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

Version 1.1
29 May 2018
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IMPAACT 2005 Manual of Procedures Summary of Changes

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Version 1.0</td>
<td>29 December 2017</td>
<td>• Version 1.0 released</td>
</tr>
<tr>
<td>Version 1.1</td>
<td>29 May 2018</td>
<td>• Section 5.2.2.2 is updated to clarify that at Screening, TST or IGRA results should be documented, <em>only</em> if done as part of standard of care.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Section 6.2.4 is updated to reflect current protocol team membership.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Section 6.3.1 is updated to include more detail regarding the specimen request list.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Section 9.2.1.1 is updated to further describe procedures for ECG assessments; for ease of reference, related information that had previously been in Section 5.2.2.2 has been moved to this section.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Section 9.4.2 is updated to include TB recurrence as a possible TB treatment outcome and footnotes have been added to Tables 4 and 5 to expand upon the definition of participant “loss to follow-up.”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Appendix III is updated to remove instruction to include participant’s initials on radiograph card.</td>
</tr>
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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.

Sample Size: Up to 48 participants total (12 per age cohort) to achieve 36 evaluable (9-12 per age cohort).

Population: HIV-infected and HIV-uninfected infants, children, and adolescents less than 18 years of age with confirmed or probable MDR-TB enrolled in four age cohorts as shown in the table below. This study will take place in Botswana, India, South Africa and Tanzania.

Stratification: All subjects enrolled into the study will be stratified by age at screening into one of four cohorts. Within each age cohort at least six participants will be HIV-infected and at least three participants will be HIV-uninfected.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Age in years</th>
<th>DLM Formulation</th>
<th>DLM Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1</td>
<td>up to 12 participants to achieve 9-12 evaluable</td>
<td>12 to &lt;18</td>
<td>Adult</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>up to 12 participants to achieve 9-12 evaluable</td>
<td>6 to &lt;12</td>
<td>Adult</td>
</tr>
<tr>
<td>Cohort 3</td>
<td>up to 12 participants to achieve 9-12 evaluable</td>
<td>3 to &lt;6</td>
<td>Pediatric</td>
</tr>
<tr>
<td>Cohort 4</td>
<td>up to 12 participants to achieve 9-12 evaluable</td>
<td>0 to &lt;3</td>
<td>Pediatric</td>
</tr>
</tbody>
</table>

Study Treatment: DLM given 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.

Study Duration: Approximately 168 weeks (40 months) total. Accrual is expected to require approximately 72 weeks from the date of first enrollment and each participant will be followed for approximately 96 weeks.
2.0 Preparing for the Study

This study will be conducted at the following IMPAACT clinical research sites (CRSs), which were selected by the Protocol Team based on review and approval of site selection materials. A copy of the approved site selection materials should be maintained in each site’s study-specific essential document files.

<table>
<thead>
<tr>
<th>CRS Number</th>
<th>Site Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRS 5118</td>
<td>Kilimanjaro Christian Medical Centre (KCMC), Moshi, Tanzania</td>
</tr>
<tr>
<td>CRS 12701</td>
<td>Gaborone Prevention/Treatment Trials CRS, Gabarone, Botswana</td>
</tr>
<tr>
<td>CRS 12702</td>
<td>Molepolole Prevention/Treatment Trials CRS Molepolole, Botswana</td>
</tr>
<tr>
<td>CRS 31441</td>
<td>BJ Medical College, Pune, Maharashtra, India</td>
</tr>
<tr>
<td>CRS 31790</td>
<td>Desmond Tutu TB Centre, Cape Town, South Africa</td>
</tr>
<tr>
<td>CRS 31929</td>
<td>Sizwe Tropical Disease Hospital, Johannesburg, South Africa</td>
</tr>
<tr>
<td>CRS 31976</td>
<td>PHRU Matlosana, Klerksdorp, South Africa</td>
</tr>
</tbody>
</table>

2.1 Investigator Responsibilities

At each site, this study must be conducted in accordance with the United States (U.S.) Code of Federal Regulations (CFR) and the International Conference on Harmonization (ICH) Consolidated Guidance for Good Clinical Practice (GCP) and national guidelines, as applicable. The Division of AIDS (DAIDS) policies on Clinical Research Policies and Standard Procedures Documents website contains information that is useful for interpreting and operationalizing the regulations and guidelines in accordance with DAIDS expectations:

