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Expand New Drug markets for TB (END-TB)

Mid-term evaluation final report

Submitted to Unitaid
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Abbreviations

aDSM	Active TB drug-safety monitoring and management
AE	Adverse Event / Adverse Effects
AMR	Anti-Microbial Resistance
Bdq	Bedaquiline
CIS	Commonwealth of Independent States
DAC	Development Assistance Committee
DALY	Disability-adjusted life years
Dlm	Delamanid
DOT	Directly observed treatment
DST	Drug Susceptibility Testing
DPRK	Democratic People's Republic of Korea
ECG	Electrocardiogram
EMR	Electronic medical record
endTB	Expand New Drug Markets for TB (project name)
FQ	Fluoroquinolone
GDF	Global Drug Facility
GF	Global Fund
HICs	High-income countries
IRD	Interactive Research & Development
KPI	Key Performance Indicator
LMICs	Low- and middle-income countries
LTFU	Lost- to-follow-up
MDR-TB	Multi-drug resistant tuberculosis
MICs	Middle-income countries
MSF	Médecins Sans Frontières
MoH	Ministry of Health
MoU	Memorandum of Understanding
NGO	Non-Governmental Organisation
NTP	National TB Programme
OEDC	Organisation for Economic Co-operation and Development
O1/O2	Output 1/Output 2
PIH	Partners In Health
PSM	Procurement and Supply Management
MDT	Programmatic Management of Drug-resistant TB
PV	Pharmacovigilance
QALY	Quality-adjusted life years ¨
Q1/Q2 etc.	Quarter 1/ Quarter 2 (etc.) – relates to quarters in a year
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event

SLD	Second Line Drugs
SRA	Stringent Regulatory Authority
STAT	Scale-Up Treatment Action Team
Swiss TPH	Swiss Tropical and Public Health Institute
TA	Technical Assistance
TAG	Treatment Action Group
TB	Tuberculosis
ToC	Theory of Change
ToR	Terms of Reference
US$	Unites States Dollar
WHA	World Health Assembly
VfM	Value for Money
WHO	World Health Organisation
XDR-TB	Extensively drug resistant tuberculosis

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Executive Summary

In 2016, there were an estimated 10.4 million tuberculosis (TB) cases and 1.7 million deaths.[1] Of the estimated 600,000 new drug-resistant TB cases, only 22% were diagnosed and enrolled on Multi-Drug Resistant (MDR) TB treatment. The treatment cohort of 2014 showed a treatment success rate of about half (54%) with many who were lost to follow-up or died.

To address this situation, the Unitaid Executive Board approved the "Expand New Drug Markets for TB" grant (henceforth "endTB grant"). This grant of US$ 60.3 million for a period of four years from April 2015 to March 2019 is being implemented by Partners In Health (PIH) together with Médecins Sans Frontières (MSF) and Interactive Research & Development (IRD) as consortium partners. The grant uses the new TB drugs bedaquiline (Bdq) and delamanid (Dlm) to help improve treatment outcomes for MDR-TB in 17 countries (Armenia, Bangladesh, Belarus, Democratic People's Republic of Korea (DPRK), Ethiopia, Georgia, Haiti, Indonesia, Kazakhstan, Kenya, Kyrgyzstan, Lesotho, Myanmar, Pakistan, Peru, South Africa, and Viet Nam).

Key outputs of the endTB project include an observational study of the use of new MDR-TB drugs (Bdq and Dlm) in eligible MDR-TB patients, and a clinical trial to find simpler, less toxic, and more effective ways to treat MDR-TB. Evidence generated from both these outputs is considered key to addressing the challenges in treating patients with drug-resistant TB.

The objectives of the evaluation are to provide Unitaid with a detailed assessment of the **programmatic progress** of the endTB grant and with recommendations to Unitaid and PIH to improve the grant implementation by the grantee and its consortium partners. In addition, in co-production with the consortium partners, the evaluators constructed a grant-specific **theory of change** in the context of the global World Health Organisation (WHO) End TB strategy and Unitaid's strategy 2017 – 2021 and developed an **impact framework** (covering both direct and indirect impact).

Data collection methods for the programmatic and country progress assessment included a desk review of the relevant documentation, interviews, meetings with the implementing partners and visits to endTB project countries.

Output 1 (O1) enrols patients on treatment containing bedaquiline and/or delamanid and in an observational study. It is on track to reach its targets on enrolment. In some countries, there was some delay with the implementation because of obtaining permission to conduct the study and to import the new medicines. The data generated by this study will have good potential to contribute to revisions of the WHO policy recommendations in July 2018 and thereafter.

Output 1 also includes the development of an electronic medical record (EMR); reporting mechanisms for pharmacovigilance (PV) and the development of a model for provision of MDR-TB services in the private sector for Bangladesh, Indonesia and Pakistan.

The consortium developed the EMR which is operational in 16 of the 17 project countries. However, the EMR serves more as a research database than as a tool for patient

management and for programmatic reporting, and at least some of the national programmes do not have routine access to it.

The project contributed substantially to establishing and operationalising PV systems, both at health facility level and at national level.
The grantee implements the project in the private sector in Bangladesh, Indonesia and Pakistan, including linkages between the private and the public sector. The consortium has not yet documented their experiences into a model of care that others could use or adapt in their own setting.

Output 2 (O2) is a clinical trial with five experimental and one control arm. There was a one-year delay in the initiation of the trial activities mainly because the activities plan was very ambitious while the protocol development and approval by all relevant authorities, including in the trial countries, took much longer than anticipated. The duration of the study is prolonged, primarily due to a design change that resulted from including an internal control arm consisting of a WHO recommended MDR-TB treatment regimen (conventional of at least 20 months duration, or the shortened 9-11 months) and the follow-up period was extended to 104 weeks (from 65). This means that the trial results will only be available by March 2021.
The enrolment, scheduled to start in February 2016, only started in February 2017 and is currently behind schedule. There are no findings to report from this outcome yet.

Output 3 aims at reducing country-level barriers to scale-up the use of new TB drugs in all endTB countries by facilitating importation of new and companion drugs and assistance in adapting national clinical TB guidelines. Currently in most project countries there are no barriers to importation of new drugs, based on special waivers or exemptions. The national guidelines have been updated to include Bdq in 11 and Dlm in 8 out of the 17 endTB countries. In many of the endTB countries the endTB project was the first to start importation of the new drugs and this may have facilitated access to the new drugs for the other stakeholders within countries. Similarly, nine countries established country-wide PV systems, which, at least in some countries, could be attributed to endTB's introduction of PV at the project's sites. Other activities under this output are improving transparency and accountability of TB programs in relation to access to new TB drugs and ensuring sustainable financing and transition of new TB drugs and regimens by means of technical assistance. In most endTB countries, the new drugs are already included or are planned to be included in the funding requests to the Global Fund (GF). Improving transparency and accountability of TB programs is considered to be done via contributions to MSF/Stop TB Partnership "Out of Step" reports.

Output 4 is designed to provide supportive structures to facilitate the sharing of knowledge and dissemination of evidence that support the use of new TB drugs. As results of Output 1 and potentially Output 2 become available, endTB is planning on disseminating the clinical and programmatic findings. Collaboration with other groups and stakeholders takes place globally and in-country; however it can be strengthened and would be assisted by implementing the recently updated endTB communication strategy. endTB disseminates market intelligence information for new TB drugs and key companion TB drugs in collaboration with the MSF Access Campaign.

The grant ends in March 2019. Enrolment targets for O1 will have been met by September 2018, to have at least 6 months outcomes for participants in O1; however, enrolment targets for O2 may not have been met, and outcomes for O2 participants will mostly not be available.

By the end of the grant, the cohort in O1 will yield very important information on the use of the new medicines in countries, on their safety and their use in people with co-morbidities such as hepatitis C and diabetes mellitus. However, there will be no results from O2 on the effectiveness of novel regimens.

Assessing the project against Unitaid's standard evaluation criteria resulted in the following:

Relevance: rated as high

The project is well aligned with Unitaid's 2017-2021 strategy. It addresses an important public health problem and it contributes to the scale up of the use of new TB medicines and to developing new treatment regimens. endTB is also well aligned with the current (post-2015) Global TB Strategy to prevent, care for and control TB and global efforts to address antimicrobial resistance. In the landscape of trials on TB, endTB remains unique because of conducting a randomised controlled trial (RCT) with the new TB medicines, in addition to a large observational study of patients receiving Bdq, Dlm or the combination of the two.

Effectiveness: rated medium to high

The outputs of the grant are consistent with the objectives and the expected outcome to establish best practices for the use of new TB medicines and novel regimens through generated and shared evidence. The consortium is implementing the project within the allocated budget, although the consortium considers this budget may not be sufficient to meet the need of the revised O2 protocol. The substantial delay that the project experienced is the reason the effectiveness is not rated as "high".

Efficiency: rated as medium

The national authorities are involved to varying extents at different stages of the project and their involvement seems to differ depending on the implementing in-country partner. The emphasis of the project is on field activities rather than on the managerial architecture, and the grant implementation can benefit from improved financial management. Planning for continuation of Output 2 activities remains unresolved and has been a source of concern since the start of the grant.

Impact: rated as medium to high

The impact as measured by the goal indicator[1] is well on target; however much more impact is expected from potential policy recommendation based on the project's results when the data from O1 show good results on patient treatment outcomes and an acceptable safety profile. When O2 data become available in 2021 (on the assumption that the consortium will receive an extension), further impact is expected if the trial shows that the shorter regimens are not inferior to the current 20 months regimen, and less toxic. Because of the long timeline to results in MDR-TB treatment, an impact assessment is not meaningful at this stage primarily because information to assess impact, based on the assumptions and scenarios made at baseline, is not yet available. If the benefits of this grant materialize, they will continue well after the donor funding ceases. Public health and economic impact are to be established, the latter by means of an in-depth economic analysis. Such analysis can measure gains in the quality of life and Return on Investment. A qualitative assessment can also be carried out, or it can be a combination of quantitative and qualitative assessments.

[1] Indicator: number of patients who are newly enrolled to receive a new TB drug as part of their MDR-TB regimen in an endTB country within the reporting period.

Transition and scalability: rated as medium

endTB contributed significantly to the scale up by quick starting the importation of the new drugs, and providing clinicians with the training and practical experience of using the new drugs. Detailed transition and hand-over plans for the majority of the countries are not yet available.

Learning and risk mitigation: medium

Learning takes place within the consortium but there is no structured approach or a system using lessons learnt in the project cycle. The grantee will be responding to WHO's public call for individual patient data on treatment of rifampicin - and multidrug-resistant tuberculosis (MDR/RR-TB), which will be used to update the WHO treatment guidelines.

Over the course of grant implementation, a new Unitaid risk tool was developed. It is a tool for internal use which was applied for the first time in December 2017 and will be applied at least every six months. In addition, the endTB consortium updates a Risk Management Matrix every six months and submits it to Unitaid as part of routine reporting.

Recommendations

To Unitaid:

1. A decision on the future of the grant, specifically regarding O2, should be taken sooner rather than later. This is important because if continuation of O2 has implications on the trial design, the earlier decisions are made the better; and in addition, if such a design change were to occur, then continued enrolment may contribute to additional loss of investments.

2. For future grants, Unitaid may wish to take into consideration that grants including clinical trials which require protocol approval of another entity, and have a significant follow-up period, such as trials for MDR, need a substantial preparatory time before initiation of the trial. Such preparatory time should be included in the grant period. The importance of follow-up time for trials on MDR-TB is not only related to the duration of the treatment (current short regimen at least 9 months, often at least 20 months), but also that the trial should look into relapse rate for which a longer follow-up time is needed.

To Unitaid and the grantee:

3. To prevent further delays on O2, Unitaid should ask the grantee to present a clear enrolment plan, which shows when trial enrolment will be completed, taking into account the fact that Kyrgyzstan still did not start enrolling and that a new site needs to be prepared to replace Georgia.

4. Unitaid and the grantee should expedite resolving the data sharing issue such that data become available as soon as possible to influence Programmatic Management of Drug-resistant TB (PMDT) guidelines and through these improve the care to patients with MDR-TB. This applies to both the data on pharmacovigilance as well as the other data from the observational study.

5. The impact framework outlines relationships between endTB outputs, outcomes and the two impact areas: public health impact and economic impact. The impact framework is linked to the endTB specific Theory of Chane (ToC). endTB consortium is encouraged to maintain the ToC co-developed during this evaluation and adjust it as the project progresses, the clinical trials landscape alters, and the assumptions and contextual drivers change. Maintaining an up-to-date ToC will assist the economic analysis of the impact. Unitaid should consider an in-depth economic analysis as soon as possible, starting with establishing the methodology, model and collecting the required data.

To the grantee:

6. The grantee should use the remaining grant time optimally to transition the experiences gained from the project to national programmes or other relevant stakeholders. This includes several aspects:
    a. Continue working on including the use of the new medicines in national guidelines where this inclusion has not yet occurred [Bangladesh, Haiti, Indonesia (Dlm only), Kazakhstan, Lesotho, Myanmar, Peru (Dlm only)];
    b. Adapt the EMR to be better usable for clinical decision making and for programmatic needs; this means - amongst others - that the system should allow for missing variable (as a variable), be available to clinicians during their consultations, include alerts (such as ‘this patient is due for bacteriological examination’); and have downloadable reports that are aligned with (inter)national recording and reporting procedures. Currently the system is mostly used for project research purposes. National programmes should have access to their patient data without restriction (apart from the usual restrictions related to patient confidentiality).
    c. Provide targeted technical assistance (TA) in endTB countries, including TA to ensure sustainable financing and transition, preferably prioritizing the capacity building needs of the national and local staff. Develop a TA plan, based on the current gaps in capacity and foreseeing the knowledge and skills the in-country specialists will need in the near future to scale up the use of the new drugs.
    d. Develop transition and hand-over plans in line with country operational plans as soon as possible, as the project nears its completion. Such plans have to be developed with a special attention to two countries (Peru and DPRK) where no funders of new drugs have been identified. In Bangladesh, Indonesia and Pakistan this should also include provisions on how to continue the activities in the private sector. The grantee should use their experience in the private sector to document a model of care for use in the wider TB community.

7. The grantee should systematically analyse O1 data to identify any safety or effectiveness concerns related to the new medicines that would warrant more caution or even an interim analysis of O2. While at present there are no reasons to consider that the new medicines would have safety or effectiveness concerns, analysis of O1 data may reveal such concerns. If this occurs, the grantee should discuss with the scientific advisory committee if an interim analysis of O2 data is warranted. Furthermore, the grantee should explain very clearly how analysis of O1 is done, and by which subgroups to avoid overestimating the effect of the new medicines.

