IMPAACT P1108

A Phase I/II, Open-Label, Single Arm Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Bedaquiline (BDQ) in Combination with Optimized Individualized Multidrug-Resistant Tuberculosis (MDR-TB) Therapy in HIV-Infected and HIV-Uninfected Infants, Children and Adolescents with MDR-TB Disease

Manual of Procedures

Version 1.2
19 February 2020
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## IMPAACT P1108 Manual of Procedures Summary of Changes

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<th>Section</th>
<th>Current Version</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Section 1 Study Overview</td>
<td>1.2</td>
<td>• Updated Table 1-1 to align with Letter of Amendment (LoA) #2 for protocol Version 1.0</td>
</tr>
<tr>
<td>Section 2 Preparing for the Study</td>
<td>1.2</td>
<td>• Updated website links to DAIDS documents and added link to the IMPAACT Network Manual of Procedures (MOP)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Added clarification and guidance regarding site investigator responsibilities</td>
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<tr>
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<td></td>
<td>• Minor clarifications and revisions throughout</td>
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<tr>
<td>Section 3 Study Resources</td>
<td>1.2</td>
<td>• Added clarifications for study related communications</td>
</tr>
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<td></td>
<td></td>
<td>• Updated Figure 3-3 for consistency with Clarification Memorandum (CM) #3 for protocol Version 1.0 and Screening Case Review process</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Minor clarifications and revisions throughout</td>
</tr>
<tr>
<td>Section 4 Informed Consent and Assent Considerations</td>
<td>1.2</td>
<td>• Added further guidance on informed consent and assent requirements for sites and procedures for participants who meet IRB/EC criteria for providing consent or assent after enrollment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Removed information on informed consent, assent and other human subjects considerations that is specified in the Network MOP</td>
</tr>
<tr>
<td>Section 5 Participant Accrual</td>
<td>1.2</td>
<td>• Updated to provide further guidance on participant accrual, screening and enrollment procedures based on study implementation to date and for consistency with LoAs #2-3 for protocol Version 1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Added guidance and requirements for Screening Case Review process</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Minor clarifications and revisions throughout</td>
</tr>
<tr>
<td>Section 6 Study Visits and Procedures</td>
<td>1.2</td>
<td>• New section added to provide guidance on key considerations for study visits and procedures</td>
</tr>
<tr>
<td>Section 7 Laboratory Considerations</td>
<td>1.2</td>
<td>• Added details and guidance related to the National Institutes of Health (NIH) recommendations for maximum pediatric blood draw volumes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Updated website links as appropriate</td>
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<tr>
<td></td>
<td></td>
<td>• Updated section to align with LoAs #1-3 and CMs #1-5</td>
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<tr>
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<td>• Added further guidance on specimen inventory QA/QC procedures and laboratory data queries</td>
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<tr>
<td></td>
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<td>• Updated guidance for pharmacokinetic (PK) specimen shipping</td>
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<tr>
<td>Section</td>
<td>Date of Change</td>
<td>Major Changes</td>
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</tbody>
</table>
| Section 8 Pharmacy Considerations | 19 February 2020 | - Added further details for local lactate and lactate/pyruvate (L/P) specimen storage and shipment, obtaining L/P testing results, and L/P results classification
- Minor clarifications and revisions throughout |
| Section 9 Expedited Adverse Event Reporting to DAIDS | 19 February 2020 | - Updated section to provide further guidance on dispensing bedaquiline (BDQ) and BDQ dosing and administration and aligning with LoAs #1-3 and CMs #1-5
- Added Section 8.4 to provide guidance on concomitant medications per the protocol and to ensure appropriate monitoring of participants
- Minor clarifications and revisions throughout |
| Section 10 Clinical Management Considerations | 19 February 2020 | - Added requirements and further guidance on cardiac safety monitoring in P1108 and ECG monitoring, clinical management and assessment, and eCRF completion
- Updated section to align with LoAs #1-3 and CMs #1-5
- Updated instructions and guidance for IGRA testing
- Updated website links as appropriate
- Added Section 10.3.4, TB Treatment Outcome, to provide guidance on TB outcome classifications
- Minor clarifications and revisions throughout |
<p>| Appendix I Bedaquiline (BDQ) Tablet Splitting Instructions for Administration in Children | 19 February 2020 | - Minor clarifications and revisions throughout |
| Appendix II Recommendations for Caregivers and DOT Supporters for Using BDQ in Children | 19 February 2020 | - Minor clarifications and revisions throughout |
| Appendix III ARUP Specimen Labeling Policy | 19 February 2020 | - No change from Version 1.1 |
| Appendix IV Sample ARUP Requisition Form | 19 February 2020 | - No change from Version 1.1 |</p>
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<tr>
<th>Appendix V</th>
<th>Digital Photographs of Chest X-Rays</th>
<th>1.2</th>
<th>19 February 2020</th>
<th>• Minor clarifications and revisions throughout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendix VI</td>
<td>Sample Informed Consent Coversheet for IMPAACT P1108</td>
<td>1.2</td>
<td>19 February 2020</td>
<td>• New appendix added for reference</td>
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</table>
1.0 Study Overview

IMPAACT P1108 is a Phase I/II, open-label, single arm, multi-site study to evaluate the pharmacokinetics (PK), safety and tolerability of bedaquiline (BDQ; trade name, SIRTURO) in combination with optimized individualized multidrug-resistant tuberculosis (MDR-TB) therapy in HIV-infected and HIV-uninfected infants, children and adolescents with MDR-TB disease.

Up to 72 participants (24 per age cohort) may be enrolled to achieve 54 evaluable participants (18 per age cohort). The study will enroll HIV-infected and HIV-uninfected infants, children and adolescents treated for clinically diagnosed or confirmed intra-thoracic (pulmonary) MDR-TB and/or selected forms of extra-thoracic MDR-TB who have received 2-12 weeks of routine MDR-TB treatment prior to enrollment. The study will take place in five sites across Haiti, India, and South Africa.

All participants will receive BDQ in combination with an optimized background TB treatment regimen (OBR) for 24 weeks. For HIV-infected participants, BDQ will also be given in combination with an acceptable antiretroviral (ARV) therapy regimen initiated at least two weeks prior to enrollment. Participants will be stratified by age at screening into one of three weight-banded cohorts as shown in Table 1-1. In each cohort, at least six participants with HIV-infection will be enrolled. Participants will be followed for 96 weeks after their last dose of BDQ (up to 120 weeks of follow-up for each participant).

<table>
<thead>
<tr>
<th>Table 1-1</th>
<th>P1108 BDQ Dosing by Cohorts and Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort</strong></td>
<td><strong>Age and Weight</strong></td>
</tr>
<tr>
<td>Cohort 1</td>
<td>≥ 6 to &lt; 18 years ≥30 kg</td>
</tr>
<tr>
<td></td>
<td>≥ 6 to &lt; 18 years ≥15 to &lt;30 kg</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>≥ 2 to &lt; 6 years ≥7 kg</td>
</tr>
<tr>
<td></td>
<td>≥ 0 to &lt; 2 years ≥3 kg</td>
</tr>
<tr>
<td>Cohort 3</td>
<td>≥ 0 to &lt; 2 years ≥3 kg</td>
</tr>
<tr>
<td></td>
<td><strong>Participants ≥ 3 to ≤ 7 kg:</strong> 100 mg once per day for two weeks and then 50 mg three times per week on Monday, Wednesday, and Friday for 22 weeks</td>
</tr>
</tbody>
</table>
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 2-1
P1108 Clinical Research Sites

<table>
<thead>
<tr>
<th>CRS</th>
<th>Site Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRS 30022</td>
<td>Les Centres GHESKIO CRS, Port-au-Prince, Haiti</td>
</tr>
<tr>
<td>CRS 31441</td>
<td>Byramjee Jeejeebhoy Medical College (BJMC), 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 CRS, Johannesburg, South Africa</td>
</tr>
<tr>
<td>CRS 31976</td>
<td>PHRU Matlosana CRS, Klerksdorp, South Africa</td>
</tr>
</tbody>
</table>

2.1 Investigator Responsibilities

At each site, P1108 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 Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials and Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials are useful for interpreting and operationalizing the regulations and guidelines in accordance with DAIDS expectations. These policies are available at the following website and must be followed throughout implementation of P1108:

https://www.niaid.nih.gov/research/daidaclinical-site-implementation-operations

The 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/daidaclinical-research-laboratory-specimens-management

P1108 must also be conducted in accordance with the IMPAACT Network Manual of Procedures (MOP) and 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 applicable regulations, policies, and guidelines should be maintained in on-site essential document files. The Network MOP is available at:

http://impaactnetwork.org/resources/policies-procedures.htm
The Investigator of Record (IoR) at each site must sign the IMPAACT P1108 Protocol Signature Page to formally document his or her agreement to conduct the study in accordance with the study protocol and all applicable protocol-related documents and in compliance with applicable US regulations; the ICH Guideline for GCP; institutional review board/ethics committee (IRB/EC) determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements and institutional policies.

The IoR at each site must also sign a US Food and Drug Administration (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:

https://rsc.niaid.nih.gov/clinical-research-sites/protocol-registration-forms

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

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 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 P1108 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 participants as described in protocol Section 13.2.

The risk category assessed by the IRBs/ECs then determines the informed consent requirements for participation in the study. Specifically, per 45 CFR 46.408 (b), the IRB/EC may find that the consent of one parent is sufficient for research to be conducted under 46.404 or 46.405. If the IRB/EC finds that the research is covered by 46.406 or 46.407, both parents must give their consent 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 (as determined locally). IRBs/ECs must document their risk determination, and study sites should adapt the signature pages of their site-specific informed consent forms as needed to accommodate the parental consent requirements associated with the IRB/EC determination.

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

After obtaining all applicable ethical and regulatory approvals, the IoR (or designee) at each site must submit documentation of the approvals and other required documents to the DAIDS Protocol Registration Office (PRO). Further information on the protocol registration process can be found in protocol Section 14.2 and in the DAIDS Protocol Registration Manual, which is available at:

https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations

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

2.3 Site-Specific Study Activation

Prior to conducting any study procedures, each site must obtain all required approvals, complete the DAIDS protocol registration process, and complete study-specific activation procedures specified by the protocol team. To help ensure site readiness for study initiation, the protocol team has specified a set of study activation requirements that must be met to obtain approval to begin study implementation. These requirements are listed on the P1108 Site-Specific Study Activation Checklist, which is available upon request from the P1108 Clinical Trials Specialists (CTSs). Activation requirements include confirmation of laboratory, pharmacy, and data management readiness and completion of study-specific training, including acquisition and training on study-provided electrocardiogram (ECG) machines. As a requirement for activation, sites must submit for review and sign-off by appropriate team members study-specific standard operating procedures (SOPs) on Participant Recruitment, Participant Retention, Study Drug Adherence/Directly Observed Therapy (DOT), and Audiology Testing.

Any questions related to the study activation process should be directed to the P1108 CTSs. 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

All P1108 visits and procedures must be conducted in accordance with the study protocol. The purpose of this manual is to supplement the protocol, not to replace or substitute for it. *If this manual is inconsistent with the protocol, the specifications of the protocol take precedence.* Please notify the CTSs of any such inconsistencies.