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

The Division of AIDS (DAIDS) Clinical Research Laboratory and Specimens Management provides links to policies and standard procedures related to requirements for DAIDS-supported laboratories and specimens derived from DAIDS supported- and/or -sponsored clinical trials:

https://www.niaid.nih.gov/research/daids-clinical-research-laboratory-specimens-management

This study also must be conducted in accordance with all site-specific regulations, policies, and guidelines applicable to human subjects research in general and/or the conduct of study procedures in particular. Copies of all the above-listed regulations, policies, and guidelines should be maintained in on-site essential document files.
The Investigator of Record (IoR) at each site must sign an FDA form 1572 to formally indicate his or her agreement to conduct the study in accordance with the protocol and all applicable regulations, policies, and guidelines. The obligations and responsibilities assumed by the IoR when signing this form are listed on the form, which is available on the DAIDS Regulatory Support Center (RSC) website:

http://rsc.tech-res.com/protocolregistration/

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, site staff 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. Upon confirming receipt of all required documentation, the PRO will issue a registration notification that indicates successful completion of the process. Site staff are 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 as described in MOP Section 2.2 above. Each site must also 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).

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

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 IMPAACT Operations Center of any such inconsistencies.

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

- **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. Additional detail is listed in Figure 3-1 and Figure 3-2.

- **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. Error! Reference source not found.

- **Other types of questions** should be managed as listed in Figure 3-1.
### 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: <a href="mailto:IMPAACT.prot2005@fstrf.org">IMPAACT.prot2005@fstrf.org</a></td>
<td>User Support <a href="mailto:user.support@fstrf.org">user.support@fstrf.org</a> 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>IMPAACT 2005 Protocol Team <a href="mailto:IMPAACT.TEAM2005@fstrf.org">IMPAACT.TEAM2005@fstrf.org</a> 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>IMPAACT 2005 CMC Team <a href="mailto:IMPAACT.2005CMC@fstrf.org">IMPAACT.2005CMC@fstrf.org</a> For cardiology management issues, including questions regarding eligibility: IMPAACT.2005 Core Cardio Team <a href="mailto:IMPAACT.2005corecardio@fstrf.org">IMPAACT.2005corecardio@fstrf.org</a></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>IMPAACT 2005 CMC Team <a href="mailto:IMPAACT.2005CMC@fstrf.org">IMPAACT.2005CMC@fstrf.org</a></td>
</tr>
<tr>
<td>Co-enrollment</td>
<td>IMPAACT 2005 CMC Team <a href="mailto:IMPAACT.2005CMC@fstrf.org">IMPAACT.2005CMC@fstrf.org</a></td>
</tr>
<tr>
<td>Data management computer and screen problems</td>
<td>User Support (FSTRF) <a href="mailto:user.support@fstrf.org">user.support@fstrf.org</a> or by phone: +716-834-0900 x7302</td>
</tr>
<tr>
<td>Subject Enrollment System</td>
<td>DMC Randomization Support Office <a href="mailto:rando.support@fstrf.org">rando.support@fstrf.org</a> or by phone: +716-834-0900 x7301</td>
</tr>
<tr>
<td>Study drug (other than study drug orders)</td>
<td>Protocol Pharmacists Justine Beck, PharmD, BCPS, RPh <a href="mailto:Justine.beck@nih.gov">Justine.beck@nih.gov</a> Oladapo Alli, PharmD <a href="mailto:oladapo.alli@nih.gov">oladapo.alli@nih.gov</a> or by phone: 301-761-5288</td>
</tr>
<tr>
<td>Study drug orders</td>
<td><a href="mailto:BIO.CRPMC.Ph@Thermofisher.com">BIO.CRPMC.Ph@Thermofisher.com</a> (Phone contact: +301-294-0741)</td>
</tr>
<tr>
<td>Expedited Adverse Event (EAE) Reporting</td>
<td>DAIDS RSC Safety Office <a href="mailto:DAIDSRSCSafetyOffice@tech-res.com">DAIDSRSCSafetyOffice@tech-res.com</a> or by phone: 800-537-9979 or +301-897-1709 or by fax: 800-275-7619 or +301-8977-1710</td>
</tr>
<tr>
<td>DAIDS Adverse Experience Reporting System (DAERS)</td>
<td>NIAID Clinical Research Management System <a href="mailto:CRMSSupport@niaid.nih.gov">CRMSSupport@niaid.nih.gov</a> (questions also may be submitted from within the DAERS application)</td>
</tr>
</tbody>
</table>
The IMPAACT 2005 CMC is composed of study team members who have been designated to receive and reply to clinical management questions and notifications. When submitting clinical and toxicity management questions to the IMPAACT 2005 CMC, please address each of the points listed in Figure 3-1, to help ensure that CMC members have adequate information to respond in a timely manner. The responding CMC member will reply to your question or notification by return email. All persons copied on the original question or notification will be copied on the reply.