8. Have a more systematic approach to learning, and document lessons learnt. All consortium partners interviewed by the evaluators indicated great learning within the project, but lacked information on how this learning was systematically documented and how it influenced implementation or change of practices. Also, it was not clear if and how lessons learnt by one partner or from implementation in one country could benefit other partners and implementation sites. Documenting lessons learnt will help continue scaling up the use of the new drugs in endTB countries after the project completion and could benefit other (non-endTB) countries in the introduction and scale up of new drugs.

9. The consortium needs to apply and follow its communication strategy in order to improve in-country visibility, communicate clearly about the objectives and the approaches of endTB with in-country stakeholders, including proactive and systematic communication with the WHO country offices. This will reduce ambiguity and increase transparency which will positively contribute to collaboration in-country. The Output 2 sites need to develop their proactive communication and community engagement plans, also with the view of improving enrolment.

10. endTB are encouraged to use more structurally their approach to removing barriers and scaling up of new drugs in line with the six elements needed for introduction of new TB drugs, as per WHO Policy Implementation Package for New TB drugs[2]. One possibility is to collaborate with other global and/or in-country stakeholders to conduct a rapid assessment similar to the readiness assessment checklist of how well a country meets the minimum requirements for introduction of new TB drugs/regimens[2]. This may help identify and prioritize the remaining barriers and focus on a small number of high impact interventions to address them within the grant life-time. This applies especially to the countries that continue to experience problems with the new drugs' importation. The transition and hand-over plans should be informed by this rapid assessment results.

1 Project Background

In 2016, there were an estimated 10.4 million TB cases and 1.7 million deaths.[1] Of the estimated 600,000 new drug-resistant TB cases, only 129,000 people were diagnosed and enrolled on MDR-TB treatment. The treatment cohort of 2014 showed an overall treatment success rate of about half (54%; ranging from 34% in Peru to 91% in the DPRK) with many who were lost to follow-up (15%) or died (16%).
MDR-TB is caused by bacteria that are resistant to isoniazid and rifampicin – the two most potent first-line anti-TB medicines. MDR-TB patients require treatment with second-line drugs (SLD) to form treatment regimens that are more complex to administer, of longer duration, costlier and with more harmful side effects than those used to treat patients that are not resistant.

In May 2014, a global strategy to prevent, care for and control TB was endorsed and adopted by the World Health Assembly (WHA).[3] The Strategy marks a critical shift from controlling to eliminating TB by 2035 and rests on three pillars that describe the pathway to elimination:

(1) integrated and patient-centred TB care and prevention;
(2) bold policies and supportive systems and
(3) intensified research and innovation.

The Unitaid Executive Board approved the "Expand New Drug Markets for TB" grant (henceforth "endTB grant"). This grant of US$ 60.3 million for a period of four years from April 2015 to March 2019 is being implemented by PIH together with MSF and IRD as consortium partners. The grant uses the first new TB drugs developed in almost 50 years (Bdq and Dlm) to help improve treatment outcomes for MDR-TB in 17 countries. Key outputs of the endTB project include an observational study of the use of new MDR-TB drugs (Bdq and Dlm) in eligible MDR-TB patients, and a clinical trial to find simpler, less toxic, and more effective ways to treat MDR-TB. Evidence generated from both these outputs is considered key to addressing the challenges in treating patients with drug-resistant TB.

In 2013/2014 and prior to the start of the endTB grant, WHO issued an interim policy guidance on the conditional use of Bdq[4] and Dlm[5] for a duration of six months. At the time, the low quality of evidence did not allow for stronger recommendations. In 2016, WHO issued an update to the treatment guidelines for drug-resistant TB[6] with no change to the interim guidance on Bdq[4] and Dlm[5]. The only change was the reclassification of the Bdq and Dlm to Group D2 (add-on agents, not core to the MDR-TB regimen). In addition, the 2016 update included a shorter, 9 – 12 months, MDR-TB treatment regimen (as compared to existing regimens of at least 18 - 20 months) under specific conditions. A review of the available evidence on Bdq in 2017 did not result in substantial changes in the recommendations on the use of Bdq, although an indication to consider the use of Bdq in any MDR-TB patient at risk for a poor outcome was added.[7]

While preparing the inception report, WHO released a position statement on the use of Dlm based on an expedited review of a phase III clinical trial. The trial did not find differences in cure and mortality rates between the experimental arm and the placebo control arm. However, this should be cautiously interpreted because the trial was not powered to demonstrate any difference in treatment outcomes. The position statement maintains the recommendation for the use of Dlm as an add-on drug, and advises national TB programmes (NTPs) and stakeholders to 'only add delamanid to a longer MDR-TB regimen when it cannot be composed according to WHO recommendations'.[8]

The overall **goal** of the endTB grant is to increase uptake of new TB drugs as part of treatment regimens that are more effective and less toxic. The **outcome** is to establish best practices for use of new TB medicines and novel regimens through generated and shared evidence.
Four outputs are to result in achieving the goal and outcomes of the endTB grant:
Output 1 (O1): Treatment with new TB drugs (Bdq and Dlm) and close monitoring of a large cohort of patients in early adopter sites;
Output 2 (O2): Simplification of MDR-TB treatment around a few priority regimens;
Output 3: Reduction of country-level barriers to scale up use of new TB drugs in all endTB countries; and
Output 4: Facilitate the sharing of knowledge and dissemination of evidence that support the use of new TB drugs.

Each output has a set of activities and indicators that were established to monitor progress of the project.
The implementing consortium implements the project in 17 countries:

- PIH: DPRK, Ethiopia, Haiti, Kazakhstan, Lesotho, and Peru;
- MSF: Armenia, Belarus, Georgia, Kenya, Kyrgyzstan, Myanmar and South Africa;
- IRD: Bangladesh, Indonesia, Pakistan, South Africa, and Viet Nam.

The estimated burden in the project countries is 3.2 million patients with TB and 144,000 patients with rifampicin resistant TB, representing about 33% and 24% respectively of the global burden. Ten of the project countries (Bangladesh, DPRK, Ethiopia, Indonesia, Kazakhstan, Kyrgyzstan, Myanmar, Pakistan, South Africa and Viet Nam) are in the top twenty countries with highest estimated MDR-TB burden in terms of number of patients.[9]

The grant agreement was signed on 28 April 2015 by Unitaid, and on 05 May 2015 by PIH, representing the consortium for a total value of US$ 60,369,772.

2 Objectives and Scope of the Mid-Term Evaluation

2.1 Objectives

According to the Terms of Reference (ToR) for this mid-term evaluation (Appendix 2), the objectives of the evaluation are to provide Unitaid with a detailed assessment of the **programmatic progress** of the endTB grant towards increased uptake of new TB drugs as part of treatment regimens that are more effective and less toxic; and with recommendations to Unitaid and PIH to improve the grant implementation by the lead grantee (PIH) and consortium members (MSF, IRD).

In addition, in co-production with the consortium partners, the evaluators constructed a grant-specific **theory of change** in the context of the global WHO End TB strategy and Unitaid's strategy 2017 – 2021 and developed an **impact framework** (covering both direct and indirect impact). The impact framework includes a suggested methodology to measure impact and the key assumptions.

2.2 Scope

The mid-term evaluation examined the endTB grant implementation against the objectives and deliverables in the endTB project plan and logical framework. The initial project plan and especially the timelines have been modified considerably due to changes in the project design and delays in project implementation.

The mid-term evaluation of the endTB grant was guided by the Organisation for Economic Co-operation and Development's (OECD) Development Assistance Committee (DAC) standard evaluation criteria[10] of grant relevance, effectiveness, efficiency, impact, transition and scalability, and lessons learnt. A check list of the project performance against the DAC standard evaluation criteria is in Appendix 2.

In relation to Unitaid's key performance Indicator (KPI) 4 (overcoming market barriers), the evaluators evaluated if the endTB project addressed:

> Demand and adoption: Countries, programmes, providers (e.g. healthcare providers, retailers) and end users rapidly introduce and adopt the most cost-effective products within their local context
>
> Innovation and availability: There is a robust pipeline of new products, regimens or formulations intended to improve clinical efficacy, reduce cost, or better meet the needs of end users, providers or supply chain managers. It means that new and/or superior, evidence-supported, adapted products are commercially available and ready for rapid introduction in low and lower-middle income countries.

3 Approach and Methodology

Unitaid called for a mid-term evaluation in order to provide recommendations to Unitaid and PIH for improved grant implementation. This chapter describes the methodology and the approach of the mid-term evaluation.

3.1 Programmatic and country progress assessment

The data collection methods for the programmatic and country progress assessment included a desk review of the relevant documentation, interviews, meetings with the implementing partners and visits to some endTB project countries.

Desk review

The evaluation team assessed progress of the grant implementation through a review of the documents and the logical framework. The documents used mainly were the project plan and annual reports (including annexes). Reports available included the annual reports of 2015 and 2016, and the semi-annual report of 2017 with its annexes.

The process for the desk review was:

- Extracting outputs (activities), outcomes and impact from the project plan
- Following up on the outputs, outcomes and impact in the annual reports
- Assessing overall project progress towards targets and where possible and necessary - by country, based on the project logical framework;
- Assessing timely implementation of the activities through comparing the time of delivery against the project plan.

The logical framework has gone through several changes during the implementation of the grant up-to-date, and the 2017 version of the logical framework used for the purposes of this mid-term evaluation. The evaluators assessed reasons for deviations of implementation and for non-achievement of the targets in the logical framework from the reports and through discussions with the implementing partners and Unitaid.

Interviews

The evaluators conducted interviews with a large number of stakeholders:

- The lead grantee (PIH in Boston) through a visit to their office in Boston, and by teleconferencing with the consortium members (MSF, IRD). IRD and MSF participated in some parts of the meeting in Boston via teleconferencing.
- In-country organisations/stakeholders in the project countries visited (Georgia and Indonesia), such as the implementing team, policy makers / key decision makers at the country level, including NTP managers;
- Organisations directly or indirectly involved with the endTB grant such as technical bodies, experts/resource persons, TB implementing agencies, civil society groups. and
- Relevant staff at the Unitaid Secretariat.

The evaluators maintained confidentiality for all interviews, meaning that findings are not linked to individuals or organisations. This allowed participants to speak freely and also share criticism, if relevant. A full list of people interviewed is included in Appendix 3.

Meeting with the grantee in Boston

The general objectives of the two-day meeting were:

- To discuss programmatic progress of the whole project and per country. Country level progress was discussed focusing on registration issues for Bdq and Dlm, as well as potential for transition and scale-up.
- To develop collectively using a participatory process the impact framework by using theory of change approach.
- To assess achievements for Output 1 in terms of results expected to be available by March 2019 that may impact the policy recommendations by countries and by WHO.
- To discuss project managerial arrangements (including staffing), transition/scalability, risks and learning.

In addition to the document review and the discussion at the PIH office, the evaluators conducted a more in-depth assessment of six endTB project countries beyond project documentation: two through country visits, and an additional four through telephone interviews.

Country visits

An in-depth assessment took place through Unitaid's selected country visits to Georgia (implementing partner MSF) and Indonesia (implementing partner IRD). The evaluation team visited each country for four days and met with the project implementation team and with important in-country stakeholders. A full list of people met and interviewed is included in Appendix 3. The interviews provided insight regarding barriers and lessons learnt from the implementation of the project. The evaluators discussed potential for transition and scale-up of achievements of the project, and identified and discussed challenges related to treatment potentially remaining at the end of the endTB project in March 2019. The discussions with the stakeholders focused on the embedding of the project in the MDR-TB care and treatment services provided through the NTP and by partners.

Telephone interviews

The evaluators conducted interviews with representatives of NTP and the implementing partners in an additional four countries. They selected the countries using the following criteria

- To include at least two countries of each implementing partners. Therefore, two countries of PIH and one of both IRD and MSF were selected.
- To include a country of each implementing partner that did relatively well on enrolment for O1, and one that did relatively not so well on enrolment for O1.
- Geographical representation.

This resulted in selection of the following countries additional to the countries visits:

- IRD: Pakistan
- MSF: Kyrgyzstan

- PIH: Lesotho and Peru

For the interviews, the evaluators used an interview guide that underwent some small changes along the evaluation process. For example, the evaluators added a question on TA provided or received. The interview guide is included in Appendix 4.

The objectives of the telephone interviews were the same as these of the country visits, however, the level of detail was lower.

3.2 Development of Theory of Change and Impact Framework

Theory of Change is part of Unitaid's new Grant Agreement Development package. The endTB project was formulated before this requirement was in place and therefore did not contain a ToC. The ToC outlines the change pathway from the inputs and activities to the specific outputs that unlock access barriers and generate positive change in patient outcomes and collectively decrease the burden of disease.
Together with the implementing organisations, the evaluators took the following steps:

1) Mapped out the change pathway from endTB project outputs to the outcomes and further to the indirect market outcomes and the long-term public health and economic impact;
2) Made the relevant assumptions;
3) Discussed if and how the project could ensure its long-term success and a stronger case for transition and scale up.

This participatory approach and consultations with the implementing partners were meant to leave the ownership of the process and the resulting ToC with the implementers.

The impact framework essentially takes off from the change generated through the project and, based on plausible assumptions, demonstrates the potential and possible public health and economic impact.

3.3 Data handling and triangulation

In desk review of the documents and the interviews, the evaluators focused on delay of the implementation and the reasons for the delay, how the grantee mitigated the effect of the delay, and how this may impact the results of the project. During the interviews the evaluators also focused on whether the recent position paper on Dlm of WHO[8] should influence the research component of the project, and if yes, what direction the influence should take.

Data triangulation was achieved by means of using several data sources. Findings of the document review were validated in interviews and during the country visits. Where possible and necessary, the evaluators asked several interviewees for background and explanations on the same issues, to ascertain the findings. Where necessary, the evaluators requested proof of activities having being carried out, such as minutes of meetings or other products produced.

3.4 Tools

The evaluators developed generic interview guides (Appendix 4) for interviews with endTB project implementers, stakeholders and patients. This interview guide served as guidance allowing for flexibility during interviews. The interviews were not transcribed.

4 Findings

4.1 Programmatic and country progress

The progress of the project is measured against the log frame indicators. For the overall goal of the project to increase uptake of new TB drugs as part of treatment regimens that are more effective and less toxic, the project achieved considerably more compared to their targets, as shown by the cumulative though not yet verified numbers until the end of 2017. These figures clearly show the need for the new medicines in the project countries. The achievement indicates that the target may have been too cautious, however, the uptake of innovations such as new medicines is not easy to predict.