The protocol team has identified study-specific contacts for various types of issues and questions, as shown 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 24-48 hours.

To ensure receipt of important information about study implementation and conduct, sites should email user.support@fstrf.org to have relevant site personnel added to the protocol email group (impaact.protp1108@fstrf.org).

Site staff should avoid sending messages to the protocol email group (impaact.protp1108@fstrf.org) as this group is used for broadcast distribution to all protocol team and site staff members. The group is comprised of many individuals and is not intended to receive site-specific or participant-specific queries. Questions related to protocol interpretation, study implementation, or participant management should be emailed to the P1108 Core Team (impaact.p1108core@fstrf.org)
<table>
<thead>
<tr>
<th>Topic</th>
<th>Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adding site staff to protocol team email group: <strong><a href="mailto:IMPAACT.protp1108@fstrf.org">IMPAACT.protp1108@fstrf.org</a></strong></td>
<td>User Support <strong><a href="mailto:user.support@fstrf.org">user.support@fstrf.org</a></strong> include “P1108” 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 P1108 Core Team <strong><a href="mailto:IMPAACT.P1108core@fstrf.org">IMPAACT.P1108core@fstrf.org</a></strong> for triage to other team members as needed</td>
</tr>
<tr>
<td>Clinical management, audiology, and PK related queries</td>
<td>IMPAACT P1108 Core Team <strong><a href="mailto:IMPAACT.p1108core@fstrf.org">IMPAACT.p1108core@fstrf.org</a></strong></td>
</tr>
<tr>
<td></td>
<td>For cardiology management issues: IMPAACT P1108 Core Cardio Team <strong><a href="mailto:IMPAACT.p1108corecardio@fstrf.org">IMPAACT.p1108corecardio@fstrf.org</a></strong></td>
</tr>
<tr>
<td>Participant eligibility, potential enrollment of an ineligible participant, and/or deviation from protocol requirements for eligibility determination and/or enrollment</td>
<td>IMPAACT P1108 Core Team <strong><a href="mailto:IMPAACT.p1108core@fstrf.org">IMPAACT.p1108core@fstrf.org</a></strong></td>
</tr>
<tr>
<td></td>
<td>For cardiology questions regarding eligibility: IMPAACT P1108 Core Cardio Team <strong><a href="mailto:IMPAACT.p1108corecardio@fstrf.org">IMPAACT.p1108corecardio@fstrf.org</a></strong></td>
</tr>
<tr>
<td>Co-enrollment</td>
<td>IMPAACT P1108 Core Team <strong><a href="mailto:IMPAACT.p1108core@fstrf.org">IMPAACT.p1108core@fstrf.org</a></strong></td>
</tr>
<tr>
<td>Data management computer and screen problems</td>
<td>User Support (Frontier Science Foundation) <strong><a href="mailto:user.support@fstrf.org">user.support@fstrf.org</a></strong> or by phone: +716-834-0900 x7302</td>
</tr>
<tr>
<td>Subject Enrollment System</td>
<td>DMC Randomization Support Office <strong><a href="mailto:rando.support@fstrf.org">rando.support@fstrf.org</a></strong> or by phone: +716-834-0900 x7301</td>
</tr>
<tr>
<td>Study drug (other than study drug orders)</td>
<td>Protocol Pharmacist Thucuma Sise, Pharm.D, BCPS, RPh <strong><a href="mailto:thucuma.sise@nih.gov">thucuma.sise@nih.gov</a></strong> or by phone: 240-292-4848</td>
</tr>
<tr>
<td>Study drug orders</td>
<td>Clinical Research Products Management Center <strong><a href="mailto:BIOC.RPMC.Ph@Thermofisher.com">BIOC.RPMC.Ph@Thermofisher.com</a></strong> All orders should be submitted electronically (inquiries please phone: +301-294-0741)</td>
</tr>
<tr>
<td>Expedited Adverse Event (EAE) Reporting</td>
<td>DAIDS RSC Safety Office <strong><a href="mailto:DAIDSRSCSafetyOffice@tech-res.com">DAIDSRSCSafetyOffice@tech-res.com</a></strong> or by phone: 800-537-9979 or +301-897-1709 or by fax: 800-275-7619 or +301-897-1710</td>
</tr>
<tr>
<td>DAIDS Adverse Experience Reporting System (DAERS)</td>
<td><strong>NIAID Clinical Research Management System <a href="mailto:CRMSsupport@niaid.nih.gov">CRMSsupport@niaid.nih.gov</a></strong> (questions also may be submitted from within the DAERS application)</td>
</tr>
</tbody>
</table>
The P1108 Core Team is composed of study team members who have been designated to receive and reply to clinical management questions and notifications. When submitting clinical management questions to the P1108 Core Team, please address each of the points listed in Figure 3-2 to help ensure that Core Team members have adequate information to respond in a timely manner. The responding Core Team member will reply to your question or notification by return email.

Replies can generally be expected within 24-48 hours. When it may not be possible to provide a complete response within 24-48 hours, the person who submitted the question or notification will be provided with an interim response and informed that more time is needed to provide a complete response. Always retain a copy of correspondence with the Core Team in the relevant participant’s study file.

Figure 3-2
IMPAACT P1108 Core Team Communications

Questions for IMPAACT P1108 Core Team: Please copy and paste this listing into the body of your email message to IMPAACT.p1108core@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.p1108corecardio@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, or 3
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 Core Team:
The P1108 protocol also details circumstances in which IoRs must consult with the Core Team. All protocol requirements must be followed. For ease of reference, a summary of issues requiring consultation with the Core Team, and those for which consultation is available but not required, is provided below in Figure 3-3. IoRs are encouraged to contact the Core Team with any other issues, questions, or concerns related to study drug regimens for study participants.

**Figure 3-3**
Requirements for Consultation with the IMPAACT P1108 Core Team

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

**Screening Case Review**
- After written informed consent and assent (if applicable) is obtained for potential participants and all screening evaluations are performed, a Screening Case Review should be submitted to the Core Team as soon as possible for potentially eligible participants. See further details and requirements for the Screening Case Review process in Section 5 of this manual.

**Study Implementation**
- Requests for co-enrollment in other studies
- A participant is administered any disallowed medications listed in protocol Section 5.7.
- Investigator or designee determines continued participation in the study would be unsafe or otherwise not in the best interest of the participant.
- Any individual dose adjustments for clinical purposes
- Initial reports of pregnancy in a study participant

**General adverse events**
- Any Grade 3 or 4 toxicity

**ECG-determined or clinical cardiac toxicity**
- Grades 1-4 ECG reading
- Grades 1-4 clinical criteria

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

**Lactate Toxicity Management**
- Repeat lactate if ≥ 3 mmol/L

**Myalgia, Nausea or Vomiting Toxicity Management**
- Any Grade 3 or 4 toxicity events
3.2 Study Webpage

The P1108 protocol and associated documents are available on the study-specific webpage:

http://www.impaaactnetwork.org/studies/P1108.asp

Additional resources available on the study webpage include:

- Study contacts
- Study implementation materials, including this manual and Laboratory Processing Chart (LPC)
- Study training materials
- Application for import permit for biological substances for UCT PK samples
- ARUP Checklist and Connect Information Sheet
- Financial Disclosure Form

3.3 Data Management Center (DMC) IMPAACT Portal

The IMPAACT Portal of the DMC website provides information, documents and tools to assist site staff with the data management aspect of conducting IMPAACT studies, including electronic Case Report Forms (eCRFs), data collection form schedules, participant calendar, Subject Enrollment System (SES) and study-specific messages. The IMPAACT Portal can be accessed from the Frontier Science Foundation webpage at https://www.frontierscience.org/

For clinical user support, an email message may be sent to impaact.support@fstrf.org or dial +1 (716) 834-0900 x7302 (x7200 if outside U.S. hours). Please contact webmaster@fstrf.org for any problems or questions about the IMPAACT portal.

3.4 Case Report Form Completion and Data Entry

The DMC has developed a Forms Manual to assist site staff in the accurate completion of 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

eCRFs and other related materials can be accessed through the Medidata RAVE system. The eCRFs may be used as a guide for source documentation purposes. The IMPAACT P1108 eCRF Completion Guide and IMPAACT P1108 Print Matrix (blank eCRFs) are located in the DMC IMPAACT Portal under Site Support, Medidata Rave Resources.
4.0 Informed Consent and Assent Considerations

This section contains operational guidance for obtaining informed consent and assent for P1108. This guidance complements but does not duplicate the comprehensive information on informed consent, assent, and other human subjects considerations provided in Section 8 of the Network MOP. Please refer to the Network MOP as needed. Also refer to protocol Section 13.3, Section 4.8 of the ICH Guideline for GCP, and the informed consent section of the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials as needed.

Consistent with inclusion criterion 4.1.1, this study requires that written informed consent be obtained from each participating child’s parent or legal guardian. In addition, when applicable per IRB/EC policies and procedures, assent must be obtained from the participating child. Each site must have on file a study-specific SOP for obtaining informed consent and assent that addresses all aspects of the informed consent and assent processes that are applicable to this study. All sites must follow their SOPs consistently for all P1108 informed consent and assent processes. All site staff involved in obtaining informed consent must be designated on the study-specific delegation of duties log and listed on the Form FDA 1572 for the study. These staff must be qualified by education, experience, training, and knowledge of the study, as determined by the IoR, and appropriate training documentation must be available to support the IoR’s delegation to these staff.

4.1 Study-specific Informed Consent and Assent Processes

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

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

4.2 Assessment of Understanding

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

4.3 Documentation Requirements

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

In addition to completing required entries on informed consent and assent forms, each informed consent and assent process should be documented in a signed and dated chart note. For the study informed consent and assent processes, the note should document that informed consent and assent when applicable were obtained before any study procedures were performed. The note also should document adherence to the requirements of the informed consent section of the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. However, if an informed consent coversheet is used, it is not necessary to transcribe information recorded on the coversheet into the chart note. Informed consent and assent decisions should also be entered in appropriate eCRFs.

4.4 Considerations Regarding Death of a Guardian

The expectation is that permission for participation in P1108 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 BDQ 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 Participant Accrual

5.1 Overview

The study aims to enroll up to 72 participants to achieve 54 evaluable participants (18 in each cohort), with a minimum of six HIV-infected participants per cohort. In Cohort 1, the number of participants will be balanced across two weight bands (≥15 to < 30 kg and ≥30 kg). Participants with confirmed or probable intra-thoracic (pulmonary) and/or selected forms of extrathoracic MDR-TB will be considered evaluable if they contribute appropriate PK data for PK modeling of BDQ dosing.

Initially, participants will be enrolled into Cohort 1 only. Enrollment into Cohorts 2 and 3 will be initiated if the following are achieved in the first 12 participants enrolled in Cohort 1:

- At least eight of the 12 participants are evaluable (in total, across the two weight bands),
- PK criteria are met based on all available PK data and the summary statistic described above
- No pre-defined safety issues have been identified.

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

5.2 Site-specific Accrual

The study accrual plan is based on site-specific accrual projections established during the site selection process. For each site, accrual will begin after all required approvals are obtained and a site-specific study activation notice is issued by the IMPAACT Operations Center. As a condition for study activation, each site will establish SOPs as described in Section 2.3 of this manual. All sites are responsible for following these SOPs, and for updating them as needed throughout study implementation.