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.

Please print and file a copy of the email exchange in the participant’s study chart.

**Figure 3-1**
IMPAACT 2005 CMC Communications

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.

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

The IMPAACT 2005 protocol also details the circumstances in which IoRs must consult with the CMC. All protocol requirements must be followed. For ease of reference, a summary of issues requiring consultation with the IMPAACT 2005 CMC, and those for which consultation is available but not required, is provided below in Figure 3-2. IoRs are also encouraged to contact the CMC with any other issues, questions, or concerns related to study drug regimens for study participants.
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

### Hepatotoxicity Management (bilirubin, AST, ALT)

- Any events that meet Hy’s law
- Confirmed ≥ Grade 3 event regardless of relatedness

### 3.2 Data Management Center IMPAACT Portal

The documents and tools that can be found in the Portal are Drug Code Lookup, Forms Manual, calculator utilities, quality assurance (QA) tools, and Participant Calendar ages. The Subject Enrollment System can also be accessed on the Portal.

Site staff members apply for access to the Portal by submitting a registration form located on the Frontier Science and Technology Research Foundation (FSTRF) 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

Confirmation of registration will be sent via email from User Support. The portal can be accessed from the FSTRF home page at:

https://www.frontierscience.org/

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 in the FSTRF 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 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.”

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

### 3.2.2 Obtaining CRFs and other related materials

CRFs 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 2005 eCRF Completion Guide and 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:


Resources available on this site include:

- Current version of the protocol
- Study contacts
- Current study implementation materials, including this Manual of Procedures (MOP) and the Laboratory Processing Chart (LPC)
- Study training materials
- Application and examples for import permit for biological substances for UCT PK samples

### 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:**

**Essential Documents Recordkeeping Requirements:**

**4.0 Informed Consent and Assent**

Obtaining informed consent/assent is a process by which an individual voluntarily expresses his/her willingness to participate in research, and/or his/her child’s participation, after having been informed of all aspects of the research that are relevant to the decision. Both the informed consent and assent process are rooted in the ethical principle of respect for persons and involve information exchange, assurance of comprehension, determination of voluntariness, and appropriate documentation. Each of these aspects of the process is described in greater detail below. Please also refer to Section 4.8 of the International Conference on Harmonization (ICH) *Consolidated Guidance for Good Clinical Practice* (GCP) and the informed consent section of the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* for further information.

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

**4.1 Considerations for Consent Process**

Responsibility for informed consent does not end with preparation of an adequate Informed Consent Form (ICF). It also is the responsibility of the IoR and designated study staff to:

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

Further guidance related to each of these requirements is provided below. Each site must have on file a 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.

**4.1.1 Deliver All Required Information in a Manner that is Understandable to the Consenter**

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

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

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

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

During informed consent discussions, take care to not overstate the possible benefits of the study, nor to understate the risks. Describe the alternatives to study participation and emphasize that the availability of medical care and other services routinely obtained from the study site institution will not be affected by the consenter’s decision whether or not to take part in the study. Encourage the consenter to take as much time as he/she needs — and to talk about study participation with others if he/she chooses — before deciding.

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

4.1.3 Document the Process

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

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

If the consenter is not literate, the witness who was present during the informed consent process must sign and date the ICF to attest that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the consenter, and that informed consent was freely given by the consenter.

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

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

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

4.2 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 Recruitment

Prior to activation, each site will be required to prepare an SOP on IMPAACT 2005 participant recruitment. 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

5.2 Screening and Enrollment

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

Logs should include the following information:

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

For additional information, refer to the NIAID/DAIDS website:


5.2.1 Obtaining a Screening Number

For all potential participants who provide written informed consent, a Screening Checklist must be entered through the DMC Subject Enrollment System on the FSTRF Portal:

- Log into the FSTRF Portal:
  https://www.frontierscience.org/apps/cfmx/apps/common/Portal/index.cfm
- Click on the “IMPAACT” tab.
- Under the “Systems” header, click on “Subject Enrollment.”
• Choose your institution from the Institution dropdown menu.
• Choose the “PS2001 Screening Checklist” from the Study dropdown menu.