Table 1. Overview of G1 indicator

Indicator	Reporting frequency	Latest report available	Target up to latest report	Achievement (%)
G1: number of patients who newly enrolled to receive a new TB drug as part of their MDR-TB regimen in an endTB country within the reporting period	Annual	Updated numbers provided by the consortium; cumulative numbers until the end of 2017	4,045	13,950 (345%)

Note1: the numbers are still being verified.
Note2: the indicator includes not only patients receiving the medicines through endTB activities, but also through other implementers in the country.

The purpose of the project is to establish best practices for the use of new TB medicines and novel regimens through generated and shared evidence, measured through the indicator 'Evidence of sufficient quality for a GRADE based review to support development of WHO PMDT guidelines on the use of new drugs in treatment regimens (as described in the observational study of Output 1 and the clinical trial of Output 2)'. Whether the evidence of sufficient quality will be assessed by those who review the data for the GRADE based review and as such, the evaluators cannot assess progress on this indicator. However, in the section on O1, the evaluators assess the data quality assessment procedures that the project has in place to form an opinion on the quality of the evidence produced for O1. Progress on O2 is not sufficient at the time of the evaluation and is therefore not included in this quality assessment.

4.1.1 Output 1 Treatment with new TB drugs and close monitoring of a large cohort of patients in early adopter sites

Short description of the activities

The main activities in O1 are enrolment of patients on treatment regimens containing Bdq and/or Dlm and an observational study of MDR-TB patients enrolled in the 17 project countries on either Bdq or Dlm, or a combination. Activities supporting this study include

procurement of the TB medicines and ancillary medicines; to prepare an observational research protocol and submit this to the relevant bodies to obtain permission for the study; to evaluate patients for their eligibility and to initiate those eligible on the new medicines; to monitor the patients during their treatment and once after the end of treatment; to establish an EMR and a PV system; and to develop a model of care for private sector pulmonologists in Bangladesh, Indonesia and Pakistan.

Implementation and progress

Implementation of the activities started in 2015, with the first patients enrolling as early as quarter two of 2015 in Armenia, Belarus and Georgia. In Armenia and Georgia this was not yet in the observational study, but in the full cohort. Participants enrolled in the full cohort if they gave permission to receive the new medicines and to PV monitoring. If participants also gave permission to enrol in the observational study with their data analysed, they would become part of the observational study. The observational study participants are thus a subset of the full cohort. However, the implementing partners faced several challenges that resulted in delays in enrolment:

- The funds from Unitaid arrived with a delay after grant signature, which resulted in delay of start of the activities. MSF had an advantage over the other partners because they had the medicines already in some of the countries. Besides MSF has a reimbursement arrangement which puts them in a unique position to implement activities awaiting Unitaid funds;
- The development of the study protocol, its subsequent submission and approval took considerable time, and by the end of 2015, only one country (Belarus) had the protocol approved. This meant that patients in all project countries could receive Bdq (Dlm was not available in any country during 2015 except for Georgia, Armenia and Belarus) and enrol in the full cohort, however, they could not enrol in the observational study. By mid-2017, 14 countries had received the approval of the relevant bodies.
- The ethical approval of the observational study occurring after clinical enrolment of patients did not result in many “full cohort” patients being excluded from the observational study, as endTB got approval from ethical boards to retroactively enter data on patients from their medical charts.

Selection of project countries occurred mostly pragmatically: countries where one of the three consortium partners was already active and there was a substantial burden of MDR-TB. During grant implementation, several challenges resulted in changing some of the project countries:

- Not all countries had already mechanisms in place to import Bdq or Dlm. The medicines were not registered in any of the countries, and obtaining authorisation to import took much time in some countries. Due to the delay with country approval in Nepal, the consortium agreed not to implement the project under Unitaid’s advice.
- Subsequently, Durban (South Africa) was added in 2016, as well as Haiti and Viet Nam in 2017. This change in project countries resulted in shifting targets of patients among the project countries. These changes resulted in further delays in enrolment of patients in O1: Haiti enrolled the first patient in Q3 2017 only and at the moment of this evaluation, Viet Nam has not yet enrolled any patient.

- The decision to include Viet Nam, which had already started using Bdq in three pilot sites before it was considered as an endTB project country, resulted from a request of the NTP to IRD for assistance with access to Dlm. In combination with very slow (initial) enrolment in Indonesia, this led to the consortium requesting Unitaid to include Viet Nam in February 2017, which Unitaid subsequently approved.

Although a pragmatic selection is a practical approach, it did not prove always efficient and effective:

- Kenya: enrolment was so low because there were not enough patients for which the new drugs were indicated that enrolment stopped in 2016.
- Kyrgyzstan is potentially a good choice because WHO estimates that 4,800 people have RR- or MDR-TB[9]. However, approval of the O1 protocol was not received by the end of 2016, hence the enrolment was delayed. By the end of 2017, only 10 patients were enrolled. The targeted enrolment for Kyrgyzstan for the grant period is 28, which relates to the number in the MSF catchment area. The project could have been more ambitious in Kyrgyzstan because of the existing burden. Other implementers beyond endTB have contributed substantially as shown in the Bdq orders received from the Global Drug Facility (GDF). Kyrgyzstan received the first shipment of Bdq in December 2016, and ordered in total 930 units[11].
- Durban, South Africa: the country already uses Bdq on a large scale, and by the end of 2017, only 16 patients were enrolled. The projected enrolment is 39, and contributes only modestly to the objectives of the project. The Durban site is focusing on overcoming the hurdles of programmatic Dlm use, which is a big issue in South Africa.
- Nepal was removed as project country because the necessary approvals took too long; and Viet Nam has not yet started enrolling.

By the end of 2017, all countries apart from Viet Nam had started initiating patients on the new medicines, and in Georgia and Armenia enrolment for O1 had stopped due to meeting the enrolment targets. Initiation of the process for regulatory approvals to start activities in Viet Nam started in Q3 2017 as permission from Unitaid to include it as an Output 1 site was only granted in July 2017.

Cumulative enrolment (unique patients) in the full cohort as of 31 December 2017 was 1,848 participants, 68% against the project target of 2,703. Of these, 93% (1,750 or 66% of the project's target of 2,650) were enrolled in the observational study.

Information on enrolment in the individual countries is included in Appendix 5. As targets changed during implementation the evaluators did not consider it useful to assess each country's enrolment against targets.

Progress on the log frame indicators

In the initial log frame O1 indicators O1.1 and O1.2 were related to procurement of the medicines. These indicators were dropped because the information was provided in the procurement reports, and to avoid duplication. The table below provides an overview of the progress of the O1 indicators.

Table 2. Overview of the progress of the O1 indicators

Indicator	Source of data	Achievement / Numerator	Target / denominator up to latest report	Proportion
O1.3 % of targeted endTB Output 1 patients on Bdq or Dlm enrolled according to WHO protocol within the reporting period	Updated figures provided by PIH during Boston visit (enrolment until Q4 2017)	1,848	1,948 (Target)	95%
O1.4 (NEW)% of patients who started new drug treatment within the period under evaluation with at least one Serious Adverse Event (SAE) (regardless of the cause) within their first 6 months of follow-up	2017 semi-annual	87	822 (denominator)	11%
O1.5 % of patients who started new drug treatment within the period under evaluation with the following interim outcome:				
O1.5 a) culture negative at 6 months	2017 semi-annual	309	519 (denominator)	60%
O1.5 b) died by 6 months		30	519 (denominator)	6%
O1.5 c) Lost- to-follow-up (LTFU) by 6-month post start of new drug		24	519 (denominator)	5%
O1.6 % of patients who started new drug treatment within the period under evaluation with the following final outcome: a) Cured, b) Treatment completed, c) Treatment failed, d) Died, e) LTFU, f) Not evaluated by 24 months post start of new drug (by countries; by full cohort vs. observational study)	2017 semi-annual	No end- of treatment results yet known by Q2 2017		

The project is well on track for indicator O1.3 with an achievement of 95% of the enrolment target. The consortium aims at enrolling the full target for the full cohort (2,703) and the observational study (2,650). By the end of 2017, 95% of the full cohort formed also part of the observational study.

For indicators O1.4-O.16 there are no targets for the semi-annual reports, therefore a denominator is included in the table rather than a target. A proportion of 11% SAE is slightly lower than the results presented by the consortium partners at the Union conference in 2017 (16%), which related to a different number of patients.
The interim outcomes at 6 months presented in the semi-annual report 2017 with 60% having a negative culture, is lower than the 82% conversion rate presented at the Union conference in 2017. The figures are not comparable; hence it is not meaningful to draw

conclusions on these results at this moment. Furthermore, although interim outcomes are important, the ends of treatment outcomes are much more important.

Electronic Medical Record

The project plan contains the following on the EMR "… the necessary data management system to do clinical care, Monitoring and Evaluation[2], pharmacovigilance and data analysis across the endTB treatment sites. …". An EMR is an electronic data capture system that is meant to be used by clinicians who are directly managing patients. Generally, EMRs allow clinicians quick and secure access to a patient's complete health history without having to locate the patient's paper chart; reduces medical errors by restricting entry to only plausible value ranges; can alert clinicians to missing data and abnormal or dangerous signals; provide indications that the patient is not responding to therapy, and can be used to compile aggregate statistics and reports".

The development of the EMR started in 2015 and gradually the endTB sites implemented its use. The experience in the field led to improvements of the system and by mid-2017, 16 of the 17 sites used it; only Viet Nam was not yet operational. The country visits, interviews and document review allowed the evaluators to assess the use of the EMR and data quality procedures in place.

Most sites use paper forms and patient charts for capturing data and clinical care purposes. Clinicians fill out the forms related to the project, which may or may not be the same as used in the national programme, and data entry officers enter the data in the EMR. Most clinicians don't use the EMR during consultations with their patients, and as such don't use the EMR as intended by the project plan. Reasons for this include that the clinician is not used to working with an electronic system or that they don't have access to the system.

The EMR does not include alerts for clinicians to missing data and abnormal or dangerous signals, although abnormal laboratory values are in red font. Such alerts could potentially increase patient safety and facilitate a systematic approach to patient monitoring and care. Within the project this systematic approach is conducted retrospectively by the data officers, and appeared a rather complex system with downloading data to excel files, alerting clinicians to the missing variables through paper forms who would then obtain the information from the patient chart, if the patient chart contained the information. Although this process was comprehensive, the complexity may not be useful in routine programmatic care.

In Georgia, the national TB centre has no access to the EMR even though patients' treatment takes place at the centre. MSF maintains the EMR, and would want a data agreement with the national TB centre in place before providing access. This has to do with the research-oriented functioning of the EMR.

In conclusion, the EMR functions more as a research database than tool for clinicians in their patient management as described in the project plan. This limits the potential for supporting clinical decision making and also results in a larger burden for maintaining all the

[2] Monitoring and Evaluation

paper forms and the EMR. Contributing to this is the fact that many clinicians do not have access to a computer, and national programmes may insist on using a paper patient record.

The data quality assessment processes in place are robust. The EMR gradually developed and included in later stages data quality assessment and reporting tools. Data quality assessment tools produce lists of data that are not complete, generated by the data entry staff. The data staff communicate the missing data to the clinicians who will then search in the patient chart if the data is available. If available, the clinicians report the missing data to the data entry staff who then update the EMR. If the data are not available and will not become available, for example missing bacteriological tests at a certain month in the follow-up period, the EMR does not have the possibility to record this information. The missing information continues to appear on the lists generated by the data entry staff.

Further data quality assessments are driven from the central level by the study data managers of the consortium and its partners. Also, these data checks focus on missing data. Sites do not seem to have in place a systematic verification with source documents. A limited check of two patient charts in each country visited, between the EMR and source documents done during the country visits, did not reveal any discordance between the data in the EMR and the source documents.

The reports generated by the EMR download the data into excel. To come up with the relevant information, for example the number of patients scheduled to end their treatment in the next quarter, or the patients that should come for the 6-month post treatment follow-up, the data officers still need to manipulate the data in excel. The evaluators observed that the data team maintain several excel files and paper lists related to data checks made, variables that need checking or updating, which carries a risk for data errors. However, such errors were not observed in the limited data verification check done during the country visit. With rising patient numbers, such a system will be much more difficult to maintain.

Pharmacovigilance

WHO defines PV as ‘the science and activities relating to the detection, assessment, understanding and prevention of adverse effects (AE) or any other drug-related problem’[12]. Close monitoring of TB patients has received much more attention lately because of the scale-up of treatment of MDR-TB. MDR-TB treatment contains medicines that are much more toxic and therefore cause many more AE, including SAE compared to the treatment of drug-susceptible TB. Also, PV has become much more important as a result of the introduction of new medicines such as Bdq and Dlm, because their use has so far been in a limited number of patients and the rarer (S)AEs may not yet have come to light. However, many countries do not have well developed systems for PV.

Within the endTB project, PV monitoring is crucial and implemented in all project countries. Systematic recording and reporting mechanisms are in place in the EMR and SAE are reported to the PV unit (within MSF) within 24 hours using separate forms and procedures. This allows for a quick response with support from the central team if necessary. The project clinical team discusses systematically all reported SAE.

With the exception of Indonesia, Kazakhstan and Pakistan, the original endTB project countries did not have a functioning PV system in the country. In all other countries, the endTB project introduced the topic in the country and the project contributed to national systems being discussed or developed.

Model of care for private sector pulmonologists in Bangladesh, Indonesia and Pakistan

The project plan states on the model of care for the private sector: "IRD's approach to establishing a social business model provides a sustainable solution for the private sector, through quality diagnostics and treatment at a subsidized cost. Prior to the start of the project, efforts have been set in place to work together with GF and other key stakeholders, along with the NTP, for a transition mechanism to be put in place at the end of the project. This would ensure that patients who are receiving care in the private sector towards the end of the project complete their treatment. It also works toward a long-term solution that strengthens public-private sector linkages. Therefore, as soon as endTB Project data is available, this shall be shared with the NTP to influence national policy for drug registration and to adapt national guidelines.

Bangladesh, Indonesia and Pakistan implement the project in the private sector because that is where a majority of the patients seek care. The experiences so far have been positive and encouraging, with links built between the public and private sector. Bangladesh and Pakistan each enrolled more than 200 patients in the private sector in O1, and although these numbers are small compared to the estimated burden in these countries, it shows potential for the future. In all three countries, patients often seek care in the private sector and engaging this sector in TB care including PMDT is therefore relevant. At this stage, a clear model of care is not yet documented, and it is not clear how activities within the private sector will continue beyond endTB.