Prior to initiating accrual into Cohorts 2 and 3, each site must obtain all required IRB/EC and applicable regulatory entity approvals of Letter of Amendment (LoA) #2, dated 28 February 2019, and LoA #3, dated 17 October 2019, for protocol Version 1.0.

For sites activated to initiate the study for all or specific cohorts prior to issuance of LoA #3:
A DAIDS PRO Registration Notice for LoA #3 must be received prior to implementation of LoA #3 and enrolling additional participants in P1108. Once the Registration Notice is received and each site has participated in a study refresher training, participant accrual may be resumed, using the updated site-specific ICFs corresponding to LoA #3 for all new participants. In addition, all previously enrolled participants must re-consent for ongoing study participation using the updated site-specific ICFs corresponding to LoA #3. Re-consenting should take place at each participant’s next study visit after the Registration Notice for LoA #3 is received.

For sites not activated to initiate the study for all or specific cohorts prior to issuance of LoA #3:
A DAIDS PRO Registration Notice for LoA #3 must be received prior to activation. Activation will occur following receipt of the Registration Notice, completion of all other study activation requirements, and receipt of a site-specific study activation notice from the IMPAACT Operations Center.
Once accrual is initiated, the Statistical and Data Management Center (SDMC) will routinely report the number of participants screened and enrolled at each site — by weight band and by month and cumulatively — to the protocol team. The team will monitor all available data in relation to site-specific accrual projections to determine whether accrual targets should be adjusted across sites to achieve the study objectives most efficiently.

5.3 Recruitment

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

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

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

5.4 Obtaining Informed Consent and Assent

Refer to protocol Section 13.3 and Section 4 of this manual for more information on informed consent and assent considerations for this study. When a potentially eligible participant is identified, written informed consent and assent (if applicable) must be obtained prior to performing any study-specific procedures and collecting information to complete the Screening Case Review (see Section 4).

5.5 Screening and Enrollment

5.5.1 Screening and Enrollment Logs

Per the DAIDS policy on Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials, study sites are required to document screening (including screening failures) and enrollment activity on screening and enrollment logs. Additional information is provided at: https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations

5.5.2 Assigning Participant Identification Numbers

A Participant Identification Number (PID) must be assigned to each potential participant for whom informed consent (and assent if applicable) for study participation is obtained. The only exception to this requirement applies when a participant has previously been assigned a PID for another IMPAACT study. In that case, the previously-assigned PID would be used for P1108. Study site staff should assign PIDs from lists provided by the DMC. Contact the protocol Data Managers with any questions related to use of PID lists.

5.5.3 Screening for Eligibility

The study eligibility criteria are provided in protocol Sections 4.1 and 4.2; procedural eligibility screening requirements are described in protocol Sections 6.1 (Screening Visit) and 6.2 (Enrollment Visit). Contact the Core Team with any questions related to eligibility.
A PID will be assigned to all potential participants for whom informed consent (and assent if applicable) for study participation is obtained. In addition, a study-specific screening number will be obtained for each potential participant using the PS2001, IMPAACT Screening Checklist, located in the DMC’s SES. Sites are encouraged to perform screening procedures that are least burdensome and/or most likely to identify ineligibility first.

Following site SOPs for eligibility determination, eligibility assessment for potential participants should be completed by the site IoR or designee. For potential participants assessed as eligible for P1108, a Screening Case Review as specified in Figure 5-1 should be prepared and submitted to the Core Team (impact.p1108core@fstrf.org). This email should be submitted as soon as possible after all screening evaluations are performed to ensure that the Core Team has at least three business days to review and respond with findings and recommendations within the 30 day screening window. As per protocol Section 6.2, for potential participants who do not meet the eligibility criteria, screening may be discontinued once ineligibility is determined, including the Screening Case Review.

![Warning icon]

Please use the Screening Case Review in Figure 5-1 for all potential participants. Prior to enrollment, the IoR or designee should incorporate feedback from the Core Team into the final eligibility determination for the potential participant.

The Core Team’s response may include considerations for the evaluation of exclusion criterion 4.2.1 or any other eligibility criteria. For potential participants who are subsequently enrolled, the Core Team’s response may also guide and provide key reminders for monitoring participant safety during follow-up visits.

It is the responsibility of the IoR and other designated study staff to ensure that all required screening procedures are performed and adequately documented, and that only participants who meet the study eligibility criteria are enrolled. Each site must have on file a study-specific SOP for eligibility determination that describes how study staff will fulfill this responsibility; all sites must follow their SOPs when assessing eligibility for all potential participants. In the event that study staff identify that an ineligible participant has been enrolled, the Core Team must be consulted as soon as possible and within 24 hours per the communication procedures described in Section 3 of this manual.
**Figure 5-1**

**P1108 Screening Case Review**

Please copy and paste the listing below into the body of your email message to IMPAACT.p1108core@fstrf.org to ensure that all required information is included. Include the protocol number, PID, and “Screening Review” in the subject line of your email.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Site number:</td>
</tr>
<tr>
<td>2.</td>
<td>PID:</td>
</tr>
<tr>
<td>3.</td>
<td>Age:</td>
</tr>
<tr>
<td>4.</td>
<td>Sex:</td>
</tr>
<tr>
<td>5.</td>
<td>HIV status:</td>
</tr>
<tr>
<td>6.</td>
<td>For potential participants with HIV-infection:</td>
</tr>
<tr>
<td></td>
<td>a. Date of diagnosis:</td>
</tr>
<tr>
<td></td>
<td>b. Current ARV regimen (include drug names, dose and duration of each and when started)</td>
</tr>
<tr>
<td></td>
<td>c. Most recent CD4 count and viral load (include dates):</td>
</tr>
<tr>
<td></td>
<td>d. History of immune reconstitution inflammatory syndrome (IRIS):</td>
</tr>
<tr>
<td></td>
<td>e. World Health Organization (WHO) clinical stage:</td>
</tr>
<tr>
<td>7.</td>
<td>TB diagnosis</td>
</tr>
<tr>
<td></td>
<td>a. Date of diagnosis:</td>
</tr>
<tr>
<td></td>
<td>b. Diagnostic tests used:</td>
</tr>
<tr>
<td></td>
<td>c. Type of disease (include all sites of disease):</td>
</tr>
<tr>
<td></td>
<td>d. Drug-susceptibility testing (DST) rifampicin-resistant TB results (if available):</td>
</tr>
<tr>
<td>8.</td>
<td>History and current TB treatment regimen (include start and end dates for each medication in case description):</td>
</tr>
<tr>
<td>9.</td>
<td>Known anti-TB drug intolerance and adverse effects (describe in case description):</td>
</tr>
<tr>
<td>10.</td>
<td>History of renal problems:</td>
</tr>
<tr>
<td>11.</td>
<td>History of cardiac problems:</td>
</tr>
<tr>
<td>12.</td>
<td>Most recent notable intercurrent illness(es) in the past six months</td>
</tr>
<tr>
<td>13.</td>
<td>Signs or symptoms of ongoing or recurrent diarrhea, vomiting, or electrolyte losses:</td>
</tr>
<tr>
<td>14.</td>
<td>Known comorbidities, including underlying chronic lung disease:</td>
</tr>
<tr>
<td>15.</td>
<td>Nutritional Status</td>
</tr>
<tr>
<td></td>
<td>a. Weight-for-age Z-score:</td>
</tr>
<tr>
<td></td>
<td>b. Height-for-age Z-score:</td>
</tr>
<tr>
<td></td>
<td>c. History of nutritional edema:</td>
</tr>
<tr>
<td></td>
<td>d. Signs of current stunting or wasting:</td>
</tr>
<tr>
<td>16.</td>
<td>List all concomitant medications (including over the counter medicines and herbal remedies):</td>
</tr>
</tbody>
</table>

### 5.5.4 Screening Failures

For potential participants who provide informed consent but are ineligible, or who do not enroll in the study for any reason, a P1108 Screening Failure and Non-Enrollment Results eCRF (SCR0058) must be completed and keyed in the study database. As noted above, the IoR or designee should incorporate the Core Team’s response to the Screening Case Review into the final eligibility determination for potential participants. If a potential participant is determined to be ineligible, per exclusion criterion 4.2.1 or other eligibility criteria, based on team consultation during the Screening Case Review process, sites should respond “Yes” to question 3e on eCRF SCR0058 and specify the reasons for non-enrollment. The reason(s) for screening failure, Screening Case Review and all correspondence with the P1108 Core Team should be documented in participant study files. Potential participants identified as ineligible should be referred for non-study care as needed.
5.5.5 Enrolling Eligible Participants

Participants will be considered enrolled in P1108 upon successful entry of the eligibility checklist data into the SES, which will result in generation of a Study Identification Number (SID). Refer to protocol Section 6.2 for Entry visit requirements, including requirements related to the timing and ordering of Entry visit procedures, which should be taken into consideration when planning for logistical and staffing needs for the visit.

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

6.0 Study Visits and Procedures

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

Clinical evaluations and laboratory tests that comply with the requirements specified in protocol Section 6.14 and performed as part of clinical care within the Screening visit window may be abstracted from the participant’s medical record to meet the Screening requirements and do not need to be repeated. Operationally, specimen collection for required evaluations should be managed by the site investigator or designee to minimize needle sticks and avoid specimen collection for potential participants who are not confirmed to be eligible, when possible.

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

- Target visit dates are counted from the day of study entry; day of entry = Day 0.
- Each visit should ideally be conducted on the target date but may be conducted on any day within the protocol-specified visit window.
- Every effort should be made to conduct all study visits within the protocol-specified visit window. Failure to conduct any study-specific procedures within the protocol-specified visit window is a deviation from the protocol and should be documented as such. See Section 6.2 below for further guidance on protocol deviations.
- Site-specific procedures should be established among clinic and laboratory staff to ensure that all laboratory results are reviewed in a timely manner for participant safety monitoring and entry of results in appropriate eCRFs per protocol Section 7.2. This includes procedures and management for critical laboratory results that require additional follow-up per the protocol and Figure 3-3.
- In preparation for each visit, sites should review the protocol required evaluations for the visit and any laboratory tests from the prior visit.
• BDQ daily dosing is initiated at enrollment and should continue through the Week 2 visit. BDQ dosing three times per week on Monday, Wednesday and Friday should be initiated following the Week 2 visit and continued through the Week 24 visit.
• At the Entry visit, blood and urine biomarker collections should only be done if the visit is conducted more than two weeks from the Screening visit.
• Samples for lactate/pyruvate (L/P) and local lactate testing must be obtained on a fasting sample. Therefore, it may be preferable to schedule visits with these collections in the morning. The sample for L/P must be collected prior to the sample for local lactate.
• If initial local lactate is greater than or equal to 3 mmol/L, repeat testing should be performed as soon as possible (see SoE footnote #3).
• Reflex fT4 testing should be done if TSH is elevated.
• If a participant discontinues BDQ prior to the Week 24 visit, an Early BDQ Discontinuation visit should be done with evaluations conducted per the SoE “Early D/C” column and protocol Section 6.12. The participant’s follow-up visit schedule should be determined based on the time of BDQ discontinuation.