For potential participants who provide informed consent but are ineligible, or who do not enroll in the study for any reason, a Screening Failure and Non-Enrollment Results Form must be completed and keyed into Medidata Rave.

5.2.2 Overview of Screening Visit

5.2.2.1 Information and Consent

• During this initial screening visit, detailed study information will be presented. Informed consent for screening and study participation should also be obtained. Screening evaluations must occur within 30 days prior to entry and multiple visits may be conducted to complete all required screening procedures, if necessary.
• The child’s parent/guardian (or the participant, if of age of assent) will be encouraged to ask questions.
• If the parent/guardian or participant needs additional time to consider the screening process, another visit will be scheduled and no procedures will be done.
• Ensure that the parent/guardian and/or the participant has authorized or denied authorization for use of samples for future studies.
• Offer the parent/guardian and/or participant a copy of the signed informed consent that they can take home with them.
• Ensure parent/guardian and/or participant has signed any required medical release to obtain records of any AEs that might occur which necessitate medical record clarification or confirmation. Only those portions of the medical record that are pertinent to the study will be maintained in the study chart.

5.2.2.2 Screening Procedures

• Conduct visit as per protocol, Section 6.1. Procedures include administrative, clinical (to include recording of M. tuberculosis infection status through TST or IGRA depending on what is available at the site, if done as part of standard of care), laboratory, chest x-ray and ECG.

5.2.3 Screening Failures

If a participant consented for the study fails to meet all the inclusion/exclusion criteria to participate in the study, or fails screening evaluations, the participant will be considered a screen failure. The reason for screen failure should be documented appropriately in the source documentation, and must be entered into the appropriate eCRF to record the screening outcome. In some cases, if the reason for screen failure changes, the patient may be rescreened in the future, using the original PID number. The child should be referred to routine care providers as required.
5.3 Accrual and Retention

The study involves four cohorts of HIV-infected and HIV-uninfected infants, children, and adolescents with MDR-TB disease stratified by age and weight:

Age at enrollment:
- Cohort 1: 12 to < 18 years of age at enrollment
- Cohort 2: 6 to < 12 years of age at enrollment
- Cohort 3: 3 to < 6 years of age at enrollment
- Cohort 4: 0 to < 3 years of age at enrollment

Weight at enrollment:
- Cohort 1 and 2: At least 15 kg
- Cohort 3 and 4: At least 5.5 kg

The study aims to enroll up to 48 participants to achieve a minimum of 36 evaluable participants: 9-12 participants in each age cohort, who will have appropriate data for the PK modeling upon which dosing depends. 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.

Accrual is expected to require approximately 72 weeks and will follow an algorithm in which Cohorts 1 and 2 will open immediately upon study start. Cohort 3 will open to enrollment following review of safety data from children in that age group enrolled in Otsuka trials 232 and 233. Safety data reviewed must include data from at least six children who have received 24 weeks of DLM plus all other safety data available from 232/233. Cohort 4 will open to enrollment following review of safety data among participants in Group 4 in 232/233 (similar to the process for Cohort 3) as well as review of PK data (to confirm the appropriateness of dose selection).

Sites were required to provide projected enrollment into each of the cohorts as an element of site selection. A study accrual plan, which lists monthly accrual projections for each (activated) site based on those initial projections, will be updated and distributed to the team at least monthly. Accrual to this study will be monitored by the protocol team and IMPAACT leadership in accordance with standard IMPAACT operating procedures (SOP) and the Study Monitoring Plan.

As part of the site activation process, sites will be required to prepare an SOP on participant retention. Participant retention will also be closely monitored by the study team. If accrual or retention rates fall below target, team members will work with study sites to identify operational issues or problems and to take appropriate action to address below-target rates.

5.4 Participant Withdrawal

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

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

6.1 Introduction

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 the Schedule of Evaluations (Appendix I) of the protocol and the Laboratory Processing Chart (LPC), located here:


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

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

6.2 General Overview Guidelines

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

It is essential that all staff collecting IMPAACT 2005 specimens have been trained in proper collection techniques, container types, and any special requirements. 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.