Results potentially available by mid-2018 and at end of project

An important result of O1 is to provide evidence of sufficient quality for a GRADE based review to support WHO PMDT guidelines' revision, planned for June/July 2018. Recently, the WHO communicated a newsflash requesting industry, researchers, NTPs and other agencies to provide suitable datasets for revision to inform an update of the treatment guidelines for RR- and MDR-TB.[3] The endTB consortium received the newsflash as well and responded positively to the request.

The grant will end by 31 March 2019. Enrolment under O1 will stop by 30 September 2018 or earlier if the enrolment target is met. This means that for participants enrolled in Q3 2018, 6-9 months of follow-up is available. Unless participants have unfavourable treatment outcomes such as death or lost to follow-up, there are no treatment outcomes available for these participants. Although medication of the enrolled participants is guaranteed under the grant, the detailed data collection may not continue in all sites.

[3] Received on 16 February 2018

The observational study is very relevant for the revision of the PMDT guidelines 2018 and beyond, therefore the evaluators assessed what results for O1 could be available for the 2018 guideline revision.
To assess the results potentially available for 2018 WHO guideline revision, the evaluators used the following method:

- Include all participants enrolled until 30 June 2017;
- Assess the numbers with a 6, 12, 24-month treatment result available, and numbers with one 6-month post treatment follow-up visit
- Available results assessed using the following definitions
    - 6-month outcomes = at least 6 months passed since the last day of the enrolment quarter (enrolment up to Q2 2017)
    - 12-month outcomes = at least 12 months passed since the last day of the enrolment quarter (enrolment up to Q4 2016)
    - 24-month outcomes = at least 24 months passed since the last day of the enrolment quarter (enrolment up to Q4 2015)
    - 30-month outcomes (includes 6-month post end treatment follow-up) = at least 30 months passed since the last day of the enrolment quarter (enrolment up to Q3 2015)
    - this method leads to some overestimation because it takes some time to have the bacteriological results
- Assuming that the proportion of the full cohort that enrolled in the observational study has been constant throughout the enrolment period; this proportion was assessed based on the number enrolled in the full cohort and the observational study by 31 December 2017, and was 95%.

Furthermore, the evaluators assessed what results are available at the time of the final report of the project, currently expected June 2019, assuming that the detailed data collection for O1 enrolled participants will not continue beyond the project.
The evaluators used a similar method to assess the results available for at the end of the grant in March 2019:

- Include all participants enrolled (real numbers until 31 December 2017 and projections thereafter) until 30 September 2018;
- Assess the numbers with a 6, 12, 24-month treatment result available, and numbers with one 6-month post treatment follow-up visit
- Available results assessed using the following definitions
    - 6-month outcomes = at least 6 months passed since the last day of the enrolment quarter (enrolment up to Q3 2018)
    - 12-month outcomes = at least 12 months passed since the last day of the enrolment quarter (enrolment up to Q1 2018)
    - 24-month outcomes = at least 24 months passed since the last day of the enrolment quarter (enrolment up to Q1 2017)
    - 30-month outcomes (includes 6-month post end treatment follow-up) = at least 30 months passed since the last day of the enrolment quarter (enrolment up to Q3 2016)
- Assuming that the proportion of the full cohort that enrolled in the observational study has been constant throughout the enrolment period; this proportion was assessed based on the number enrolled in the full cohort and the observational study by 31 December 2017, and was 87%.

The above assessment results in the following numbers (Table 3):

	Outcomes available for	Potentially available results for the 2018 WHO PMDT revision	Potentially available results at end of grant period (31 March 2019)
Full cohort	6 months	1,357	2,588
	12 months	935	2,141
	24 months	197	1,153
	30 months	113	935
Observational study	6 months	1,037	1,978
	12 months	715	1,636
	24 months	151	881
	30 months	86	715

Note: Participants in the full cohort gave permission to receive the new medicines and to PV monitoring. Participants of the observational study form a subset of this full cohort and they gave permission to enrol in the observational study with their data analysed.

Appendix 6 contains the table with the numbers expected per country. For the in 2018 planned revision of the WHO guidance, the observational study participants with 6-month outcomes available come from all project countries except Haiti and Viet Nam. The 30-month outcomes available from the observational study include participants from Armenia, Belarus and Georgia.
The numbers available for the 2018 with full treatment results are still relatively small, but are important because of the availability of detailed data of good quality.

An important aspect in the discussions with stakeholders has been whether WHO's recently released position statement on Dlm should influence studies including this medicine, such as the endTB studies. The general opinion is that it should not, because the results that led to the position statement came from a trial that was set up for registration purposes and not powered to show significant treatment outcome differences at the end of treatment. In fact, most interviewees considered it important to continue with the studies because of the need of more data on the use of Dlm in patients.

However, stakeholders pointed out several aspects that the consortium needs to take into account when analysing the results of O1:

- The potential for selection bias: participants in O1 enter the study at the time when they start a new medicine (Bdq or Dlm); this can be at any time during treatment and therefore many characteristics are not easily comparable with routine outcomes of NTPs where patients mostly continue with the same regimen throughout the entire treatment;
- Culture status at the initiation the new medicines: because participants enrol when they start Bdq or Dlm, irrespective of the number of months of treatment they received without these drugs, the culture status at start of the new medicine varies greatly: for example, already converted on the conventional regimen, never had a positive culture at all, still positive, and so on; this complicates the analysis and needs to be carefully clarified when presenting the results;

- Indication for initiation of Bdq or Dlm, or the combination: analysis of treatment outcomes may differ if the new medicines initiation was because of resistance reasons [pre-extensively drug-resistant TB (pre-XDR), or XDR-TB] compared to reasons of intolerability of other second line medicines. Patients with (pre-)-XDR-TB have a higher a priori risk of poorer treatment outcome compared to those without these conditions.

The observational study protocol contains a data analysis plan, which does not clearly outline how these aspects will be taken into account. That is not entirely to be expected because not all the factors were known at the start of the study; however, analysis should be clearly explained to avoid overestimating the effect of the new medicines.

4.1.2 Output 2 Simplification of MDR-TB treatment around a few priority regimens

Short description of the activities

The main activity in output 2 (O2) is a clinical trial to assess effectiveness of new treatment regimens for MDR-TB patients in six project countries (Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru, and South Africa). Activities supporting the trial include the preparation of a trial protocol and submission to the relevant bodies to obtain permission for the trial; procurement of the commodities for the trial including the TB and ancillary medicines; to prepare the trial sites; and to analyse and disseminate the data obtained through the trial. The trial includes five experimental arms and one control arm. All experimental arms consist of innovative all oral and of 9-month duration treatment regimen. The experimental arms the following regimen:

1. bedaquiline-linezolid-moxifloxacin-pyrazinamide
2. bedaquiline-clofazimine-linezolid-levofloxacin-pyrazinamide
3. bedaquiline-delamanid-linezolid-levofloxacin-pyrazinamide
4. delamanid-clofazimine-linezolid-levofloxacin-pyrazinamide
5. delamanid-clofazimine-moxifloxacin-pyrazinamide

Implementation and progress

Output 2 experienced substantial delay in start-up. It should have started early 2016, but the first enrolment occurred a year later. The main reasons for the delay include:

1. The original timeline was rather ambitious: the Gantt chart of the project plan included less than 6 months for preparation of the O2 trial protocol. Although the development of a protocol can be done in 6 months, obtaining approval from all the consortium partners' Institutional Review Boards and approval in 6 countries is very optimistic.
2. After grant approval but before grant signing, Unitaid initiated a process to review the trial protocol by people external to both Unitaid and the grantee, the due diligence process. The consortium did not oppose the improvement of the trial protocol; however, it did not receive clear information on what grounds the original trial plan was not considered adequate. The due diligence process recommended to:
    a. Include a control arm (not foreseen in the original plan) which resulted in an increase of the number to enrol from 600 to 750 participants;

   b. Enrol only fluoroquinolone (FQ) susceptible patients compared to include both FQ susceptible and FQ resistant participants; and
   c. Extend the follow-up period from 65 to 102 weeks, which resulted into a longer overall study duration.
3. The control arm outlined in the previous bullet point as well as an arm including both Bdq and Dlm in combination, for which the manufacturers gave the green light in December 2015, were not included in the original research plan submitted with the proposal. The addition of the control arm and extension of the follow-up period, constituted major changes that required a revision of the protocol.

The extension of the follow-up period prolonged the duration of the study. The original duration for O2 was three years, and with the prolonged follow-up period, this is now four years, meaning that results are expected only in 2021.

By mid-2017, the study had approval from the relevant bodies in five of six countries (Georgia, Kazakhstan, Kyrgyzstan, Lesotho, and Peru), with the decision pending in South Africa. Since then the consortium received approval for the trial in South Africa too. According to projections of the consortium by 25 September 2017, the last site (South Africa) would start enrolling in Q2 2018. By 16 February 2018, a total of 61 participants enrolled in the O2 trial, considerably lower than the 87 anticipated by the end of December 2017 (projections made on 25 September 2017). Enrolment in Kyrgyzstan was foreseen for mid-February 2018, but this did not occur. In South Africa enrolment is supposed to start in mid-March 2018.

Enrolment of the first patient started in February 2017 in Georgia. However, in February 2018 it was decided that Georgia would not continue to enrol participants in O2 because of very low enrolment numbers and actions to address the reasons for low enrolment (see below) did not lead to increased enrolment. During the country visit, the evaluators assessed the process and reasons that led to the decision to discontinue in Georgia.

Reasons that contributed to low enrolment:

1. The change in epidemiological context in Georgia: MDR-TB patient numbers have declined substantially. Programme data show that the number of patients starting MDR-TB treatment declined from 665 in 2012 to 444 in 2016. The target for Georgia was to enrol 150-180 participants, and reaching about 5-6 per months after a start-up phase. In the period of about 12,5 months that Georgia enrolled, only 13 patients were enrolled, on average 1 per month.
2. Limiting inclusion to Tbilisi. Potential participants were discussed in the MDR-TB consilium of Georgia. 170 people were discussed for potential enrolment, of which only 42% came from outside the capital.
3. High refusal rate from potential participants: 19 (43%) potential participants of a total of 44 that passed the screening refused informed consent.
4. Competition with other trials, specifically the STREAM2 trial which aimed for the same or similar patients.
5. Staff from the National TB Centre, where the trial is conducted, were not satisfied with the level of compensation they received for their work in the trial. Staff members mentioned that – although they were not content – it did not demotivate them from enrolling patients, however, there were no patients to enrol.

In June 2017, the study team discussed the low enrolment and suggested potential solutions such as extending it to additional regions within Georgia and explaining the study more carefully to the potential participants. Extending the study to the regions required prior approval. A new participant leaflet also required prior approval. The study team met barriers in obtaining these approvals, hence the decision to discontinue the enrolment altogether.

In this process, there were three major players: the central (headquarters) MSF study team, the Georgian MSF team and staff at the National TB Centre. The evaluators perceived that the three players did not operate as a team and that the MSF study involved the local MSF team in decision making, but the National TB Centre to a much lesser extent. This, together with the discontent regarding the compensation paid, did not improve relations, and has probably contributed to the low enrolment.

The discontinuation in Georgia is a further setback for O2, especially because the targets for enrolment were 150-180 participants, around 20-24% of the total enrolment. The endTB consortium had taken into account the possibility that one country would drop out of the study. Unfortunately, the consortium did not share a contingency plan with the evaluators when the evaluators asked how the target for Georgia would be distributed among the other trial countries. This plan included Karachi as an alternative location, which has been chosen to replace Georgia. The number of potential candidates for enrolment is higher in Karachi, potentially resulting in enrolment according to plan.

Globally, endTB has a Scientific Advisory Committee to oversee the O2, endTB also consults with the Global Community Advisory Board on a regular basis. Community oversight at the country level varies by site, although all sites have meetings with stakeholders and the national programs. Peru and South Africa have community advisory boards; Kyrgyzstan and Kazakhstan are currently developing them at this writing. In Georgia information and regular updates on the trial are presented on a quarterly basis to the TB research Working Group that includes former patients and members of the Patients Union.

Possible scenarios for O2

Given the delays that occurred for O2 and the extension of the follow-up period for participants in the trial from 65 to 104 weeks, enrolment will not yet have completed by March 2019, but certainly the follow-up period of 104 weeks will not have been achieved for all participants enrolled.

The consortium estimates a budget gap of US$ 3-6.5 million to complete O2. The original (March 2015) budget of the project plan contained US$ 10.7 million for O2. The revised (2017) budget included US$ 12.5 million for O2. The total value of the revised budget is US$ 54.2 million, which is US$ 6 million less compared to the amount approved by Unitaid' board. The consortium considers that this amount is still available to them, and would be part of a no-cost extension. This means that currently there is US$ 18.5 million available for O2.

The evaluators discussed O2 with the lead grantee in Boston, and came up with the following scenarios.

1. The grant has no extension beyond March 2019: there may be a few early enrolled participants with treatment outcomes available, and 6-month results for those enrolled up to September 2018 however, the numbers will be too small to draw any meaningful conclusions. Most if not all investments into O2 will be a waste.
2. The grant receives a no-cost extension: the endTB consortium has mentioned that the current O2 budget is not sufficient to conduct the trial with the present protocol. The grantee outlined the options for conducting the trial with the presently available budget:
    a. Design change: dropping an experimental arm which would mean less data available on potential new regimens.
    b. Design change: reduction of the follow-up period from 104 to 73 weeks. This would lead to less information on the relapse rates of the different arms and ultimately affect data available on the effectiveness of the regimen.
    c. Statistics change: reduce the sample size. This would result in reduced certainty in the available evidence.

    All of the options would affect the underlying strategy to come up with 1-3 priority regimens including new TB medicines that treat all forms of MDR-TB including (pre)-XDR with 5-8 priority medicines. In addition, it would be a matter of urgency to make decisions on potential design changes, especially the first one (dropping an experimental arm), because all investments on participants enrolling in an arm that is going to be dropped, will be lost.
3. The grant receives a costed extension: the consortium estimates a budget gap of US$ 3-6.5 million and considers the possibilities to obtain the funding elsewhere as non-existent given the long processes usually involved in obtaining research funding. If the grantee and Unitaid agree on a costed extension, the grantee can run the trial as per current protocol.

Irrespective of an extension, the care of the patients enrolled into the study needs to be provided until the end of their treatment according to the protocol.

The change from the original trial plan to include also fluoroquinolone resistant forms of MDR-TB to include only fluoroquinolone susceptible forms on MDR-TB in O2, made it impossible to work on the original objective to arrive at 1-3 priority regimens including new TB medicines that treat all forms of MDR-TB including (pre)-XDR with 5-8 priority medicines.