6.1 PK Visit Considerations

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

• Prior to each PK visit, ensure availability and access to required supplies, including specimen collection materials, study drug supplies, source documents, eCRFs and meals as appropriate.
• BDQ administration should be directly observed by study staff on the day of PK sampling during BDQ dosing.
• BDQ and all routine TB drugs and ARVs will be administered by the research team on the day of PK sampling and on the previous evening, where relevant.
• Doses, including administration date and time, of BDQ, OBR and ARVs for the two days preceding PK sampling should be obtained and recorded on eCRFs.
• Weeks 3 – 24 on-treatment visits with sparse PK collections should be scheduled to ensure that BDQ is administered on a Monday, Wednesday or Friday and at least 48 hours between doses. If BDQ is administered less than 48 hours from the prior dose, it is important that the time of the preceding dose is entered in eCRFs.
• Sparse PK (pre-dose) samples should be collected prior to directly observed administration of BDQ at Weeks 1, 4, 8, 12, 16, 20 and 24 visits.
• At Weeks 4 and 24 visits, L/P and local lactate samples must be collected prior to BDQ administration and on a fasting sample. The sample for L/P must be collected prior to the sample for local lactate testing.

6.2 Protocol Deviations

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

All protocol deviations should be adequately documented in study records consistent with DAIDS SOPs for Essential Documents at Clinical Research Sites. This documentation should include a description of the deviation, the reasons why it occurred, and corrective and preventive actions taken in response.
Protocol deviations that meet the criteria for network level reporting, as specified in Section 12.4.2 of the Network MOP, should be entered in the P1108 study database. Specifically, a protocol deviation eCRF (DEV0001) should be completed and entered in the study database as soon as possible and within 10 working days of site awareness. A copy of the completed eCRF should also be emailed to IMPAACT.deviation@fstrf.org, along with any supplemental documents. Of note, the site IoR retains responsibility for the final determination of reportability. Consultation with the Core Team and Operations Center on reportability is available as needed.

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

7.0 Laboratory Considerations

For detailed information on tests and specimens required for each visit, please refer to protocol Section 6 and SoE and the P1108 LPC. Please also refer to Section 17 of the Network MOP as needed. Information on specimen shipping and processing are available in the LPC.

NIH recommendations for maximum pediatric blood draw volumes will be followed in this study. The volume of blood drawn at any study visit should not exceed 5 mL/kg in a single day and 9.5 mL/kg over any eight-week period. It is important that blood draw volumes are documented at each visit and are easily accessible for calculating maximum draw volumes at study visits, particularly as higher volumes are needed for HIV-infected participants. In the event that the calculation performed at any given visit indicates that the full blood draw volume specified in the SoE cannot be collected, refer to protocol Section 6.14.1 to determine the prioritization of allowable blood draw volumes. When the full volume specified in the SoE cannot be collected, this should be documented in the participant’s study file, along with the reason for drawing less than the total blood volume amount in the SoE. An example of this type of determination is shown below.

Sample Case 1: An HIV-infected nine-month old participant who weighs 5.2 kg at Week 8 and whose blood draw volume in the past eight weeks was generally consistent with the SoE:

<table>
<thead>
<tr>
<th>Screening</th>
<th>11.5 mL (includes 4 mL for documentation of HIV status and 4 mL for IGRA testing)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry</td>
<td>9.5 mL</td>
</tr>
<tr>
<td>Week 1</td>
<td>3.5 mL</td>
</tr>
<tr>
<td>Week 2</td>
<td>5.5 mL</td>
</tr>
<tr>
<td>Week 4</td>
<td>4.5 mL</td>
</tr>
<tr>
<td>Week 6</td>
<td>0 mL</td>
</tr>
<tr>
<td>Total</td>
<td>34.5 mL</td>
</tr>
</tbody>
</table>

For this Cohort 3 participant, on the day of the Week 8 visit:

- The “single day” maximum blood draw volume = (5.2 kg*5 mL/kg) = 26.0 mL
- The “last 8 weeks” maximum blood draw volume = (5.2 kg*9.5 mL/kg) – 34.5 = 14.9 mL

Based on these calculations, up to **14.9 mL** could be drawn at the Week 8 visit. This volume (14.9 mL) is greater than the total volume specified in the SoE for the Week 8 visit for a Cohort 3 participant (9.5 mL, presuming that 4 mL must be collected for IGRA testing per footnote #2 in the SoE). Therefore, the total volume specified in the SoE may be drawn at the Week 8 visit.
Regardless of where tests are performed, personnel who collect specimens and/or perform assays must be trained in proper collection techniques and special requirements, container types, 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 SOPs for proper collection, processing, labeling, and transport of specimens. Transport of all specimens must comply with federal, state, local, IATA and ACTG/IMPAACT specimen shipping regulations.

Key elements of specimen management include collection, transport, storage and shipping. Also essential for clinical trials is a Chain of Custody, as described in Section 7.2 below, which refers to the tracking of specimens and results. Specimens must be transported within the predefined time limits to the laboratory under proper conditions. The remainder of this section provides information intended to standardize specimen collection and laboratory procedures across sites.

### 7.1 Infection Control and 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 P1108 in both the clinical and laboratory setting, as recommended by the U.S. Centers for Disease Control and Prevention (CDC). Respiratory infections like *M. tb* may be transmitted by droplet aerosolization and fomites. All study staff should take appropriate precautions when collecting and handling biological specimens. Guidance on Universal Precautions/Body Substance Isolation is available from the CDC at [http://www.cdc.gov/niosh/topics/bbp/universal.html](http://www.cdc.gov/niosh/topics/bbp/universal.html)

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

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

### 7.2 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. Participant names or initials may NOT be used on research samples or the accompanying tracking forms.
7.3  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.

7.4  Laboratory Data Management System (LDMS)

The LDMS should be used at each site or designated contract laboratory to track the collection, storage, and shipment of P1108 laboratory specimens. All sites should use the current version of the LDMS. Detailed instructions for use of the LDMS are available at: https://www.ldms.org/.

P1108 includes testing that requires processing to begin at the clinical site, immediately following sample collection (examples include the PK and L/P ratio specimens). For these samples, it is essential that all study-specific processing information is transferred from the clinical site to the laboratory, where it may be entered into the LDMS as needed. Site-specific specimen inventory QA/QC procedures should be performed routinely and through the end of the study to ensure complete and accurate entries in the LDMS. Any laboratory data queries and delinquencies should be resolved as soon as possible and within two weeks.

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

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

Contact LDMS user support as listed below for further information. Questions about the LDMS, shipping and storage for P1108 should be directed to the protocol Laboratory Data Managers.

7.4.1  LDMS User Support

Regular business hours for LDMS user support are 12 AM – 6 PM Eastern Time (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

If site staff are locked out of LDMS or experiencing errors that prevent completion of LDMS lab work after business hours, LDMS User Support may be accessed using the LDMS Web Pager utility or by emailing the paging system directly at ldmspager1@fstrf.org. Please allow at least 15 minutes for a response.
7.5  PK Specimen Collection and Processing

Intensive PK sampling is performed at the Week 2 visit, with a pre-dose sample collected prior to BDQ administration and then 2, 4, 6 and 8 hours after BDQ dosing. Sparse PK sampling at Weeks 1, 4, 8, 12, 16, 20, and 24 visits should be collected prior to BDQ administration. Sparse PK sampling at Weeks 32, 40, 48, 60, 72, 96, and 120 may be drawn at any time during the visit. If a participant prematurely discontinues BDQ or the study, the participant should return for an Early BDQ Discontinuation (D/C) or Early Study D/C visit, respectively, and sparse PK sampling performed at any time during this visit.

As the PK sampling collection tubes are drawn, invert the tubes 8-10 times gently. Process PK specimens within two hours of collection. Maintain cold chain at all stages, if possible; room temperature for centrifugation is acceptable, if necessary.

PK specimens should be stored at sites as specified in the LPC until requested to ship by the protocol team to the testing laboratory. A site-specific shipping request will be issued by the protocol Laboratory Data Manager when PK samples should be shipped. Further details on PK specimen management and shipping are available in the LPC.

7.6  L/P Ratio and Local Lactate Evaluations

All P1108 Cohort 1 participants (age ≥ 6 to < 18 years) will have lactate and pyruvate testing performed at entry and during follow-up visits as a marker for potential mitochondrial toxicity. Lactate and pyruvate testing (i.e., L/P ratio and local lactate evaluations) will not be performed for participants enrolled in Cohorts 2 and 3.

There are two types of lactate and pyruvate testing in this study:

- L/P testing performed at a central U.S. laboratory: ARUP (http://www.aruplab.com).
- Lactate testing performed at each site’s approved testing laboratory.

Collection for both L/P and local lactate assays will be performed for Cohort 1 participants at entry and at Weeks 4, 24 and 96 visits (i.e. a total of four times during the 120-week study duration). The L/P blood draw should be collected prior to the local lactate blood draw and on a fasting sample.

7.6.1  Operational Considerations for L/P and Local Lactate Sample Collections

Collection of L/P and local lactate samples requires that the participant is fasted, i.e. the participant should not eat or drink anything other than water for 8-10 hours prior to sample collection. Participants also should not exercise for several hours prior to sample collection. Note that TB medications, ARVs and other required medications are allowed prior to sample collection. Site staff should remind participants/parents/guardians of these requirements in advance of visits with L/P and lactate collections. As noted above, it may be preferable to schedule these visits for early morning.

As protocol Section 5.3 specifies that BDQ is required to be given with food, L/P and lactate samples that must be obtained while fasting should also be collected prior to study drug administration at entry and on treatment visits (see Clarification Memorandum (CM) #3).

Local lactate testing may require Na-fluoride/K-oxalate or Na-fluoride/Na-heparin (gray top) tubes so the anticoagulant for these lactate assays may NOT be the same as for L/P and therefore, precludes both measurements coming from the same blood draw. If initial local lactate is greater than or equal to 3 mmol/L, repeat testing should be performed as soon as possible (see SoE footnote #3).
During study visits with lactate and L/P collections, at least two staff are required to assist with the blood draws: one staff member to initiate the sample processing while the second staff member remains with the participant.

### 7.6.2 Blood Draw Instructions for Lactate and L/P Collections

The L/P blood draw must be done prior to collection of the local lactate sample, preferably from a stasis free vein. Sites should avoid the use of a tourniquet, if possible. If a tourniquet must be used for the L/P collection, follow the directions provided in the LPC. For the local lactate blood draw, sites must follow the specific instructions provided by their testing lab regarding tourniquet use. Tourniquet use for both samples should be documented in appropriate eCRFs.

The participant should remain resting during sample collection. Once the blood draws for L/P and local lactate are completed, site staff may offer a light snack or drink to the participant. Remaining blood draws may then proceed per the protocol.

*Note: If a fasting gastric aspirate needs to be obtained on the same day as the lactate and L/P blood draws, collect the specimen for gastric aspirate prior to offering any food or drink.*

It is strongly recommended that site staff perform practice runs of sample collection and procedures for study visits with L/P and lactate collections in advance and prior to enrolling participants. Sites should designate staff, functioning as a team, to perform these collections and establish SOPs for L/P and lactate collections. This will help ensure that time and temperature requirements for both lactate and L/P assays are met and allow for efficient completion of all study visit procedures.