6.2.1 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 (U.S.-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 U.S. Centers for Disease Control and Prevention:

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:

6.2.2 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. Subject names or initials may NOT be used on research samples or the accompanying tracking forms.

6.2.3 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.

6.2.4 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
6.2.4.1 24-Hour LDMS User Support

Technical support is also available from LDMS User Support. Usual 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

6.2.4.2 Off-Hours Contact Information

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

6.3 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.

6.3.1 DLM PK, Both Sparse and Semi-Intensive

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

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

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 plasma within one hour of collection. Protect the plasma from light at all times. Store two aliquots of equal volume of plasma in amber cryovials at -70°C or lower. 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.

Prior to shipment the Laboratory Data Manager will send the site/lab a specimen request list; no specimens can be shipped without this request. Further details of the specimen management are found in the LPC.

6.3.2 Collection of Specimen For Biomarkers

- Biomarkers (serum and urine) are collected on all cohorts at: Entry, Week 24, and Week 72.
- As these specimens must be processed rapidly, clinic staff should be familiar with the specimen management procedures in the LPC.
- Network SOPs for the collection of specimens for TB biomarkers are in development; until these are developed, the following guidance should be observed.
- 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.
o 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.

o 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.

o Cotton wool balls, gauze and sanitary towels should not be used.

o The urine SOP used at the Desmond Tutu TB Centre is available here as an example: https://www.dropbox.com/sh/tbdrcl7jw9boofc/AADZYiIiVX4uBtTM4BWOSr6pVa?dl=0

6.3.3 Collection of Specimen for TB Testing

• For this trial, 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 child 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.

• There is an ACTG-IMPAACT SOP for the Collection Storage and Transport of Expectorated Sputum (refer to link below). Note, this is typically more useful in older children (>6 years of age) who are able to expectorate sputum, with or without assistance.


• There is also a video that can be viewed at this link:
  Respiratory Specimen Collection for TB Investigation *

  *Enter password "IMPAACT2017" in Vimeo to watch.

• Network SOPs for the collection of respiratory specimens other than expectorated sputum for TB testing in children are in development. Until these SOPs are completed, the following key elements should be observed. References are also provided below the tables.

Table 2. Key Elements for Collection of Respiratory Specimens

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Key Element/Critical Step</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expectorated Sputum collection</td>
<td>Participant is to rinse mouth with boiled/sterile/bottled or distilled water prior to sputum collection</td>
</tr>
<tr>
<td>Expectorated /Induced Sputum collection</td>
<td>Collect at least 3 to 5 mL of sputum. If larger volumes cannot be obtained, a minimum of 1 mL is acceptable.</td>
</tr>
<tr>
<td>Gastric aspirate collection</td>
<td>Collect at least 5 to 10 mL after fasting.</td>
</tr>
<tr>
<td>Gastric aspirate collection</td>
<td>Collect the gastric content by aspiration first, after fasting, as lavage introduces dilution. If adequate volumes are not obtained, lavage can be performed.</td>
</tr>
<tr>
<td>Gastric aspirate collection</td>
<td>Neutralize the gastric aspirate as soon as possible after collection. Unless the laboratory is available to pH neutralize the sample within 4h of specimen collection or process it, it should be neutralized at the clinic. See LPC for details.</td>
</tr>
</tbody>
</table>
### 6.4 Specimen Processing & Shipping Procedures


### 7.0 Pharmacy Considerations

#### 7.1 Dosing

Per protocol, Section 5.1, “The doses and weight banding in IMPAACT 2005 Cohorts 3 and 4 will be reassessed prior to opening these cohorts, as per Section 3.1."

#### 7.2 Study Treatment Administration

For participants who are able to do so, delamanid (DLM) should be swallowed whole with water and taken with high-fat food. When taken once daily, 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).


7.3 Ensuring 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 will be required to prepare an SOP on ensuring adherence and DOT.

7.4 Instructions for dispersing and administration of DLM

In the younger age dose cohorts, DLM will be dispersed/dissolved as per protocol Section 5.2.2. Instructions for study drug preparation for the pediatric formulation, are provided in Appendix I.

8.0 Expedited Adverse Event Reporting to DAIDS

This section presents information related to expedited adverse event reporting in IMPAACT 2005. Also refer to Section 7 of the protocol and the following resources:

- DAIDS Table for Grading Adult and Pediatric Adverse Events (DAIDS Toxicity Table), Corrected Version 2.1, dated July 2017
- DAIDS Adverse Experience Reporting System (DAERS) Reference Guide for Site Reporters and Study Physicians
- Investigator’s Brochure for Delamanid

All of the above are available on the DAIDS RSC website: http://rsc.tech-res.com/clinical-research-sites/safety-reporting

8.1 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.