The evaluators discussed the potential results obtained from O2 in interviews with a large variety of stakeholders. In general, interviewees expressed the need for trials to come up with a better evidence base for MDR-TB treatment. Furthermore, the general consensus included the high need for shorter, less toxic and more effective MDR-TB treatment regimens for patients.

Some interviewees have doubts about the potential to come up with 1-3 priority regimens including new TB medicines that treat all forms of MDR-TB including (pre)-XDR with 5-8 priority medicines. They considered the cascade approach to MDR-TB treatment important, meaning that simple MDR-TB (resistance to Isoniazid and Rifampicin and no additional

resistance to other SLD) is treated with a preferably standardised treatment regimen, and that new medicines such as Bdq and Dlm are maintained for the treatment of (pre-)XDR. Interviewees considered the shortened regimen as the preferred option for treatment of simple MDR-TB because it is more acceptable to the patients and easier to administer for the health care staff. If a future shortened regimen is all oral and does not contain injectable medicines, it will be more acceptable to patients and easier to administer for the health care staff compared the current short regimen. However, history has shown that whenever a medicine is in use, resistance development by the micro-organism will develop. This highlights the need for continued medicine development, and the need for careful introduction, including continuous monitoring of drug resistance, of newly developed medicines.

4.1.3 Output 3 Reduced country-level barriers to scale up use of new TB drugs in all endTB countries

Output 3 of endTB is: “to reduce country-level barriers to scale-up use of new TB drugs in all endTB countries”. The related indicator O3.1 is: “the number of endTB trainings to NTP leadership or appropriate national expert MDR-TB committees/personnel that facilitate the adoption of new TB drugs into national guidelines within the reporting period (by countries)”.

Progress towards targets

In terms of progress reporting, the numbers of trainings and meetings carried out are counted as well as the number of persons who took part in a training or a meeting. In 2015, out of the 18 planned trainings/meetings, 11 were carried out, and in 2016 out of the 51 planned trainings/meetings, 53 were carried out.

According to the 2016 annual report, cumulatively the project is below the targets for output 3.

Table 4. Overview of output 3

Indicator	2015-16 cumulative targets	2015-16 cumulative results	Achievement (%)
O3.1 Number of trainings and meetings	69	64	93%

Activities under Output 3 are:
3.1 Facilitate importation of new and companion drugs in endTB countries;
3.2 Adapt national TB guidelines in all endTB countries to include new TB drugs;
3.3 Improve transparency and accountability of TB programs, both national and Non-Governmental Organisation (NGO), as they relate to access to new TB drugs;
3.4 Provide TA to ensure sustainable financing and transition of new TB drugs and regimens in endTB countries.

It is the evaluators' opinion that the O3.1 indicator is not designed to adequately capture the progress of all activities under Output 3. The evaluators were informed by Unitaid that the current approach to developing indicators, under the new Unitaid strategy, ensures a better match between indicators and outputs. For the purposes of this evaluation, the evaluators have looked at the implementation of each other activities under Output 3 to provide quantitative, as well as qualitative information, such as:

- For activity 3.1.: if the project and/or the country experienced import barriers/regulatory hurdles, if the importation by endTB has facilitated importation by other stakeholders in the country, the number of countries where the new drugs were registered, and if endTB contributed to facilitating the registration;
- For activity 3.2.: the number of countries where the national guidelines were updated to include the new drugs and if endTB contributed to the guidelines review;
- For activity 3.3.: activities undertaken by endTB to improve transparency and accountability of TB programs;
- For activity 3.4.: if TA to ensure sustainable financing and transition of new TB drugs and regimens in endTB countries was provided.

Facilitation of importation of new and companion drugs in endTB countries

According to the endTB consortium, the project is at a stage that both Bdq and Dlm can be imported into all 17 countries (except routinely for Dlm for Peru). Full registration is a more complicated process and many countries have started the process whenever the respective companies have submitted a dossier for registration; while for other countries, given the conditional approval by stringent regulatory authorities, or for other country policy reasons, full regulatory approval cannot be sought after at this time. The stakeholders indicated that in most countries, endTB initiated importation through compassionate use and other legal mechanisms, which was an important factor to expedite the introduction of the new drugs. NTPs (with GF funding) and other stakeholders currently continue using the same mechanisms as endTB. In most endTB countries it was the endTB project (PIH, MSF or IRD) that initially raised awareness about new drugs and advocated for their use with the Ministry of Health (MoH).

In many of the endTB countries the endTB project was the first to start importation of the new drugs and this may have facilitated access to the new drugs for the other stakeholders within countries. Even if on a limited scale, at the time of the evaluation, Bdq and Dlm were used in programs beyond endTB in nine countries, they were not used in five countries and for three countries information was not available.

Out of the 17 project countries, Bdq is registered in three countries (Armenia, Peru and South Africa) and has a conditional registration in one (Indonesia). Although registered in Peru, Bdq is not yet in the national guideline which is one of the prerequisites to be used in routine practice in the country; currently it is imported under regulatory policy as a donation. A registration file is under assessment for Bdq in Bangladesh, Belarus, Ethiopia, Indonesia, Kenya and Vietnam among the endTB countries. Dlm is not registered in any of the endTB project countries, but a registration file is under assessment in Indonesia. Importation of Dlm to Peru is impossible except under compassionate use because Dlm is not registered in Peru. Similarly to Bdq, Dlm is imported to the rest of endTB countries which have the

mechanisms (humanitarian waivers, exemptions) to provide access to unregistered medicines.

The interviewed stakeholders indicated that new drugs' registration is usually facilitated by:

- WHO's clinical recommendations and indications, and pre-qualification
- Stringent Regulatory Authority (SRA) approval (Food and Drug Administration, European Medicines Agency)
- Size and attractiveness of the in-country market to manufacturers
- Advocacy
- The introduction of a drug in the NTP guideline
- More routine use of a drug
- Availability of safety and efficacy data collected from the local population
- Official MoH support

Generally, the lack of the drugs' registration did not seem to hinder importation in eleven endTB countries; regulatory hurdles to importing the new drugs were experienced by endTB in four countries: Kyrgyzstan, Kazakhstan, Peru (for Dlm) and Vietnam. No information about regulatory hurdles was available for South Africa and Haiti. Whether or not a lack of the drugs' registration will hinder scalability may differ per country, especially in connection with GF's transition out policies that restrict access to the GDF pooled procurement mechanism for the countries that are no longer eligible for the GF's funding. However generally no major problems are expected if there are no hurdles currently, the country regulations remain the same and the same mechanisms of importation are used.

Adapting national TB guidelines

The information received from the stakeholders in different countries varies from situations where endTB Clinical and Programmatic Guide for Patients Management with New TB Drugs is relied on fully in the absence of an updated national guideline (e.g. Lesotho) to situations where the endTB assistance to adapt the guidelines was neither offered (e.g. Indonesia) nor sought after (e.g. Georgia 2017 update).

Being ahead of the national guidelines is usually not a comfortable position for the clinicians. While they recognize that the guidelines may sometimes need time to change, having the new anti-TB drugs in national guidelines is an important factor for the scale up. The inclusion of the new anti-TB drugs in the national guidelines largely depends on the WHO indications. According to endTB reports many national guidelines in endTB countries integrated the principles laid out in *"endTB Clinical and Programmatic Guide for Patient Management with New TB Drugs*". Among the endTB countries, information about the guidelines' update was available for 14 countries; of them the national clinical guidelines included the use of Bdq in 11 countries and the use of Dlm in eight countries. From six countries interviewed in-depth, four countries' guidelines were adapted to include Bdq; of these countries, the endTB project was noted for contribution to guideline revision in one country.

Improving transparency and accountability of TB programs

The “Out of Step” reports by MSF/endTB and the Stop TB Partnership are supposed to contribute to improving transparency and accountability of TB programs, as they relate to access to new TB drugs. However, the information in the “Out of Step” report is rather unspecific to endTB countries, it does not cover all endTB countries and there is variance between the information in the “Out of Step” report and endTB information; e.g. the “Out of Step” report indicated the status of PMDT guidelines in Bangladesh and Kazakhstan as updated to contain the use of new drugs as per NTPs shared information, whereas according to endTB information this is not (yet) the case.

TA to ensure sustainable financing and transition

Beyond short notes regarding assistance with putting new TB drugs in the countries’ GF funding requests no information is available regarding the endTB TA to ensure sustainable financing and transition of new TB drugs and regimens in endTB countries. In most countries transition and hand-over planning has not commenced, although the project plan and the country operational plans had a transition component. To address this shortcoming Unitaid developed a transition plan template for endTB project by Unitaid, which was being circulated at the time of the evaluation.

Transition plans are not featured prominently in endTB project, although the project plan specifies different possible approaches to transition planning from outlining a few concrete steps (e.g. Kenya) to more abridged “all recommendations will be agreed and endorsed by the MoH” (Belarus). During the visits/interviews with the six selected countries the evaluators were not made aware of any transition plans, except for Georgia, where the endTB project is closing out. Armenia is the second country where MSF is no longer going to operate and a transition plan is being developed. For other countries, the information is either not available (five countries, including Kenya where the endTB project stopped enrolment in O1), or there are no transition plans (ten countries).

Partially this is because the consortium partners intend to continue operations in the majority of the countries where endTB is currently implemented. The most important steps undertaken by the project, in line with the plan, were to ensure that the new drugs have been budgeted in the GF funding requests. The source of financing information was available for 13 out of 17 countries:

- In 11 countries, there are other non-endTB funders identified and they have already or are planning to start funding the new drugs procurement: GF (eight countries), GF/ with government taking over by 2020 (one country) or NTP/GF (one country);
- In two countries (Peru and DPRK) problems may be expected since no other funders have been identified.

However, in line with the Unitaid’s transition plan template, in addition to ensuring another source of funding for the new drugs, there are other areas that need to be addressed. These include but are not limited to maintenance and ability to operate the EMR system, availability of funding for and procurement mechanisms of adjuvant drugs and consumables, capacity of the national civil society to advocate for the patients’ access to the new drugs.

endTB approach to reducing country-level barriers to scale up

According to endTB, the issues related to Output 3 are addressed on a country-by-country basis when there is a blockage in any of the six elements needed for introduction of new TB drugs, as per WHO Policy Implementation Package for New TB drugs[2]:

1. Minimum requirements for country preparedness and planning
2. National implementation plan for introduction of new TB drugs and/or regimens
3. Monitoring and evaluation of new drugs and regimens, including PV and drug resistance surveillance
4. Private sector engagement
5. Systems approach for ensuring uninterrupted supply of quality-assured drugs
6. Operational research

Usually the first step is for the endTB in-country team to identify the bottlenecks and propose solutions to resolve them. Often, getting support from the local WHO country office is an early step to demonstrate the new TB drugs are indeed on the WHO essential drug list and have clear indications for patients with MDR-TB. However, in the two countries visited by the evaluators, the collaboration of endTB with WHO seemed neither active nor systematic. There was also no evidence of a documented or uniform approach to identification of bottlenecks related to the scale up of the new TB drugs. Documenting the approach to reducing country-level barriers would provide useful lessons for other countries to consider.

Information on the use of the new drugs beyond endTB was available for 16 out of 17 endTB countries. At the beginning of 2018, 11 countries used the new drugs beyond endTB. The use of the new drugs was characterized as limited in three countries (Ethiopia, Kazakhstan, Kenya), while in Vietnam the use of Bdq preceded endTB. Roll out with support/TA from endTB to at least one non-endTB site was still pending in Bangladesh.

Adoption and scale up factors and endTB contribution

During in-depth stakeholders' interviews the following factors were mentioned as important for adoption and scale up of the new drugs in-country, so also relevant post endTB are:

1. Registration
2. Clinical experience of using the new drugs
3. Inclusion in the national clinical guidelines

Based on the interviews, the clinicians in endTB countries get accustomed to using the new drugs as a result of clinical management of DR-TB patients and training. According to endTB giving experience to clinicians is their number one strategy, including experience in a range of populations (pre-XDR-TB, XDR-TB, patients with co-morbidities), access to drug susceptibility testing (DST) to guide regimen selection, experience in electrocardiograms (ECGs) readings, access to audiometry, having good companion drugs, having training and practicing PV and active TB drug-safety monitoring and management (aDSM).

Importantly, in some endTB countries (e.g. Georgia, Kyrgyzstan), the use of PV was initially only limited to endTB O1 sites and later scaled up to the whole TB program. Of the 14 countries for which information was available, nine established PV beyond endTB sites.

endTB was commended by stakeholders for technical assistance to endTB countries in introducing and strengthening PV. In the future, good PV systems will facilitate adoption of other new anti-TB drugs because it is one of the pre-requisites for introducing new drugs.

Globally, the endTB reports to contribute to the regular advocacy meetings organised by MSF Access Campaign with key manufacturers to register their compounds in all high burden TB countries, to push for countries and manufacturers to use WHO Collaborative Registration Procedure, and to coordinate Civil Society Organisations pressure on Janssen, Otsuka and related partners to register Bdq and Dlm.

To summarise, the most recognized contribution of endTB to reducing country-level barriers has been a combination of jump-starting the importation and making the new drugs available in endTB countries while providing an opportunity for the clinicians to gain experience with them.

Prices of new drugs and other costs per patient

One factor that had not come forth out of the discussions with most of the in-country stakeholders, but was flagged by the global level stakeholders, is the price of the new anti-TB (and companion drugs) that potentially has a large influence on scale-up. In endTB countries, besides the costs of the Group 5[4] drugs (US$ 3,000-4,000/patient), MoH, GF, PIH, MSF or other NGOs would typically pay for GeneXpert testing, DST to second-line drugs, regimen with Group 1-4[5] drugs, Directly observed treatment (DOT), and patient support and accompaniment.

The price of Dlm in GF eligible countries is US$ 1,700 for a 6-month course. Current pricing for a 6-month course of Bdq is US$ 900 in low- and middle-income countries (LMICs), US$ 3,000 in middle-income countries (MICs), US$ 30,000 in high-income countries (HICs), US$ 1,700 in Russian Federation and US$ 1,351 in other countries in the Commonwealth of Independent States (CIS) countries.[13] At the same time the estimated generic prices are US$ 8-17/month for Bdq, and US$ 5-16/month for Dlm.[14] Many endTb countries still benefit from the USAID Bdq donation programme. However, what will happen after this donation programme stops is unclear. Currently, there is no information about any possible extension of the donation programme.