Prior to each visit with L/P collections, sites should carefully review the LPC for details on the following L/P steps:
- Participant Preparation
- Staff Preparation
- Specimen Collection
- Specimen Preparation

### 7.6.3 L/P Specimen Storage and Shipment

L/P samples will be shipped to ARUP laboratory in the U.S. for testing. Instructions for L/P specimen storage and shipment are provided below. Please see Figures 7-1 through 7-3 for ARUP L/P collection tubes, transport tubes, and bags for specimen transport.

- Store specimens at -20°C and ship frozen samples to ARUP in real-time. All samples collected within a one-week period (seven days) - may be "batched" and then must be shipped the next day. ARUP receives samples 24 hours a day, seven days a week.
- L/P specimen stability frozen is 30 days. Sites that require export permits to ship samples to ARUP should carefully track permit expiration dates and apply for renewals in advance to avoid shipping delays and ensure appropriate participant safety monitoring.
- Sites will use ARUP Requisition Forms, which have been customized for each site (including site name, barcode etc.) A PDF file of this form will be sent to each site from the ILC. These are to be completed and shipped with the specimens to ARUP. A generic ARUP Requisition Form is found in Appendix IV.
- Please observe the ARUP Specimen Labelling Policy in Appendix III and use the ARUP specimen transport bags (see Figure 7-3) supplied by the IMPAACT Lab Center (ILC) with the assay tubes.
• For additional details please review the ARUP Checklist on the P1108 study webpage: http://www.impaaactnetwork.org/studies/P1108.asp.
• Site accounts for L/P results reporting will be set up with ARUP Connect (see Section 7.6.4 below).
• Results should be available within two days following receipt of samples at ARUP and recorded on eCRF LBW0160 (P1108 Lactate-Pyruvate Ratio Results). Site staff are responsible for entering results on eCRFs per protocol Section 7.2. ARUP results may be downloaded, printed and retained as source documentation.

Figure 7-1
ARUP L/P Collection Tubes

Figure 7-2
ARUP Standard Transport Tube

Figure 7-3
ARUP Bag for Specimen Transport
7.6.4 Obtaining L/P Testing Results

L/P testing results may be obtained from ARUP Connect, a secure online system that provides registered ARUP clients with management of their referral testing. Each site should have at least two staff members designated for managing the site’s ARUP Connect account. For assistance in designating site staff to access the site-specific ARUP Connect account, please contact the protocol Lab Specialists.

For more information on the ARUP Connect system, including accessing site-specific accounts, requesting a test, responding to specimen issues and obtaining test results, please refer to the “ARUP Connect Information Sheet” on the P1108 study webpage.

7.6.5 L/P Results Classification

L/P results should be classified according to the following guidelines:

- **HIGH**: L-P ratio greater than 30, in the presence of elevated lactate ("elevated" is considered to be greater than the reported upper limit of normal)
- **LOW**: L-P ratio less than 25, in the presence of elevated lactate
- **INDETERMINATE**: L-P ratio could not be determined
- **NORMAL**: L-P ratio does not meet any of the above criteria

This classification should be recorded in Question 5 on the LBW0160 eCRF as shown in Figure 7-4.

![Figure 7-4](Image)

7.6.6 Local Lactate Testing

Local lactate testing will be done according to the assay protocol used by each site’s testing laboratory. In general, this testing requires:

- Samples are collected without the use of a tourniquet and hand-clenching avoided
- Collect whole blood using a Na-fluoride/K-oxalate or Na-fluoride/Na-heparin (gray top) tube
- Due to the instability of lactate in whole blood, processing steps are temperature and time sensitive

*Please follow the instructions provided by the site testing lab for all aspects of local lactate sample collection and processing.*
7.7 Biomarker Specimen Collection

Biomarkers (serum and urine) are collected for all participants at screening, entry (only if more than two weeks from the screening visit), Week 24 and Week 120 visits (see CM #1). As these specimens must be processed rapidly, it is important that clinic staff are familiar with the LPC specimen management procedures.

For collection of urine for TB biomarkers:
- Precautions must be taken to reduce cellular and microbial contamination that could prevent optimal results.
- Urine should be collected with the same care as when collecting a urine to diagnose bacterial urinary tract infections (UTIs), i.e. midstream collection after cleansing. However, for young children, invasive collection methods such as catheterization or suprapubic aspiration which are used to diagnose bacterial UTIs should not be used.
- If midstream specimens after cleansing cannot be obtained in young children, collecting the urine using a sterile urine bag, although not recommended for the diagnosis of UTIs, will therefore be allowed for TB biomarker research specimens.
- Disinfectants used as cleansers (benzalkonium or hexachlorophene) can interfere with the growth of some organisms causing a false negative result. Most references recommend liquid soap cleansers, rather than disinfectants, which do not significantly affect the common organisms causing UTI. Similarly, for TB biomarkers, disinfectants should not be used. Instead, use soap and water to clean the area before midstream collection or applying urine collection bag. Let the area dry after.
- Cotton wool balls, gauze and sanitary towels should not be used.
- The Desmond Tutu TB Centre urine SOP is available as an example at: https://www.dropbox.com/sh/tbdrcl7jw9boofc/AADZYIiVX4uBiTM4BWOSr6pVa?dl=0

7.8 Specimens for TB Testing

For P1108, 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 at sites used for each participant throughout the study duration. Ideally, the collection of early morning sputum (expectorated or induced) or overnight gastric aspirate after fasting (at least six hours, nil per mouth) should be encouraged as much as possible.


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

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

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

8.0 Pharmacy Considerations

For detailed information on study drug considerations in P1108, please refer to protocol Section 5.

8.1 BDQ Dosing

BDQ daily dosing is initiated at enrollment and should continue through the Week 2 visit. BDQ dosing three times per week on Monday, Wednesday and Friday should be initiated following the Week 2 visit and continued through the Week 24 visit. See LoA #2 for BDQ dosing for Cohorts 2 and 3.

Per protocol Section 5.2, Table 2A, BDQ dosing increases will be considered for children who enroll in the study weighing less than 30 kg and gain weight to be ≥ 30 kg during the 24 weeks of BDQ dosing in Cohort 1. The dose increase should be made in accordance with children weighing ≥ 30 kg and recorded in the participant’s study file and eCRFs.

In addition, following interim analyses, individual dose adjustments may be considered as clinically relevant, in consultation with the Core Team, clinical care provider, sponsor and IMPAACT Study Monitoring Committee as needed, to allow for appropriate individual clinical management. Individual dose adjustments should also be recorded in source documentation and eCRFs.

8.2 BDQ Administration

For participants who are able, BDQ should be swallowed whole, or cut as half a tablet, with 10-20 mL of water and taken with food. Instructions for crushing BDQ are provided in Appendix I of this manual for participants who are unable to swallow BDQ whole. Recommendations for care providers and DOT supporters on dispensing BDQ are also available in Appendix II.

When taken Monday, Wednesday, and Friday (TIW) during Weeks 3 – 24, there should be at least 48 hours between doses. If BDQ is administered less than 48 hours from the prior dose, it is important that the time of the preceding dose is entered in eCRFs.

Per protocol Section 5.3, if a participant misses a BDQ dose during the first two weeks on study, participants should not make up the missed dose but continue the dosing schedule. From Week 3 onwards, if a BDQ dose is missed, participants should take the missed dose as soon as possible and within 48 hours, and then resume the Monday, Wednesday, and Friday (TIW) schedule, maintaining 48 hours between doses. For example, if a dose is missed on a Wednesday and taken on Thursday, the next dose should be given on Saturday and Monday-Wednesday-Friday dosing would then restart the following week. If a BDQ dose is missed or administered less than 48 hours from the prior dose during Weeks 3 – 24, the reasons why this occurred, and corrective and preventive actions taken in response should be documented appropriately per Section 6.2 of this MOP.

BDQ and all routine TB drugs and ARVs will be administered by the research team on the day of PK sampling and on the previous evening, where relevant. BDQ, routine TB drugs and ARVs may be administered by routine personnel or caregivers on all other occasions.
BDQ should be given with food to assure better absorption. Food intake prior to BDQ dosing at the Week 2 intensive PK sampling should be documented in eCRF PKW0404, including the start time of the meal and the type (full meal or snack). Meals provided on PK sampling days should be standardized as much as possible at each site. Participants should avoid large fatty meals as this can impair absorption of some of the other anti-TB drugs (cycloserine/terizidone, isoniazid (INH), etc). The following order is recommended at study visits with PK sampling during Weeks 1 – 24: provide meal, administer BDQ, wait 10-20 minutes and then administer OBR and ARVs if applicable.

http://www.ncbi.nlm.nih.gov/books/NBK247434

8.3 Adherence

DOT is expected to be used for BDQ administration throughout the study, per local guidelines. The exact time of BDQ dosing on the two days prior to study visits with PK sampling will be recorded on eCRFs. BDQ will be directly administered by the research team on the day of PK sampling.

Sites should work closely with participants and/or parents/caregivers and with hospital personnel, as relevant, to ensure adherence and provide them with resources to document dosing of BDQ, OBR and ARVs, as appropriate. As an element of activation, each site is required to submit for team review an SOP on ensuring adherence and DOT.

8.4 Concomitant Medications

All participants receiving high-dose INH as part of their OBR regimen will receive Vitamin B₆ (pyridoxine), provided by sites per local standard of care. All TB medications, Vitamin B₆ and ARVs should be recorded in eCRFs. A log of all concomitant medications, including non-TB and non-ARV medications, should be documented in each participant’s study file and entered into eCRFs consistent with protocol specifications and applicable form instructions. Refer to protocol Section 5.7 for guidance on prohibited and precautionary medications in P1108 (see CM #1, LoA #1 and LoA #3). Based on the potential risks of BDQ, all sites should closely monitor participants taking concomitant medications that are potentially QTcF prolonging and consult the Core Team regarding the clinical management of any such participants.
9.0 Expedited Adverse Event Reporting to DAIDS

Refer to protocol Section 7 and the following resources to guide expedited adverse event (EAE) reporting for P1108:

- DAIDS Table for Grading Adult and Pediatric Adverse Events (DAIDS Toxicity Table), Corrected Version 2.1, dated July 2017: [https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables](https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables)
- DAIDS Safety Training Resources: [https://rsc.niaid.nih.gov/clinical-research-sites/safety-training-resources](https://rsc.niaid.nih.gov/clinical-research-sites/safety-training-resources)
- Package insert for BDQ

*Note:* It is the responsibility of the IoR and designated study staff to review and be informed of the current package insert for BDQ and any updates during the study.

9.1 Selected Definitions

Key definitions associated with EAE reporting in P1108 are provided below. Refer to the Manual for Expedited Reporting of Adverse Events to DAIDS for additional terms and definitions.

**Adverse event (AE)** The AE definition specified in protocol Section 7 applies to infants, children and adolescents enrolled in P1108 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 P1108 must be source documented in participant study files, including the severity of the AE and its relationship to BDQ assessed by the IoR or their designee.

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

**SUSAR**

Suspected unexpected serious adverse drug reaction

SUSARs are SAEs that are assessed as both suspected and unexpected:

- **Suspected** = related ⇒ there is a reasonable possibility that an AE may be related to an investigational agent
• **Unexpected** ⇒ 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 9-1, SAEs are a subset of all AEs, and SUSARs are a subset of all SAEs.