8.1.1 Adverse Event (AE)

*Any untoward medical occurrence in a clinical research participant administered a study agent and which does not necessarily have a causal relationship with the study agent. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a study agent, whether or not considered related to the study agent (ICH E2A).*

The above definition is applied 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 charts, including the documented assessment of the Investigator of Record (IoR) or designee of the severity of the AE (see MOP Section 8.2) and its relationship to each study product the participant has taken (see MOP Section 8.4).

### 8.1.2 Serious (SAE)

*An AE that:*

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

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

### 8.1.3 SUSAR (Suspected 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
- **Unexpected** \(\Rightarrow\) the nature or severity of an AE is not consistent with an investigational agent’s current package insert

As indicated in the definitions above, and as shown in Figure 8-1, SAEs are a subset of all AEs, and SUSARs are a subset of all SAEs.
8.1.4 Expedited AE (EAE)

An AE that meets protocol criteria for reporting in an expedited manner to the DAIDS Regulatory Support Center Safety Office. See MOP Section 8.3

8.2 AE Grading Severity of Events

The term severity refers to the intensity of an AE. All AEs occurring among infants, children, and adolescents enrolled in IMPAACT 2005 must be assessed for severity on the following scale according to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Corrected Version 2.1, dated July 2017:

- Grade 1 = Mild
- Grade 2 = Moderate
- Grade 3 = Severe
- Grade 4 = Potentially Life-Threatening
- Grade 5 = Death

8.3 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 expedited AE 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). 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).
8.4 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 to the study product according to the categories shown in **Figure 8-2**. The categories are also used when recording AEs on eCRFs.

<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*, protocol Section 7.3.4, the IoR or designee must report the relationship of EAEs to the investigational dose of DLM according to the categories shown in **Figure 8-3**, which shows how the five relationship categories used for toxicity management should be mapped to the two relationship categories used 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>

8.5 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*:

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.

If 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.

8.6 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.

9.0 Clinical Considerations

9.1 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:

9.2 Cardiac Safety

Given that QT prolongation 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 the conduct of IMPAACT 2005. IQVIA (formerly Quintiles) has been selected as the vendor to provide study-specific ECG machines to all participating sites.

Toxicity grading of ECG changes and symptoms related to cardiac conduction abnormalities may be found in protocol Appendix VII and toxicity management in protocol Appendix IX.

9.2.1 ECG Monitoring and Clinical Management

Due to the inherent challenges in obtaining an accurate ECG reading in a pediatric population, ECGs should be conducted in triplicate by the same member of the study team, to the extent possible, at each time point specified in the protocol schedule of evaluations. 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 reasonable approach would be to allow one minute in between each of the ECGs (i.e. the 3rd ECG should be completed within approximately five mins of the first). Details of obtaining these ECGs are provided in IQVIA Investigator’s Manual and Visit Code Poster.

9.2.1.1 Assessment of ECGs During the Study

Per the protocol Schedule of Evaluations (SoE), all potentially eligible participants for IMPAACT 2005 should have an ECG performed at the Screening visit. ECGs should be conducted in triplicate and should be uploaded to the IQVIA portal, as described in the IQVIA Investigator’s Manual. 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 protocol). The IQVIA interpretation will be available within 72 hours, posted to the study-specific IQVIA Web Portal, and sent to the site.

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 (IMPAACCT2005corecardio@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.

9.2.2 Obtaining an ECG Machine and ECG-Related Materials at Site

IQVIA will provide a pre-tested ECG machine and accessories to participating sites throughout the duration of the study. Details of how to obtain the ECG machine and materials will be provided in the IQVIA Investigator’s Manual.

http://www.hospicepatients.org/karnofsky.html
9.2.3 ECG Site Staff Training

ECG training materials, including a CD-ROM and the IQVIA Investigator’s Manual, will be sent to sites together with the IQVIA-provided ECG machine and accessories. It is the responsibility of the site staff to complete the training on ECG machine, which includes the successful transmission of a test ECG. After completion of the training, sites should notify the Operations Center, as this is a required element of study activation. It is highly recommended that sites print their “Training Completion Certificate” and maintain a copy in their essential document files for IMPAACT 2005.