Manufacturing, commercialization, licensing or other measures that could engender competition and a reduction in the price of Dlm are not clear. In January 2013, J&J/Janssen entered into a licensing agreement with the Russian company, Pharmstandard, to register and commercialise Bdq in the countries of the CIS and Georgia. From May 2017, Pharmstandard supplies Russia with locally produced Bdq. The broader impact on Bdq worldwide pricing will not be clear until the end of the USAID and J&J/Janssen donation programme. As MICs become ineligible for GF support, they will no longer have full or any access to GDF's pooled procurement mechanism, while the relatively small quantities of drugs they require will not meet manufacturers' minimum order requirements[15]. Therefore, the prices of Bdq and Dlm and companion drugs, and access to

[4] Group 5 drugs date from previous WHO guidance on Programmatic Management of DR-TB. Current guidelines have adopted a different grouping. For consistency with the project plan, the evaluators maintain the term 'group 5' drugs.
[5] See previous footnote.

affordable, quality-assured MDR-TB medicines will continue to be important factors influencing the scale-up and have to be considered e.g. while developing the transition and hand-over plans.

4.1.4 Output 4 Facilitate the sharing of knowledge and dissemination of evidence that support the use of new TB drugs.

Output 4 of endTB is: “to facilitate the sharing of knowledge and dissemination of evidence that support the use of new TB drugs”. The related indicators are:
O4.1: number of users who accessed the endTB website within the reporting period
O4.2: number of content updates to the endTB website within the reporting period
O4.3: number of multi-stakeholder international meetings held within the reporting period
O4.4: number of people attended multi-stakeholder international meetings held within the reporting period

Progress towards targets

According to the information available at the time of the mid-term evaluation, the project exceeds targets across all four indicators.

Table 5. Overview of output 4 indicators

Indicator	2015-16 cumulative targets	2015-16 cumulative results	Achievement (%)
O4.1	500	1660	332%
O4.2	2	40	2000%
O4.3	24	52	216%
O4.4	375	1030	274%

Activities under Output 4 are:
Activity 4.1: Disseminate endTB clinical and programmatic findings globally.
Activity 4.2: Collaborate with other groups implementing uptake of new TB drugs and novel regimens.
Activity 4.3: Disseminate market intelligence information for new TB drugs and key companion TB drugs.

Similarly to the indicator designed to measure output 3, O4.1-O4.4 indicators do not seem suitable to fully capture the progress of all the O4 activities. The O4.1-O4.4 indicators are quantitative only and tell little about the quality of the information, pro-activeness and nature of the collaboration. More information is found in the sections below.

Dissemination of information

Communication and data sharing

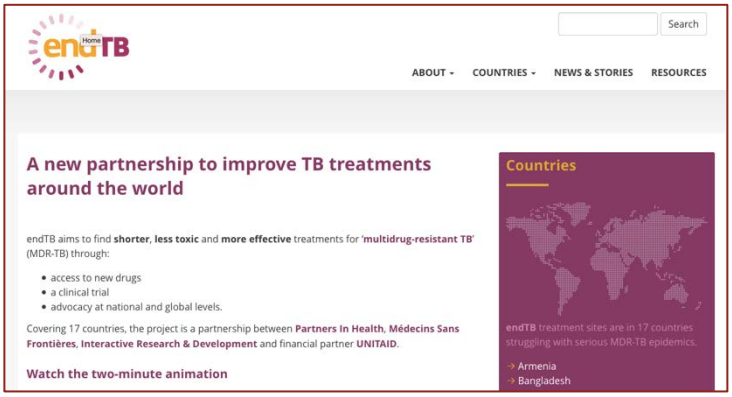
The evaluators have been informed that both the consortium partners and Unitaid consider that the communication between them has markedly improved. However a more timely, open, transparent bi-directional communication will improve efficiency and hopefully enable nimbler decision-making process including, but not limited to project changes.

Section 9 of the endTB Supplemental Terms and Conditions (April 2015) is relatively clear about data sharing and a Memorandum of Understanding (MoU) of data sharing agreement within the consortium was signed prior to start of data collection activities. These were to ensure there are no risks to one of the project's main goals, which is broadening WHO policies and guidelines, based on date/evidence generated by endTB. However, challenges related to data sharing were noted by the evaluators at the global (PIH/Unitaid) as well as country levels (Georgia; possibly Indonesia, Kazakhstan and Myanmar). At the global level, there were fears that the data will not be made available in a timely manner for the WHO guideline revision which is due to start in July 2018. At the country level the problem was around access to EMR for recording/reporting and decision making.

A new (2018) data sharing agreement between PIH and Unitaid was developed to solve the global level bottleneck. The analysis of the legal aspects of the new data sharing agreement between PIH and Unitaid is beyond the terms of reference of this evaluation. In Georgia, the challenge was being discussed and planned to be resolved between the MSF headquarters and the national stakeholder.

It appears very important for endTB to communicate and manage expectations of the global and in-country stakeholders regarding exactly what data is sharable, how, when, why (or why not). It is also important to enable the national TB programs as much as possible to have low-threshold access to and be able to use the data for clinical decision-making.

Website and social media



The endTB website was launched in June 2016 and since then had 29,733 unique page views. The viewers who accessed the site were from the following countries:

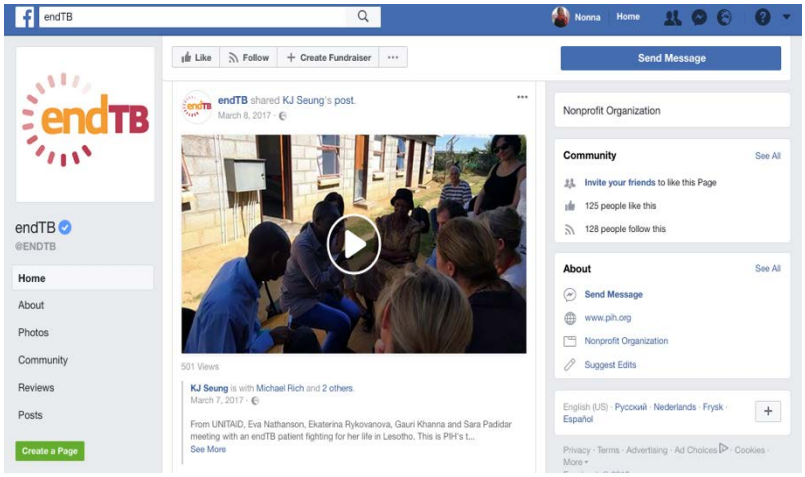
1 - USA (21.29%)
2 - France (8.9%)
3 - UK (8.6%)
4 - Russia (5.9%)
5 - Georgia (5.3%)

Besides the home page, the most frequently accessed website pages were:

1 – Resources
2 – About
3 – News & stories
4 – Q&A

Average time the users spent on the site was 2 minutes and 46 seconds, which is generally considered very long.

endTB's activity on Twitter is rather humble in terms of the number of tweets but it has a relatively good number (701) of followers. Many organisations that conduct studies or clinical trials do not have a twitter account or are less visible in social media.



endTB's Facebook page has little content and few followers.

Social media can help drive traffic to endTB website and are themselves the tools to interact with the global and in-country audiences, rapidly respond to queries and concerns, learn about the attitudes of the users, correct misinformation and engage with influencers.[16]

The other channels that endTB uses to disseminate their clinical and programmatic findings globally are via:

- DR-TB Scale-Up Treatment Action Team (DR-TB STAT) monthly calls. DR-TB STAT is a task force within the Global Drug-Resistant TB Initiative and consists of key global TB organizations, including civil society. Their objectives are to quick-start access to new drugs, optimize DR-TB treatment and prioritize regulatory approvals. PIH hosts DR-TB STAT secretariat.
- Yearly MSF symposia, stakeholder meetings and endTB regional workshops to which PIH and MSF invite non-endTB countries if their funding allows.
- The Union World TB conferences.

Communication strategy including branding and country-level plans

The endTB communication strategy was developed in 2016 and updated in 2018. It is accompanied by design guidelines, including key brand elements. The evaluators note that in the visited countries, the endTB project brand did not seem to be used and was not recognized as such by stakeholders. In Georgia, endTB activities are referred to as MSF's and in Indonesia as Muhammadiyah's. Similar observations were made during the

interviews with the stakeholders in the other four countries. Likewise, the Unitaid logo was not used systematically together with the endTB logo.

According to the communication strategy, a short communications and community engagement plan should be developed for clinical trial sites, identifying how proactive and reactive communications will be implemented to suit the national and site-specific context. Out of six countries the evaluators contacted for in-depth information, three countries were supposed to have a communications and community engagement plan. One of them (Georgia) had a plan, however it mostly resembled a report rather than a communication and engagement plan, as it gave an account of the situation (per 2016), activities that were carried out at that time and listed stakeholders, some of which are no longer active in the country.

Crisis communication response procedure was already a part of 2016 communication strategy version and was practically unchanged in the 2018 version. Until now the endTB consortium did not have to use crisis communication.

The renewed 2018 endTB communication strategy, which delineates the global, country and internal audiences, communication goals and tools, will be beneficial all endTB project implementers at the country level. This communication strategy can contribute to improvements in the other Output 4 activity: collaboration with other groups implementing uptake of new TB drugs and novel regimens.

Collaboration

With respect to endTB trial design, the consortium partners do not see any overlap with other MDR-TB clinical trials. endTB communicates at the global level with other groups implementing uptake of new TB drugs and novel regimens. Globally these are such groups as DR-TB STAT, implementers such as the Union and KNCV, advocates such as Treatment Action Group (TAG), GDF with its technical assistance to countries regarding scale-up plans, quantification and forecasting as well as the GF – all of them have contributed to the scale-up of the new drugs in countries.

There is active collaboration between endTB and TAG at the global level and in some countries. There is also collaboration at the global level with WHO, USAID and KNCV.

The evaluators observed and inferred from the stakeholders' interviews that there is variance between the countries in the level of collaboration with other stakeholders. Successful examples of in-country collaboration include:

- Joint trainings
- Joint participation in clinical review committees
- Assistance (from endTB/MSF) with drugs procurement
- Sharing information which enabled learning of stakeholders from endTB sites
- Joint assistance to guideline development and update to include new drugs

Improvements can mainly be made by informing the stakeholders better about endTB, particularly about:

- How endTB (is planning to) work on transition/scale up, including knowledge transfer to local national TB programs
- The amount of non-routine work involved in Output 1 observational study and any related incentives that are paid by endTB to the staff of the NTPs
- Any updates in output 1 and 2 as the in-country stakeholders appreciate this information is provided timely and in-country. Currently the stakeholders have to wait till e.g. the yearly MSF symposium to learn about the progress of endTB activities in their respective countries.

Thus, approaching collaboration more systematically: more regular contacts and better synergies/coordination could optimize the benefits for all parties.

endTB visibility in the two visited countries is low. It can be improved by consistent branding, but also through increased collaboration, and systematic, focused and pro-active communication.

Dissemination of market intelligence

Beyond being reported annually to Unitaid, market intelligence is disseminated by endTB in close collaboration with the MSF Access Campaign. endTB provides MSF Access Campaign with funding and field experience about access to new TB drugs and repurposed drugs in the endTB countries. MSF Access Campaign combines this information with other information gathered from non-endTB countries to get an overall picture of the market. MSF Access Campaign regularly publishes "DR-TB Drugs Under the Microscope" which analyses barriers to access of all second-line TB drugs including new and repurposed drugs. In addition, the Patent Opposition Database was created by the MSF Access Campaign as another way to disseminate and coordinate market intelligence about TB and other drugs (https://www.patentoppositions.org/en/about).

4.2. Theory of Change and Impact Framework

4.2.1. Theory of Change

Theory of change is a living document that ideally would be owned, maintained and updated by the endTB consortium to reflect changes in endTB project, changes in the assumptions and risks and the dynamics in the context that can influence the attainment of the project outputs, and consequently the outcomes and impact. Because the endTB grant was a legacy one[6], signed under previous Unitaid processes, the grant did not include a ToC from the beginning. The evaluators developed the ToC in close collaboration with the consortium partners.

endTB ToC starts with revisiting the market shortcomings and problems to be addressed by the project. Then project-related and broader contextual assumptions are identified, as well

[6] endTB signing was not under Unitaid's new operational model where grants are required to have a results framework with a clearly articulated theory of change, impact and logical framework.

as the contextual drivers. Taking them into account the ToC is mapped to include project inputs, project outputs, broader outcomes and eventual public health impacts.

Problems to be addressed

In 2014-15 endTB identified a number of market shortcomings, which it aimed to address, and their underlying reasons that created or contributed to the shortcomings. The project has been successful in supporting endTB countries overcome some of the market shortcomings (see section on Public Health Impact []). The remaining problems that the ToC addresses are:

- Current MDR-TB treatment regimens are long and toxic resulting in poor treatment outcomes:
    - Current MDR-TB treatment regimens generally include an intramuscular injection for 8 months in combination with oral medications for a total duration of 20 months, which makes them challenging for health care providers to administer and for patients to adhere to.
- Remaining gap between the need and access to new drugs for TB (Bdq, Dlm):
    - NTPs are reluctant to use new TB drugs because of the lack of safety evidence and clinical experience.
    - There is insufficient scientific evidence on how to use new TB drugs, leading to uncertainty on how to incorporate them as part of MDR-TB treatment regimens.
    - New TB drugs are approved based on data from very small clinical trials that provide insufficient evidence about adverse events in field conditions.
    - New TB drugs are approved by stringent regulatory authorities under the condition of post-marketing pharmacovigilance, but many resource-limited settings have weak or even no pharmacovigilance infrastructure.
- MDR-TB drugs market is small and fragmented:
    - The MDR-TB market is too small to provide incentives for manufacturers to invest in development of new MDR-TB drugs, and manufacturers usually invest in medicines rather than regimens:
    - Current MDR-TB regimens' complexity leads to both low and variable demand.
    - Many countries lack the regulatory expertise and infrastructure to evaluate new drugs, and few stakeholders are focused on understanding and navigating regulatory processes.

In addition to access barriers specific to endTB countries, globally TB remains a large and urgent public health problem.

Alignment with endTB Strategy

The endTB project contributes to the global endTB Strategy that was endorsed and adopted by the WHA in 2014[3]. The strategy contains three pillars to ensure elimination of TB rather than controlling it as in the Stop TB strategy that had guided global efforts until the new strategy replaced it:

1. Integrated and patient-centred TB care and prevention: the current global strategy emphasises the importance of treatment for all TB patients, including those with drug

resistant TB, including MDR- and XDR-TB. Of the 600,000 estimated MDR-TB patients, only 22% initiated treatment in 2016. Treatment outcomes are poor at 54% success for MDR-TB and 30% for XDR-TB. Various reasons contribute to these poor outcomes, among them the fact that current treatment regimens are long and toxic. The endTB project works on generating the evidence for shorter, saver and more effective regimens. O1 includes also patients with co-morbidities such as HIV, diabetes mellitus and hepatitis C and will generate evidence for the management of such patients.