**Figure 9-1**
Adverse Event, Serious Adverse Event, and SUSAR Subsets

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

### 9.2 EAE Reporting Requirements

For infants, children, and adolescents enrolled in P1108, SAEs as defined in Version 2.0 of the DAIDS EAE Manual, should be reported as EAEs per protocol Section 7.3.

The EAE reporting period for this study is the entire study duration of follow-up for an individual participant (from study enrollment until study completion or discontinuation of the participant from study participation for any reason). SAEs as defined in Version 2.0 of the DAIDS EAE Manual must be reported as EAEs.

*Note:* The severity of all AEs identified in this study — except QT interval grading and grading of cardiac symptoms related to cardiac conduction abnormalities (see protocol Appendix V) — will be graded according to the Corrected Version 2.1 of the DAIDS Toxicity Table, dated July 2017 (see LoA #1).

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

For purposes of *AE or toxicity management*, as specified in protocol Section 8, the IoR or designee must assess the relationship of all AEs identified in enrolled participants to BDQ according to the categories shown in Figure 9-2. The categories are also used when recording AEs on eCRFs.

**Figure 9-2**
Relationship Assessment Categories for Toxicity Management

<table>
<thead>
<tr>
<th>Relationship Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely related</td>
<td>The event and administration of the medication are related in time, and a direct association can be demonstrated.</td>
</tr>
<tr>
<td>Probably related</td>
<td>The event and administration of the medication are reasonably related in time, and the event is more likely explained by the medication than other causes.</td>
</tr>
<tr>
<td>Possibly related</td>
<td>The event and administration of the medication are reasonably related in time, and the event can be explained equally well by causes other than the medication.</td>
</tr>
<tr>
<td>Probably not related</td>
<td>A potential relationship between the event and the medication could exist (i.e., the possibility cannot be excluded), but the event is most likely explained by causes other than the medication.</td>
</tr>
<tr>
<td>Not related</td>
<td>The event is clearly explained by another cause not related to the medication.</td>
</tr>
</tbody>
</table>

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

**Figure 9-3**
Relationship Assessment Categories for EAE Reporting

<table>
<thead>
<tr>
<th>Relationship Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Related</td>
<td>There is a <em>reasonable possibility</em> that the EAE may be related to study-supplied BDQ. Consistent with ICH guidance, the term “reasonable possibility” is intended to convey that there are facts, evidence, or arguments to suggest a causal relationship between the EAE and study-supplied study drug. Facts, evidence, and arguments that may support a reasonable possibility of a causal relationship include:</td>
</tr>
<tr>
<td></td>
<td>- A temporal relationship between the EAE and use of the BDQ</td>
</tr>
<tr>
<td></td>
<td>- A plausible biologic mechanism for the BDQ to cause the EAE</td>
</tr>
<tr>
<td></td>
<td>- Previous reports of similar events associated with BDQ</td>
</tr>
<tr>
<td></td>
<td>- Resolution of the event after de-challenge (hold/discontinuation of BDQ)</td>
</tr>
<tr>
<td></td>
<td>- Recurrence of the event after re-challenge (resumption of BDQ after a hold)</td>
</tr>
<tr>
<td></td>
<td>Other potential causes of the EAE (e.g., past medical history, concurrent illness, concomitant medications) should also be considered when assessing whether there is a reasonable possibility that an EAE may be related to study-supplied BDQ.</td>
</tr>
<tr>
<td>Not related</td>
<td>There is <strong>not</strong> a reasonable possibility that the EAE may be related to BDQ.</td>
</tr>
</tbody>
</table>
Figure 9-4 presents how the five relationship categories used for AE or 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>

### 9.4 EAE Reporting Procedures

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

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

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

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

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

DAERS incorporates a report printing function that should be used to print all EAE reports — including modifications and updates — for filing in participant study records. Automated email messages confirming submission of EAE reports also should be printed and filed with the print-out of the associated EAE report.
For questions about DAERS, email CRMSSupport@niaid.nih.gov. Questions may also be submitted from within the DAERS application itself.

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

10.0 Clinical Management Considerations

Refer to protocol Section 8 for participant management considerations, including management of AEs. At each follow-up visit, study clinicians must assess whether any additional evaluations are clinically indicated.

10.1 Cardiac Safety Monitoring

As QT prolongation and/or potential QT interval effects can be caused by BDQ alone and together with the use of other drugs for treatment of MDR-TB (e.g. levofloxacin and clofazimine), cardiac safety will be closely monitored in P1108. Sites should carefully monitor electrolyte levels of participants with diarrhea or vomiting, as low electrolytes can increase cardiac risk, and continue to provide participant education on signs and symptoms of possible BDQ side effects. Consultation with the protocol cardiologist is available and encouraged for any abnormal or equivocal ECG findings and/or questions related to cardiac toxicities and assessment.

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

- **Investigator Manual**: Provides guidance on implementation of the ECG machine, the ECG transmission process, accessing the IQVIA Web Portal (https://infosario.quintiles.com), and site staff responsibilities for P1108.
- **Visit Code Poster**: Provides a list of visit codes to use while obtaining ECGs.
- **Quick Reference Guide**: Highlights important reminders to conduct ECGs throughout the study.

A training CD-ROM is also included in the materials shipped with the ECG machine from IQVIA. All site staff who are conducting and/or transmitting participant ECGs in P1108 are required to complete the training and print a certificate documenting completion of the training, which should be filed in site essential document files for P1108. For any questions or problems with the IQVIA Web Portal, ECG machine and materials, sites may contact the IQVIA Helpdesk via email: eecg.helpdesk@quintiles.com

Details on obtaining ECGs are provided in the IQVIA Investigator’s Manual and Visit Code Poster. Please refer to protocol Appendix VI-VIII for details on grading and management of ECG and clinical cardiac toxicities. Study-specific pediatric ECG training is also available on the P1108 study webpage: [http://impaactnetwork.org/studies/P1108_SudyDocs.asp](http://impaactnetwork.org/studies/P1108_SudyDocs.asp)
10.1.1 ECG Monitoring and Clinical Management

Due to inherent challenges in obtaining an accurate ECG reading in pediatric populations, ECGs in P1108 are conducted in triplicate, ideally by the same site staff member. Triplicate ECGs should be completed consecutively with a minimal time (seconds to minutes) between each; however, there is no specific required time between ECGs. A recommended approach would be to allow one minute between each ECG (i.e. the third ECG should be completed within approximately five mins of the first).

For each ECG evaluation, ECGs should be immediately transmitted to IQVIA. The centralized ECG read from IQVIA will be available within 72 hours and sent to the site and posted to the study-specific IQVIA Web Portal. ECG reports transmitted to IQVIA will also be reviewed by the protocol cardiologist.

Per protocol, identification of AEs and immediate appropriate clinical management will be determined based on the site’s real-time ECG reading of the mean QT interval (see CM #4). As applicable, sites should notify the Core Team of cardiac toxicities per Section 3.1 of this MOP and protocol Appendices V and VI. Sites should not wait the centralized ECG read to determine appropriate clinical management or notify the Core Team as required per protocol. Following receipt of the centralized ECG reading, further clinical management should be performed based on the AE grade from the centralized ECG read.

10.1.2 ECG Assessment During Screening and Entry Visits

All potentially eligible participants for P1108 will have an ECG performed at screening and entry visits. ECGs conducted at these visits should be performed in triplicate and a mean value of the QTcF interval manually calculated using the Fredericia correction to confirm eligibility per exclusion criterion 4.2.5.

Per CM #4, the centralized ECG read should be used for determination of final grading for all protocol-specified ECG evaluations, including ECGs performed as part of study eligibility determination (see protocol Sections 4.2.5 and 4.2.6).

At the Entry visit, sites should confirm that potential participants meet the study eligibility criteria, including cardiac-related criteria, as specified in protocol Sections 4.1 and 4.2 prior to enrollment as part of final eligibility determination. For participants who are confirmed eligible and enroll in the study, any identified cardiac-related signs, symptoms, and/or diagnoses at Entry should be entered on appropriate eCRFs as baseline (pre-existing) conditions.

10.1.3 ECG Assessment During Follow-Up Visits

Following enrollment, participants should have an ECG performed at Weeks 2, 4, 8, 12, 16, 20, 24, and 40 visits. At the Week 2 visit (intensive PK visit), ECGs will be performed close to the baseline PK sampling (within 1 hour) and at 4-6 hours after BDQ administration. For participants that stop taking BDQ prior to Week 24 or prematurely discontinue the study, an ECG should be performed at the Early BDQ Discontinuation (D/C) or Early Study Discontinuation visit, respectively. ECGs conducted at all follow-up visits should be performed in triplicate, and a mean value of the QTcF interval manually calculated using the Fredericia correction. ECGs at each visit should be immediately transmitted to IQVIA.
10.1.4 eCRF Guidance for ECGs and Cardiac Toxicities

ECG and cardiac-related signs, symptoms, or diagnoses that meet eCRF safety-related recording requirements per protocol Section 7.2 should be entered on appropriate eCRFs as AEs within 48 hours of availability of the relevant clinical findings and test results. As indicated above, identification of AEs and immediate appropriate clinical management will be determined based on the site’s real-time ECG reading of the mean QTcF interval. Refer to protocol Appendices V and VI for grading and management, respectively, of ECG and clinical cardiac toxicities (see CM #3).

ECG results for all follow-up visits should be entered in eCRF DGW0112, along with the grade of the mean QTcF interval, and any cardiology consultation and clinical actions taken. Following receipt of the centralized ECG read, sites should review and confirm that the grade for ECG AEs entered in the study database is consistent with the grade based on the centralized read. If there is an inconsistency, the eCRF should be updated to reflect the grade per the centralized ECG read for the study analyses (see CM #4).

Example: At the Week 4 visit, a participant has a grade 3 mean prolonged QTcF interval based on the site ECG reading. Per protocol, BDQ and fluoroquinolone (if applicable) would be temporarily held and the ECG would be repeated within 72 hours and the Core Team notified. The BDQ treatment interruption and ECG grade per the site reading would be recorded on applicable eCRFs within 48 hours. Subsequently, the centralized ECG read evaluates the mean prolonged QTcF interval as grade 2. Site staff would then update eCRFs to reflect the centralized ECG read (grade 2) and consult the Core Team regarding clinical management and resuming study drug. All ECG results and associated grading, clinical management, study drug start and stop dates, and consultation with the Core Team must be documented in the participant’s file.

10.2 Contraception and Pregnancy

BDQ is considered Pregnancy Category B. Therefore, any female potential participant of reproductive potential and engaging in sexual activity that could lead to pregnancy must agree to use at least two contraceptive methods as specified in inclusion criterion 4.1.10 throughout study participation to be eligible for the study. Additionally, per protocol inclusion criterion 4.1.9, female potential participants of reproductive age must have a negative pregnancy test within 48 hours prior to enrollment. Any male potential participant engaging in sexual activity that could lead to pregnancy of a female partner must agree to use a barrier method of contraception (i.e. male condom) throughout the first 28 weeks on study (i.e., until four weeks after discontinuation of BDQ), per inclusion criterion 4.1.8. Please refer to protocol Section 8.8 for further guidance on contraception and pregnancy in P1108.