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.

9.3 Contraception and Pregnancy

As per the DLM (trade name, Deltyba) Investigator’s Brochure (IB), 13th 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 in pregnant or breastfeeding women. Because animal reproduction studies are not always predictive of human response, 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 as an element of eligibility. Sites are expected to provide contraceptive counseling throughout the duration of the study and to monitor closely for pregnancy.

9.3.1 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 (whether male or female). To supplement local SOPs on provision of contraceptive counseling, sites are encouraged to download the following publications from the WHO:


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.

9.3.2 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 the schedule of evaluations (protocol Appendix I) or when pregnancy is suspected or considered clinically indicated during study follow-up. If a participant becomes pregnant during the study, she should be discontinued from study drug treatment but will continued to be followed until the outcome of the pregnancy is known; refer to protocol Section 8.8. If the outcome of the pregnancy is not known at the time of the End of Study visit, 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, it will be important to track pregnancies in partners of male participants. Male participants of reproductive potential should be queried as part of standard contraceptive counseling about whether a sexual partner has become pregnant during the course of the study. If the outcome of the pregnancy is not known at the time of the End of Study visit, study staff should continue to contact the participant until that information is available.
9.4 TB Monitoring and Treatment Outcome

9.4.1 Centralized Chest X-Ray

Chest X-rays are taken from all children at timepoints described in the protocol Schedule of Evaluations. These X-rays are uploaded to a file exchange utility, as explained below for centralized review.

**Uploading the chest X-ray (CXR) to the FSTRF File Exchange Utility:**

Each study site is asked to upload all chest X-rays to the 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 xray 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 FSTRF Portal to upload image files: [https://www.frontierscience.org](https://www.frontierscience.org).

3. Make sure you are signed into the FSTRF 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.

4. Navigate to the IMPAACT tab on the FSTRF portal, and click on File Exchange Utility under the Utilities heading.

   **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)

   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

9.4.2 TB treatment outcome

Treatment outcomes in children, specified in the protocol Section 8.5, are bacteriological cure, probable cure, treatment failure, TB recurrence, death, and loss to follow-up. These outcomes are defined in protocol Section 8.5. 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 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 4 and Table 5.
Table 4: Classification of Treatment Outcomes for Children with Bacteriologically Confirmed MDR-TB

<table>
<thead>
<tr>
<th>Bacteriological outcome</th>
<th>Clinical/radiological outcome                                                                ncia</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 consecutive negative cultures at least 4 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>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), but not meeting criteria below for treatment failure</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>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>3 consecutive cultures negative at least 4 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>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>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.
Table 5: 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 1a. 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.
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>
</table>
| 1 | 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. |
| 2 | Gently swirl to make a uniform suspension.  
   [Caution] Be careful not to spill the suspension. |
<p>| 3 | Administer suspension to the patient. |</p>
<table>
<thead>
<tr>
<th>#</th>
<th>Procedure</th>
</tr>
</thead>
</table>
| 4  | Pour another 15 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  | Administer suspension to the patient. |
APPENDIX IB: Delamanid Oral Suspension Preparation (Syringe) for 25 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 (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 subject. |</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.png)  
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.png)  
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>Put 1 tablet (5 mg x 1) 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>4</td>
<td>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.</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><img src="image1.png" alt="Image" /> Disassemble the oral syringe into three parts: cap, barrel and plunger.</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Image" /> Put one tablet (5 mg x 1) of delamanid pediatric formulation into the barrel of the syringe.</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Image" /> 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><img src="image4.png" alt="Image" /> 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 X-Rays

Instructions for preparation of digital photographs of Chest Xrays

Given the varying technical facilities at the various study sites, this procedure will be adapted to describe the process followed by each site to record chest x-ray 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 minimised 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)
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](image)

**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="image" alt="Poor Quality X-Ray Example 1" /></td>
<td>Picture 1</td>
</tr>
<tr>
<td><img src="image" alt="Poor Quality X-Ray Example 2" /></td>
<td>Picture 2</td>
</tr>
</tbody>
</table>

-Too small
-Under-exposed film
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

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 them 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>100</td>
</tr>
<tr>
<td>90</td>
</tr>
<tr>
<td>80</td>
</tr>
<tr>
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<td>30</td>
</tr>
<tr>
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</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>