2. Bold policies and supportive systems: the components that are relevant in the endTB context include engaging the private sector and rational drug use. Among the endTB countries are three countries where the consortium implements the project in the private sector: Bangladesh, Indonesia and Pakistan, covering more than 10% of the global estimated MDR-TB patients. The private sector is for many people in these countries the first point of the health care system where they seek care, and engaging this sector in TB care, including for MDR-TB patients, is extremely important. Furthermore, the endTB project aims at providing the evidence for a shorter, saver and more effective regimen that has the potential to reduce further resistance development. This is very important given the increasing levels of antimicrobial resistance and the time it takes to develop new medicines.
3. Intensified research and innovation: this is what the endTB project is about. Research, both in the form of a clinical trial and operational, to generate the evidence necessary for policy recommendations. The clinical trial looks into innovative and shorter, all oral MDR-TB treatment regimens. The operational research comes from implementing the use of Bdq and Dlm in the field, which contributes to learning about how this is best done.

Anti-microbial resistance

Anti-microbial resistance (AMR), where micro-organisms develop resistance against the medicines used the treat infections with these organisms, has become a global threat. This is also clear in TB control, with 600,000 people developing resistant TB each year. The WHO leads responses to this threat, and Unitaid has joined these efforts. In October 2017, Unitaid became chair of a working group of the United Nations interagency working group on AMR. This group works on access to innovative diagnostics and treatments to address AMR. endTB's efforts to scale-up the use of new medicines and the development of novel regimens align very well with the work against AMR.

ToC assumptions related to endTB project and broader

The following assumptions were developed as part of the ToC mapping process:

1. The data generated under output 1 are of sufficient quality and quantity to inform the 2018 WHO PMDT policy revision (project-related assumption)
2. Randomized clinical trials under Output 2 are completed and identify one or more non-inferior MDR-TB treatment regimens (compared to the control arm) using ~ ten medicines (1-3 priority regimens including new TB drugs that treat all forms of MDR-TB including pre-XDR-TB and XDR-TB; 5-8 priority TB drugs to treat MDR-TB), instead of the multiple medicines used currently (project-related assumption)

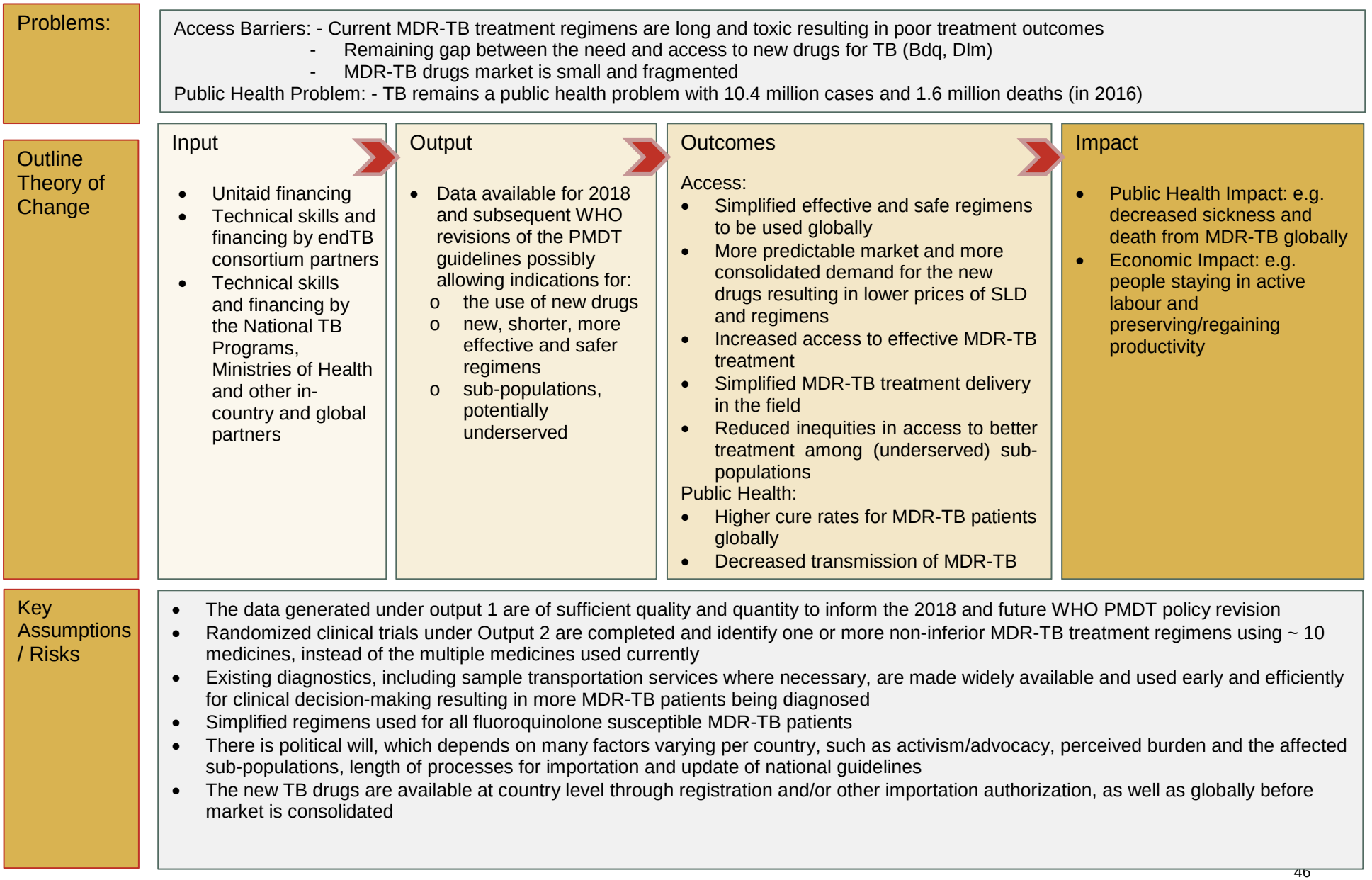
3. Existing diagnostics, including sample transportation services where necessary, are made widely available and used early and efficiently for clinical decision-making resulting in more MDR-TB patients diagnosed
4. Simplified regimens used for all fluoroquinolone susceptible MDR-TB patients
5. There is political will, which depends on many factors varying per country, such as activism/advocacy, perceived burden and the affected sub-populations, length of processes for importation and update of national guidelines
6. The new TB drugs are available at country level through registration and/or other importation authorization, as well as globally before market is consolidated
7. Suppliers and buyers collaborate with sufficient negotiating power for buyers; this includes generic manufacturers coming on board and other intellectual property interventions
8. Market remains attractive for producers of drugs: as a whole there is a larger demand but for fewer drugs and the treatment duration is shorter
9. Providing clinicians on the ground with experience using new drugs will substantially contribute to scaling up the use of the new drugs
10. Good quantification and forecasting capacity at country level provide adequate and timely information on global need.

Contextual drivers:

1. Additional evidence on Dlm is urgently needed because there are still gaps particularly regarding treatment outcomes using Dlm and long-term outcomes.
2. Improved rapid diagnostics for SLD resistance, e.g. Cepheid's Xtend cartridge and a 2nd generation Hain test will allow better information before designing the regimen, and allow an optimised regimen, therefore leading to better outcomes;
3. High level meetings such as the Moscow meeting in October 2017 and the UN general assembly on TB in September 2018, may contribute to increased funding to reduce the funding gap in End TB Global plan;
4. Link to worldwide concern on antimicrobial resistance makes TB more known among the general public including decision makers which helps increase awareness and potentially funding;
5. Development of alternative regimens may result in using about ten different medicines; one regimen will never cure all TB due to (extensive) resistance patterns, side effects, patients' idiosyncrasies;
6. Development of new drugs:
   - Bdq 2nd generation: better anti-mycobacterial effect, less influence on QTc prolongation;
   - Sutezolid: may replace linezolid
   - Otsuka working on a new class of drugs (DPRA1 inhibitor);
   - All these developments are good because (ultimately) resistance will develop, and new drugs are needed; it may also result in treating all TB with different drugs than what is being used now.
7. Addressing HIV, poverty and Diabetes Mellitus as risk factors for TB will influence what happens to TB.

Figure 1 (endTB project Theory of Change) combines the problems to be addressed, outlines the pathway from inputs to impacts and lists the most important assumptions.

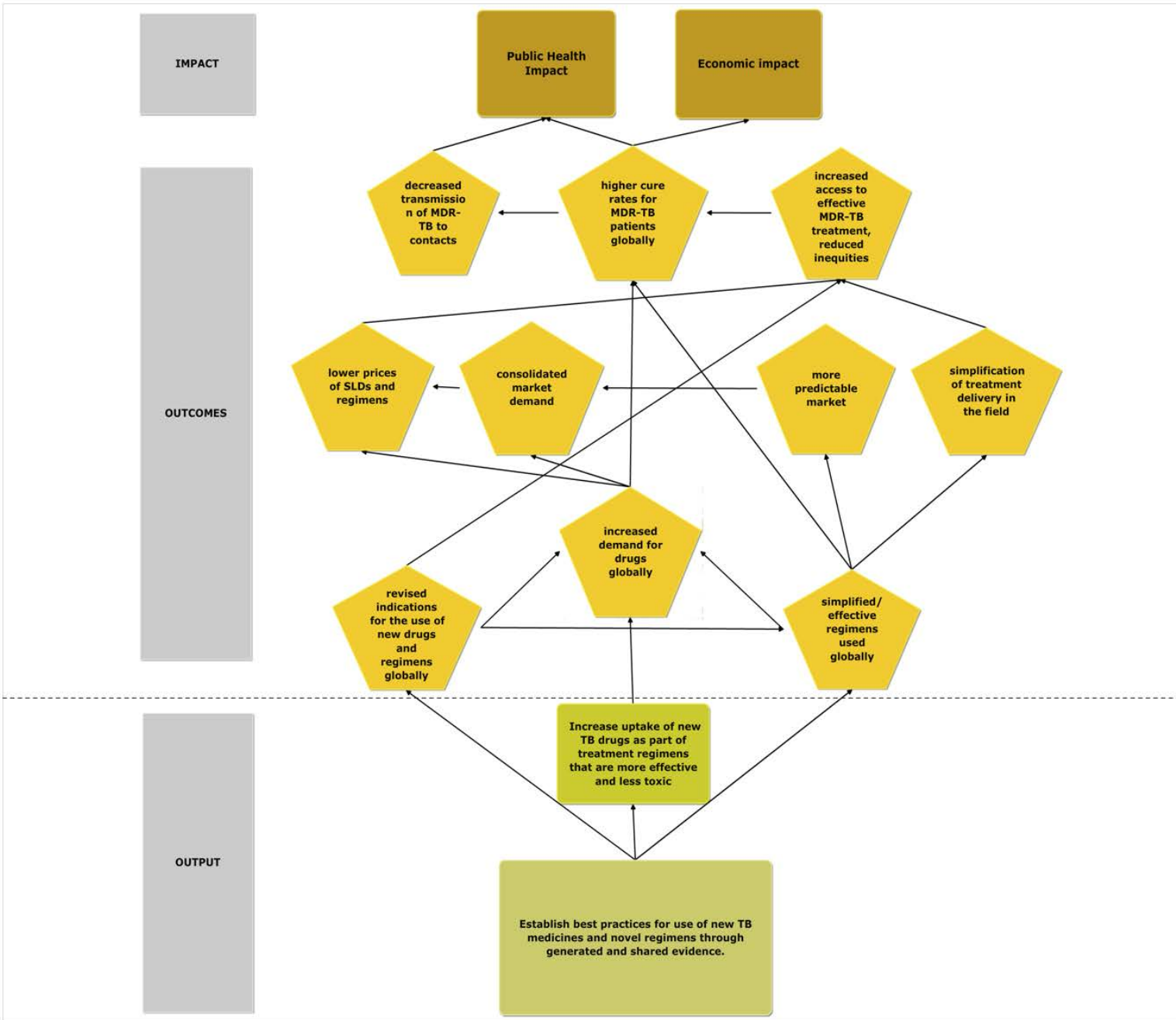
Figure 1. endTB project Theory of Change



4.2.2. Impact Framework

Figure 2 below is a simplified illustration of the relationships among various outcomes, identified in the ToC, and the relationships between the outcomes and the two impact areas: public health impact and economic impact.

Figure 2: Graphical representation of the pathway from outputs to impact



Public Health Impact

endTB has achieved marked progress in a number of areas, related to innovation and availability, and demand and adoption, which are ultimately linked with public health impact.

Achievements to date in Innovation and Availability[7]:

- Currently there are clinical trials conducted on how to combine new and old drugs into a potentially shorter and safer regimen, these include: endTB and DELIBERATE, NC-008, NIX-TB, Ze-NIX, NeXT, STREAM II, TB-PRACTECAL (See Appendix 7. Regimen Trials for DR-TB for details). However, endTB's unique contribution consists of a large cohort of patients receiving treatment under routine conditions with excellent data available; O1 remains one of the largest cohorts[8] of patients receiving Bdq, Dlm or the combination of the two. Even small subsets of special populations within the endTB O1 observational study will be relatively large.
- New TB drugs are available in most endTB countries, although new TB drugs have still not been approved everywhere. The body of scientific data is growing, also thanks to endTB.

Achievements to date in Demand and Adoption[9]:

- The insufficient scientific evidence (from small trials) remains; such evidence is even more necessary in view of the recent phase III trials preliminary results (STREAM I[10] and Trial 213) which led to confusion in some endTB countries.
- Pharmacovigilance is in place at endTB sites and in some countries endTB pharmacovigilance contributed to or was scaled up to whole TB programs.
- In endTB countries there is improved and increased willingness of the clinicians to use the new drugs, and an increased clinical experience.
    - At the beginning of 2018, 11 project countries used the new drugs beyond endTB.
    - NTPs used to be reluctant to use new TB drugs because of the lack of safety evidence and clinical experience, whereas now there is much less reluctance of the NTPs to use new TB drugs in endTB countries.

endTB achievements in areas innovation and availability, and demand and adoption contribute to achieving the two main project outputs: establishing best practices and contributing to the update of international guidelines on the new drugs. endTB outputs are linked to a number of inter-related outcomes, already noted in the ToC. Graphical representation of the pathway from outputs to impact shows, in a simplified way, the complexity of progressing from "revised indications for the use of new drugs and regimens

[7] Innovation and availability: here is a robust pipeline of new products, regimens or formulations intended to improve clinical efficacy, reduce cost, or better meet the needs of end users, providers or supply chain managers. It means that new and/or superior, evidence- supported, adapted products are commercially available and ready for rapid introduction in low and lower-middle income countries.