10.2.1 Contraceptive Counseling

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

If an adolescent participant undergoes postpartum surgical sterilization (e.g., hysterectomy, bilateral oophorectomy, tubal ligation, salpingectomy or vasectomy) she/he does not require the use of a contraceptive method to prevent pregnancy; however, these participants should continue to be reminded to use condoms to prevent acquisition/transmission of sexually transmitted diseases.
Because the potential effects of BDQ on sperm are unknown, pregnancies in partners of male participants will be reported per protocol Section 8.8. Male participants of reproductive potential should be queried as part of standard contraceptive counseling about whether a sexual partner has become pregnant during the study. If the outcome of the pregnancy is not known at the time the participant exits the study, study staff should continue to contact the participant until this information is available.

10.2.2 Pregnancy

Female adolescent participants of reproductive potential who have not undergone surgical sterilization (e.g., hysterectomy, bilateral oophorectomy, tubal ligation, or salpingectomy) should have a pregnancy test performed per the protocol SoE and when pregnancy is suspected or considered clinically indicated during follow-up (see LoA #1). If a female participant becomes pregnant during the study, BDQ should be discontinued and the participant continue study follow-up per the protocol. If the outcome of the pregnancy is not known at the time the participant exists the study, study staff should continue to contact the participant until this information is available.

10.3 TB Testing, Monitoring, and Treatment Outcome

10.3.1 Tuberculin Skin Test (TST)

For all potential participants, TST should be performed at screening to evaluate M. tb. infection status. If TST is not available on site, Interferon-Gamma Release Assay (IGRA) may be used for this evaluation (see Section 10.3.2 below). For participants with a negative TST at screening, TST (or IGRA) should be done at the Week 8 visit as well.

Each site should have its own site-specific SOP in place for the TST procedure. At a minimum, site-specific SOPs should include the following:

• Product information, including storage conditions
• Equipment required
• Procedure for preparing the syringe
• Procedure for administration of intra-dermal injection, including corrective actions
• Procedure for reading and recording outcome (documented in mm)
• Risks and contraindications
• Staff training on TST placement and reading completed

A positive TST is defined as follows:

• HIV-1-uninfected: An induration of ≥ 10 mm and no redness
• HIV-1-infected: An induration of ≥ 5 mm and no redness

10.3.1.1 Administering and Reading the TST

A Mantoux TST of purified protein derivative (PPD) will be administered. A CDC podcast, which includes guidance on administering and reading the TST, can be accessed at:

http://www2c.cdc.gov/podcasts/browse.asp?exactMatch=1&topic=TB+Skin+Test&formsButton=Go%21

Site should follow locally applicable procedures and guidelines for administration of TST. If local guidelines are not available, sites may follow procedures as described in the Clinical Policies and Protocols of the Bureau of Tuberculosis Control of the New York City Department of Health and Mental Hygiene: https://www1.nyc.gov/assets/doh/downloads/pdf/tb/tb-protocol.pdf
10.3.1.2 Reading and Interpreting TST Reaction

The TST result should be read only by a trained site investigator. Participants may not be allowed to read their own reaction. The following procedure should be used to read the reaction:

- Read the result ideally two-three days after placement and no later than seven days from administration.
- Inspect the injection site for raised areas.
- Palpate the arm for a hard, raised area known as an induration. Feel the edges of the induration with the index finger.
- Mark the two edges of the induration with a dot, using a black, watermark pen, if available.
- Measure the induration (not redness) at its widest point transversely, from one marked edge to the other, using a flexible transparent TST ruler. If the reading is between two points, the lower value should be used. Swollen areas, if they feel hard, (but not red areas) should be palpated and included in the measurement.
- Record the size in millimeters and not simply as “positive” or “negative”. If there is no induration, record the result as “00 mm.”
- Interpret the reaction as positive or negative based on the size of the induration (≥ 5mm in HIV-1-infected or ≥ 10mm in HIV-1-uninfected participants).
- Explain the meaning of a positive or negative reaction to the participant and/or their caregiver and refer for follow-up evaluation, if needed.
- A negative TST does not exclude active TB disease. A negative TST should be repeated per the protocol requirements and per discretion of the site investigator.

NOTE: If the participant fails to return for the scheduled reading but returns up to a week (seven days) after the test, examine the test site and measure any induration present; if it is large enough to be classified as positive, record the result. No further testing is needed. If there is no reaction, there is no need to repeat the test. If the induration is too small to be classified as positive, record the diameter and repeat the test, if feasible. A repeat test can be given immediately.

10.3.2 Interferon-Gamma Release Assay (IGRA)

Per protocol, if TST is not available at sites, IGRA may be done. If needed, IGRA testing using QuantiFERON®-TB Gold Plus test (QFT-Plus®) will require an additional 4 mL of blood to be collected at applicable study visits (see LoA #3). For further information on IGRA collection and processing, refer to the P1108 LPC and IMPAACT and ACTG Cross-Network QFT-Plus SOP on the HANC website at: https://www.hanc.info/labs/labresources/procedures/ACTGIMPAACT%20Lab%20Manual/QFT%20Plus%20SOP_v1.0.pdf
10.3.3 Centralized Chest X-Ray

Chest X-rays (CXRs) are performed for all participants at screening and at Weeks 8, 16 and 24 visits. For all other follow-up visits, Early BDQ Discontinuation and Early Study Discontinuation visits, CXRs should be performed if clinically indicated until the end of TB treatment, which may be up to 18 months after the first negative culture depending on the extent of disease and the treatment prescribed as per local standard of care (see protocol Sections 6 and 8.5). CXRs should be uploaded to the Frontier Science Foundation File Exchange Utility, as outlined below for centralized review.

Sites should upload all CXRs collected for each participant, beginning with images from the screening visit. All images should be uploaded as soon as possible after the visit.

1. To prepare the CXR for uploading:
   - Redact any personal identifying information (name, date of birth, hospital number) from the image.
   - 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.
   - Save the file on the computer used to access the exchange utility.
   - Save each image file you plan to upload using the following naming conventions:

   \[
   \text{P1108_PID_dateofCXR_view}
   \]
   \[
   \Rightarrow \text{PID} = \text{participant ID}
   \]
   \[
   \Rightarrow \text{dateofCXR} = \text{date the X-ray was taken (this same date is recorded on the eCRF)}
   \]
view = use AP for antero-posterior view, LAT for lateral view, PA for posterior-anterior view.

All this information must match the eCRF

2. Go to the Frontier Science Foundation portal to upload image files: [https://www.frontierscience.org](https://www.frontierscience.org).

3. Make sure you are signed into the Frontier Science Foundation 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 Frontier Science Foundation portal and click on File Exchange Utility under the Utilities heading.

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

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

TB treatment outcomes in children with bacteriologically confirmed RR/MDR-TB, specified in protocol Section 8.5, will be defined as bacteriological cure, probable cure, treatment failure, and death. 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.) per the judgment of the site investigator or designee. Attainment of radiological improvement will indicate significant improvement in radiographic findings in children with intrathoracic TB, in the judgment of the site investigator or designee. TB outcome classifications are provided in Table 10-1 and Table 10-2.

Table 10-1
Classification of Treatment Outcomes for Children with Bacteriologically Confirmed MDR-TB

<table>
<thead>
<tr>
<th>Bacteriological outcome</th>
<th>Clinical/radiological outcome</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three consecutive negative respiratory cultures obtained at least one month apart, i.e. at least four study weeks, with no positive culture result after the first negative result in the last 12 months of treatment after initiation of TB therapy</td>
<td>Completion of TB treatment with clinical/radiological improvement in the assessment of site investigators by the Week 24 visit, not meeting criteria for treatment failure AND no recrudescence of clinical/radiological criteria for TB (prior to the Week 120/End of Study visit)</td>
<td>Bacteriological Cure</td>
</tr>
<tr>
<td>Bacteriological Cure criteria above is not met (for those with confirmed MDR-TB at entry and/or at screening), and do not meet criteria below for Treatment Failure</td>
<td>AND Completion of TB treatment with clinical/radiological improvement in the assessment of site investigators by the Week 24 visit AND no recrudescence of clinical/radiological criteria for TB prior to the Week 120/End of Study</td>
<td>Probable Cure</td>
</tr>
<tr>
<td>Culture positivity (positive culture at the Week 24 visit and after starting treatment until completion of treatment)</td>
<td>OR Insufficient clinical/radiological improvement after the Week 24 visit or more on treatment or recrudescence of clinical/radiological criteria for TB while on treatment</td>
<td>Treatment Failure</td>
</tr>
<tr>
<td>Any bacteriological outcome</td>
<td>AND Death for any reason while on MDR-TB treatment or at any point prior to the Week 120/End of Study visit after start of study regimen</td>
<td>Death</td>
</tr>
</tbody>
</table>

*Contaminated samples or indeterminate results will not be counted in determining whether negative results are consecutive (e.g., if two consecutive culture results are both negative, followed by a contaminated result and subsequently a negative result, then the participant meets this criterion).
**Table 10-2**

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

<table>
<thead>
<tr>
<th>Clinical/Radiological Outcome</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completion of TB treatment with clinical/radiological improvement in the assessment of site investigators by the Week 24 visit AND no recrudescence of clinical/radiological criteria for TB prior to the Week 120/End of Study visit.</td>
<td>Probable Cure</td>
</tr>
<tr>
<td>Insufficient clinical/radiological improvement after the Week 24 visit or more on treatment or recrudescence of clinical/radiological criteria for TB while on treatment</td>
<td>Treatment Failure</td>
</tr>
<tr>
<td>Death for any reason while on MDR-TB treatment or at any point prior to the Week 120/End of Study visit after initiation of study regimen</td>
<td>Death</td>
</tr>
</tbody>
</table>

*Notes: Clarifications on the criteria may be included in the P1108 TB Treatment Outcome Endpoint Review Process Document.*
APPENDIX I: Bedaquiline (BDQ) Tablet Splitting Instructions for Administration in Children

The study participant or caregiver should be instructed on how to split BDQ tablets if needed to obtain the desired dose per dosing instructions by the site pharmacist and other study personnel to ensure participant safety and minimize chance of error and adverse events. A tablet splitter/cutter should be provided to participants and/or their caregivers where possible.

The designated, trained study staff should ensure that the participant and/or the participant’s caregiver:

1. Understands the purpose of splitting BDQ tablets if needed.
2. Understands the intended BDQ dose and treatment regimen.
3. Is physically able to easily and accurately split the BDQ tablet into two equal parts. The designated, trained study staff should demonstrate the use of a tablet cutting device (pill cutter).
4. Is encouraged to report any problems with splitting the tablets or taking the split tablets to the site study clinician, site pharmacist or other relevant staff member.
5. Understands the purpose and process of dispersing the tablet, if needed.

