Consenter’s identifier</td>
<td></td>
</tr>
<tr>
<td>Consenter’s relationship to participant</td>
<td></td>
</tr>
</tbody>
</table>
| Can the consenter read? | ☐ Yes  
☐ No ⇒ A literate impartial witness should be present during the entire informed consent process. Record name and relationship/role of witness below. |
| Language of informed consent process | ☐ [Language A]  
☐ [Language B] |
| Version number and version date of informed consent form used during informed consent process |  |
| Was the informed consent 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 consenter? | ☐ Yes  
☐ No ⇒ Explain below. |
| Were all of the consenter’s questions answered? | ☐ Yes  
☐ No ⇒ Explain below. |
| Did the consenter comprehend all information required to make an informed decision? | ☐ Yes  
☐ No ⇒ Explain below. |
| Was the consenter 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 consenter choose to provide informed consent for study participation? | ☐ Yes  
☐ No ⇒ STOP. |
| Date and time at which the consenter signed or marked the informed consent form | ☐ NA (consent declined, form not signed or marked)  
Date:  
Time: |
| Did the consenter accept a copy of the informed consent form? | ☐ NA (consenter chose not to provide informed consent)  
☐ Yes  
☐ No ⇒ Offer alternate form of study contact information. |
| Notes/Comments |  |
| Signature of study staff member completing informed consent process (and this coversheet) |  |