Tablet cutter instructions:
1. Insert the 100 mg tablet into the tablet cutter provided by the study team.
2. Place the tablet facing up on the “V” shaped holder of the tablet cutter.
3. Position the tablet such that the tablet is in line with the blade and the tablet can be cut into two equal halves.
4. The pill cutter works better if held vertically (to keep the tablet in place).
5. Close and press cover to split tablet.
6. Open and remove the split tablet.
7. Do not administer the unused half to study participants, but do not discard it either. The site may need to provide an alternate container to the participant for disposal of unused half tablets. The half tablets should be returned to the pharmacy for study drug accountability and destruction.
8. After cleaning, close the cover and store in closed position.
9. Store the tablet cutter in a secure place away from children as the cutter is sharp and must be handled with care.

Tablet cutter cleaning instructions:
1. After each use, wash with clean water, preferably warm, clean water to remove any leftover powder or particles.
2. Open tablet cutter about halfway.
3. Flush tablet cutter with clean water, preferably warm, clean water, to rinse.
4. Stand the tablet cutter on end in a partially open position to air dry in a secure place away from children.
APPENDIX II: Recommendations for Caregivers and DOT Supporters for Using BDQ in Children

1. General Instructions and Safety Information
   Your child will take BDQ through the Week 24 visit on study. Initially, your child will take BDQ once a day for two weeks. After two weeks, your child will only take BDQ three times a week, on Mondays, Wednesdays and Fridays for 22 weeks. It is important that BDQ be stored away from children so that they do not accidentally take a BDQ dose that is not meant for them and so that they do not overdose. If parents or caregivers have any questions or instructions about these instructions, please contact the P1108 study staff.

2. Should my child eat before taking the BDQ tablets?
   a. Your child should take BDQ study medication with a light meal, e.g. breakfast.
   b. Your child should not take BDQ on an empty stomach.
   c. The recommended sequence would be to provide food first, administer BDQ, then wait 10-20 minutes before taking other medicines.

3. What should I do if my child cannot swallow the BDQ tablets?
   a. The BDQ tablet should be mixed in water using an oral syringe, ideally capped or using a plastic dosing cup, depending on what is available locally. It is important that the rinse is completed for the syringe or the dosing cup method, whichever is used. Please note that 1 tablet of BDQ = 100 mg. Please see instructions below in #4.
   b. The dosing cup should have volumes indicated on the side (e.g. 10, 20, 30, 40 and 50 mL)
   c. The oral syringe or the dosing cup may be re-used as long as it is carefully washed after each use.
   d. Oral syringes and dosing cups will be provided by the study staff.
   e. Oral syringe sizes, dosing cups and the amount of water to be used will depend on the number of tablets taken as follows:
      - For ½ to 1 BDQ tablets, use an appropriately sized oral syringe with 10 mL clean water, or an appropriately sized dosing cup (should be able to hold more than 10 mL of fluid).
      - For 1 ½ to 2 BDQ tablets, use an appropriately sized oral syringe with 20 mL clean water, or an appropriately sized dosing cup (should be able to hold more than 20 mL of fluid).
      - For 3 to 4 BDQ tablets, use an appropriately sized oral syringe or an appropriately sized dosing cup (should be able to hold more than 40 mL of fluid) with 40 mL clean water. In general, 10 mL clean water should be used to mix every 1 tablet of 100 mg BDQ.
   f. No other medicines should be mixed in the water together with BDQ

4. How to use the oral syringe to disperse and dose BDQ:
   a. Remove the syringe cap
   b. Remove the syringe plunger
   c. Put the required tablets into the syringe
   d. Replace the syringe plunger
   e. The volume of clean water required is as follows:
      - For ½ to 1 tablet, draw up 10 mL of clean water
      - For 1 ½ to 2 tablets, draw up 20 mL of clean water
      - For 3-4 tablets, draw up 40 mL of clean water
   f. Place the syringe cap back on the syringe
   g. Shake gently for 4 minutes to disperse BDQ tablet(s) and check that you do not see any remaining unmixed tablet. If you do, continue shaking for 4 more minutes until completely mixed
   h. Remove the syringe cap and administer the entire volume to the participant
   i. Draw up an extra 10 mL clean water and place the syringe cap back on the syringe
   j. Gently shake the syringe to mix any remaining medication left in the syringe
5. How to use the dosing cup to disperse and dose BDQ
   a. Use an appropriately sized dosing cup
   b. The volume of clean water required is as follows:
      - For ½ to 1 tablet, put 10 mL of clean water in the dosing cup
      - For 1 ½ to 2 tablets, put 20 mL of clean water in the dosing cup
      - For 3-4 tablets, put 40 mL of clean water in the dosing cup
   c. Swirl the cup for a minimum of 4 minutes to disperse BDQ tablet(s) and check that you do not see any remaining unmixed tablet in the dosing cup. If you do, continue swirling until completely mixed (not longer than 10 minutes in total). The clean handle of a metal utensil (spoon) may be used to stir or break up the tablet if needed.
   d. Administer the entire volume to the participant
   e. Draw up an extra 10 mL clean water and put into the dosing cup
   f. Gently swirl the cup to mix any remaining medication left in the cup.
   g. Administer this rinse to the participant. If any remaining residue, repeat the rinse one more time.
   h. Clean and dry the dosing cup.
   i. Give the medication as soon as possible after preparation, and not longer than 10 minutes after it has been prepared

6. BDQ can be taken with any of the following beverages (drinks):
   a. Water that is clean and safe to drink (If necessary, clean water will be provided by the study staff for the purposes of this study)
   b. Note: Warm or fizzy drinks (for example: soda, hot tea etc.) MUST NOT be used to take BDQ.

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

8. What do I do if my child only needs half a BDQ tablet?
   If your child only needs to take a half of a tablet, you will need to cut the tablet. The study staff will show you how to do this.

9. Can I cut several BDQ tablets in half and put them back in the bottle, so I do not have to cut them every day?
   No, the BDQ tablets should not be cut in half. BDQ tablets should only be cut when needed immediately prior to administration. Keep all BDQ away from children. Place the remaining half-tablets in the container provided by study staff.

10. What should I do if my child misses their dose of BDQ study medication?
    If your child misses a dose of BDQ during the first two weeks of treatment, your child should NOT make up the missed dose, but should continue the dosing schedule.

    From Week 3 onwards, if a BDQ dose is missed, your child should take the missed dose as soon as possible and within 48 hours (2 days), and then resume the three times per week schedule (Mondays, Wednesdays, Fridays), maintaining 48 hours between doses.
Example: If a dose is missed on Wednesday and taken on Thursday, the next dose should be given on the Saturday. The following week restart the Monday-Wednesday-Friday dosing. It is important that at least 48 hours between doses is followed.

11. **What should I do if my child does not take the full dose of his/her BDQ medication?**
   You should encourage your child to complete the full dose, even if this is not immediate. Your child could take the rest of the dose within 2 hours to make up the full dose. Please notify the study staff as soon as possible if your child will not take the full dose.

12. **What should I do if my child vomits after taking his/her BDQ medication?**
   If your child vomits within 15 minutes of taking BDQ, you should try to give your child another full dose.

   If your child vomits more than 15 minutes after taking BDQ, you should **NOT** try to give your child another dose. Instead, be sure to write this occurred on the TB treatment card, notify the study staff and wait to give your child his/her next dose per the dosing schedule.

13. **Do the BDQ tablets need to be refrigerated?**
   No, BDQ tablets should not be kept in the refrigerator. BDQ tablets should be kept at room temperature or 15°C to 30°C (59°F to 86°F) and must be kept only in the plastic bottle that the study staff pharmacist gave them to you. The bottle should be kept tightly closed to protect the tablets from moisture and the desiccant pouches that were originally in the bottle should be kept in the bottle to keep the tablets dry. The BDQ study medicine bottle 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: ARUP Specimen Labeling Policy

Specimen Labeling Policy

In order to meet ARUP Laboratories specimen labeling requirements, please observe and implement the following:

A. All specimens received by ARUP Laboratories must be accompanied by corresponding test requisition forms/paperwork.

B. Each specimen must be labeled with patient name (first and last or unique coded name) AND a second unique identifier. Second identifiers commonly used are DOB and Medical Record Number. Please see the following example scenarios for labeling ideas if you only have one identifier for your specimens.

<table>
<thead>
<tr>
<th>Your single Identifier</th>
<th>Converted Acceptable Unique Identifiers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st Identifier</td>
</tr>
<tr>
<td></td>
<td>(i.e. patient name)</td>
</tr>
<tr>
<td>1200345AB1</td>
<td>1200345</td>
</tr>
<tr>
<td>1200346CD2</td>
<td>1200346</td>
</tr>
<tr>
<td>1200347EF3</td>
<td>1200347</td>
</tr>
<tr>
<td>Subject 1</td>
<td>Subject 1</td>
</tr>
<tr>
<td>Subject 2</td>
<td>Subject 2</td>
</tr>
<tr>
<td>Subject 2</td>
<td>Subject 2</td>
</tr>
</tbody>
</table>

C. All information provided on the specimen label MUST match information provided on the test requisition forms/paperwork i.e. 1st and 2nd identifiers must both be on the requisition and on the sample label. For filling out the requisition form, the 1st identifier can be written in the sample’s subject ID portion, the 2nd identifier can be written in the second identifier portion.

It is important to meet these labeling requirements so that:

i. Your specimens will be tested in a timely manner.

ii. Your specimens meet the requirements of our regulatory guidelines.

* It is advised to print copies of your requisition form rather than printing one and making copies because over time the barcode at the top of the form becomes distorted.

**If you would like to have any additional information (example: time point 1) appear on the report, please write “Chartable comment ‘time point 1’” in the lower blank portion of the requisition form.
APPENDIX IV: Sample ARUP Requisition Form
APPENDIX V: Digital Photographs of Chest X-Rays

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

Equipment
a. Light box – for viewing X-rays
b. Digital camera or tablet Connector
c. Battery charger for camera/tablet
d. Small tripod
e. Data/memory card

Procedure
1. Setting up the radiograph
   a. Confirm the information is available for the correct participant, left and right sides labelled correctly, date of CXR documented
   b. The CXR should be placed on the light box and the light switched on.
   c. Outside light entering the room should be minimized by drawing the curtain or switching off the overhead lighting. (Note the room does not need to be completely dark)
   d. Complete a card with the
      • participant’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 participant’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 participant study ID label and the entire radiograph.
   e. Make sure all identifying labels are covered (e.g. participant 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

   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.
### Figure V-2
Chest X-ray Examples

<table>
<thead>
<tr>
<th>GOOD QUALITY X-RAY</th>
<th>POOR QUALITY X-RAY</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Good Quality X-ray" /></td>
<td><img src="image2" alt="Poor Quality X-ray" /></td>
</tr>
<tr>
<td><img src="image3" alt="Participant details showing film on an angle" /></td>
<td><img src="image4" alt="Participant details showing over-exposed film" /></td>
</tr>
<tr>
<td><img src="image5" alt="Participant details showing too small film" /></td>
<td><img src="image6" alt="Participant details showing over-exposed film" /></td>
</tr>
</tbody>
</table>
Recommendations for taking digital photos with a camera:

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

2. Room and light box specifications
   a. The room should be able to turn the lights down
   b. The CXR image box should be a standard box with 2 light panels of approximately 15-20 watt fluorescent lights
   c. Only one light panel should be turned on
   d. The image can be improved by having a cardboard with a hole the size of the CXR
   e. Ensure the participant 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 VI: Sample Informed Consent Coversheet for IMPAACT P1108

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