[8] The largest cohort comes probably from routine programmatic use in South Africa, however, without the detailed data collection that occurs in O1.

[9] Demand and adoption: countries, programmes, providers (e.g. healthcare providers, retailers) and end users rapidly introduce and adopt the most cost-effective products within their local context.

[10] endTB remains important in the landscape of on-going and completed clinical trials for MDR-TB treatment, including STREAM I and Trial 231. STREAM I focused on shortened regimen using conventional drugs, whereas Trail 213 was a registration trial not powered to generate evidence on treatment outcomes using Dlm. Both were not considered to give rise to any change regarding the on-going evidence generation on the new drugs including endTB.

globally" to increasing the demand for new drugs, and adopting simplified and effective regimens in and beyond endTB countries. To help measure the project outputs and broader outcomes, one could look into such variables as: proportion of patients eligible for new medicines, disaggregated by resistance indications and intolerance reasons, and proportion of patients with favourable outcomes.
The mentioned outcomes are meant to make the MDR-TB medicines market more predictable, consolidated and ultimately lower the prices of SLDs and regimens. At the same time, simplified effective regimens are expected to result in a simplification of treatment delivery in the field. Simplified treatment delivery and lower SLD prices are expected to contribute to an increased access to MDR-TB treatment, while reducing inequities, positively contribute to cure rates and decrease transmission.

Higher cure rates, primarily because of fewer MDR-TB deaths, patients LTFU and treatment failures, and less transmission will mean decreased sickness and death from MDR-TB globally, and ultimately reduced incidence and prevalence. More people will return to or remain in the active labor force faster. Ultimately the public health impact can be measured in terms of the quality of life expressed as a loss [disability-adjusted life years (DALY)], or a gain [quality-adjusted life years (QALY). Sequels and disabilities as a result of anti-TB treatment[17] as well as mortality shortly after TB cure[18] [19] will need to be factored in to the analysis.

Economic Impact

a) Potential Value for Money Framework for Unitaid endTB project

endTB initiated before Unitaid developed a comprehensive Value-for-Money (VfM) framework. The "new" framework is designed well to hard-wire VfM into every new project supported by Unitaid from the earliest design moments right through to measuring impact long after a project has ended.

The endTB project and Unitaid would definitely benefit from retrospective efforts to apply at least some of the aspects of the framework to the on-going project implementation. It would further enhance capitalization of the post-implementation impact evaluation efforts. The challenge is that retrospective economic analysis is less than ideal and partially impossible to do. It is less efficient than planning it from the start, but the investment can still be well worth it.

Presented below is a look at the various elements of the VfM framework and how these may be applied to the endTB project.

Value for Money goal: maximizing the impact of each dollar (US$) spent by Unitaid, through the optimization of the efficiency, effectiveness and scalability of our investments.

Table 7. Efficiency, effectiveness and scalability criteria and endTB

Criteria	endTB project
Efficiency: Unitaid's resources should be used in an efficient way	This is assumed to be planned in when budgeting each project. The different country contexts and implementing partners make a de facto assessment of efficiency and comparability across contexts difficult. The exercise in itself is not complicated, it is just not clear how useful the resulting measures of use of the project budgets in each context is, in making a statement about efficiency and how to compare results across contexts.
Effectiveness: Unitaid's investments should lead to an optimal set of outcomes that add value to the global response	This is a mixed situation of partially achieved results of the two outcomes. The added value is foreseeable, but not yet clearly established. The global response is still being shaped and it is clear that the endTB project is generating very significant evidence towards this. The project evidence available will contribute to the revision of WHO policy recommendations for PMDT related to treatment planned for June 2018. The findings of endTB will also be used for future policy revisions.
Scalability: Unitaid-supported health products must have the potential to be utilised at scale to maximise the effectiveness of the global response	Some data from the mid-term evaluation: - In 11 countries there are other non-endTB funders identified and they fund already or start funding the new drugs procurement: GF (8 countries), GF/ with Government taking over in 2020 (1 country) or NTP/GF (1 country); - 4 countries – no information; - 2 countries – problems may be expected as no other funders identified (Peru and DPRK). In endTB countries, the project contributed to the scale up by: 1. Quick-starting the importation 2. Providing clinicians with experience working with the new drugs 3. Assisting to update national guidelines to include new drugs. To reach economies of scale and maximize the effectiveness of the global response, it is necessary to get countries where the highest needs are (China, India and the Russian Federation accounting for 47% of the estimated burden of MDR-TB)[1] to also adopt the new drugs to achieve real market impact.

b) Suggestions to measure Value for Money

As noted above, VfM is about maximisation of impact. VfM can be quantified in a number of ways, and for Unitaid it remains focused on public health impact. To support the measurement of VfM, Unitaid uses the ToC to assess how a potential impact framework will be designed. Different approaches could be considered:

- *Cost-effectiveness analysis*: the measurement of public health impacts through QALYs and DALYs (see above) will enable cost effectiveness considerations. One metric that could be used is the cost per DALY averted or per QALY gained. For example, the latter costs could be calculated for the endTB clinical trial and compared to similar costs of other TB or MDR-TB clinical trials.
- *Return on Investment*: It has been observed, as noted above, that even while Unitaid through endTB invests in inputs at project level, in parallel to this, partners and other

organizations are providing inputs as well. Even at this early stage in the TToC process, a form of return on investment analysis is possible:
    - Here one can consider Unitaid's investments catalysing investments of others in furthering the reach of the whole chain of the logical framework as a measure of VfM: so much Unitaid input investment has catalysed so much further investment and inputs (worth US$ xx).
- *Qualitative*: O1 results will provide a wealth of contextual qualitative data which will also help to inform where there is potential to refine approaches to be able to reach those in need.

Risk Analysis

Risk analysis is a key sub-component of impact assessment, i.e. to undertake a sensitivity analysis of the key assumptions that drive the identified impact. Also, the VfM and economic evaluation elements of the project are subject to numerous, some very far reaching assumptions, especially as the time-line extends quite far into the future. The Unitaid ToC framework foresees a solid risk analysis along the lines of the VfM drivers and the risk along the three categories of strategic, implementation and sustainability – and these along the dimensions of internal and external. The investment of adequate analysis of these various elements will be well rewarded with extended capitalization of impact assessment as the project extends into the third moment on the project timeline in Unitaid's VfM framework.

The discourse on the risk framework was mainly intended to inform the discussion on the need for sensitivity analysis as part of the economic analysis, given the many assumptions upon which the project success is founded. It is beyond the scope of the mid-term evaluation to delve into the comprehensive risk assessment framework in any detail.

Finally, Unitaid is simply encouraged to continue with initiatives already made to apply their VfM framework to the project and to engage and invest in a proper economic analysis retrospectively as soon as possible. The sooner they engage, the easier and more efficient it will be to collect the needed economic data, alongside the "typical" public health data already being collected. The potential harvest of VfM information for the endTB is substantial.

4.3. Managerial aspects of grant implementation

4.3.1. Programmatic and financial management

According to Unitaid, under the new operating model, grant management is more interactive with country missions, and there frequent touch points and engagement with the grantee requiring a deeper understanding of the evolution of the grant. The information that the consortium presented in this changing context was not perceived by Unitaid as sufficient. PIH's financial management of the consortium seems to be based on trust rather than on rigorous checks. In the past, PIH was not ready to promptly provide Unitaid with the details about prospective budgets or explain the figures in the financial reports.

Unitaid and endTB discussed the concerns and expectations of Unitaid from the lead grantee and Unitaid gave examples of process flows for financial management. In the past 18 months some areas such as budgeting and the processes of consolidation of financial reports, have improved, but it seems to have taken a lot of time of both the endTB and Unitaid and is still in need of further improvements.

Unitaid and endTB continue improving visibility of e.g. how exchange rates are managed, how the procurement is managed, and still need to work on improving reconciliation between the financial and procurement information. Because of the persisting numerical errors and unclear narrative explanations Unitaid's confidence is still not extremely high. Some reluctance from the consortium was noted and remains to date. For instance, Unitaid requested PIH to conduct financial spot checks of MSF and IRD. MSF clearly indicated that they were not managed programmatically or financially by PIH, although they highly appreciated the collaboration and the efforts PIH was making as the consortium lead. IRD does submit ledgers for financial control if needed, but programmatically the partners act as equals. IRD is also content with the collaboration of the consortium.

It is possible that MSF country offices do not know what proportion of their budget or what budget items are or will be funded by endTB. In Georgia, MSF budgets for their entire operations on a yearly basis and then the headquarters decide what gets billed to Unitaid. In case an expense turns out not billable to Unitaid it is covered by MSF's own funding, this is a retrospective process.

4.3.2. Procurement and supply management

Capacity and scheduling constraints have made it impossible for the Unitaid procurement unit to visit any of the project countries to fact-check Procurement and Supply Management (PSM) activities and achievements under the Project Plan. The PSM unit is unaware of the level of pooling and reliable quantification of the drugs and has, at best, limited PSM visibility of project implementation. The consortium partners did not indicate any PSM challenges, there were no stock outs or significant amounts of drugs expiring, according to them. At present in most of the countries, the GF either is already covering or is planning to fund the procurement of Bdq and Dlm.

4.3.3. Staffing

endTB considers that the central level staffing is rather spare. At the same time, for instance, Unitaid's suggestion to hire temporary staff to assist with the financial management was not followed up on by PIH.

At the country level endTB perceives itself as working within the existing staffing structures, not creating parallel systems where these did not exist before. The evaluators do not have sufficient information to either confirm or refute this. During the visits to two countries and interviews with four other countries, different modalities of operation were observed. In some cases, the implementing organisations had in-country presence and various staff well before endTB and will continue to do so; in some countries, the consortium partners were perceived to invest relatively little in the local systems or staff and instead implement the PMDT

programs themselves. In some cases, the local national programmes did not have the capacity to run PMDT, but their capacity was also not being built up. In a number of countries where Output 1 or 2 was considered to create a lot of additional non-routine work for NTP/MoH there were some incentives offered on case-by-case basis.

4.3.4. Learning

endTB has many learning moments: there is the Central Medical Committee, management calls and meetings, annual consortium meetings, consortium partners visiting each other's sites, and the yearly symposia. Among other things, the project conducts regional trainings, where many countries participate, and representatives of the NTPs and endTB projects staff have the possibility to network and exchange experience. Non-endTB countries can participate too, if budget allows and if their participation is justified they get funded from the project, or MSF or PIH directly. However, the consortium had some difficulty explaining their approach to learning and if and how learning was incorporated into project management cycle and decision-making. Interventions were done on individual data points and trainings were provided as needed. A more structured approach to learning and capacity building, including the capacity building of the NTP staff in endTB countries, could contribute positively to the effectiveness and efficiency of the project.

4.3.5. Risk management

The evaluators received several documents: a draft endTB/PIH risk register of 2014, a grant risk progress template used to identify and periodically assess risks, Risk Management Matrices in each report, and an internal Unitaid risk progress tool. The risk progress tool had one endTB risk assessment dated December 2017. The consortium fills out a Risk Management Matrix with each annual and semi-annual report. Two highest risks, identified at end 2017 were: (1) Delays or low patient enrolment into clinical care with new TB drugs (the clinical trial. Output 2) and (2) Delays in (or absence of) sharing the PV and efficacy data from the observational study and clinical trial with the WHO and other relevant regulatory bodies. The evaluators discussed these risks with the lead grantee during a face-to-face meeting in Boston to understand how they are managed. The consortium updates the status of reach risk every six months and also adds risks that may be introduced through the management letter they get from Unitaid after each annual and semi-annual report. Each risk is scored based on likelihood and impact, also there is a mitigation strategy articulated if the risk occurs. The systems to identify and manage risks are in place at the endTB and Unitaid's sides.

5. Conclusions

The endTB project contributed significantly to the uptake of new TB medicines in the project countries. By introducing these medicines into clinical care in both the public and private sector, clinicians in endTB countries had the opportunity to gain experience in MDR-TB treatment in practice, while directed by clear guidelines, with easy access to consultation of the consortium partners if needed for (clinical) questions and patient management. This confidence built in the clinicians is a crucial factor in use and scale-up of the medicines.
In addition, the endTB contributed to two other important factors for use and scale-up: the importation mechanisms for the medicines and the availability of national clinical guidelines stipulating the use of the new drugs.

Furthermore, the endTB project has a great potential to contribute to policy recommendations for the treatment of MDR-TB both now (the 2018 revision of the WHO guidance) as well as in the future. The O1 results available at the end of the project, and beyond, are of good quality and form a large cohort of patients. O2 is looking into innovative treatment regimen all oral and of 9-month duration, could make a large difference for patients compared to many treatment regimens in use currently.

endTB has achieved marked progress in removing market barriers to new drugs through making them more available, generating demand and promoting adoption. More long-term and global contribution of the endTB project to outcomes such as higher MDR-TB cure rates, less transmission and reduced incidence and prevalence, will take longer to become apparent. Public health and economic impacts can be expressed as gains in the quality of life and Return on Investment. It is up to a detailed impact assessment to determine the exact areas of impact and the measurements. Such impact assessment needs to be planned as soon as possible, in order to establish the methodology, model and what data need to be collected.

The evaluators assessed the endTB project against standard evaluation criteria, as developed by the OEDC's Development Assistance Committee. The results of this assessment are summarised here.

Relevance: rated as high

1. The project is well aligned with Unitaid's 2017-2021 mission, which focuses on maximising the effectiveness of the global health response, acts as a catalyst and focuses on access to good health products. endTB contributes to all three aspects of the mission because the project aims at finding more effective treatment for MDR-TB, the projects acted as a catalyst to introduction of the medicines in most of the project countries, and as such provides access to the medicines to people who may not have had access without the project.
2. The project is well aligned with Unitaid's 2017-2021 strategy. It addresses an important public health problem and it contributes to scale up of the use of new TB medicines and to developing new treatment regimens. endTB is also well aligned with the current (post-2015) Global TB Strategy to prevent, care for and control TB and global efforts to address antimicrobial resistance. In the landscape of trials on TB, endTB remains unique because of conducting a RCT with the new TB medicines, in addition to a large

observational study of patients receiving Bdq, Dlm or the combination of the two. Even small subsets of special populations within the endTB O1 observational study be relatively large.

3. The project is also relevant in the context of all three pillars of the global strategy to prevent, care for and control TB[3] . The first pillar, integrated and patient-centred TB care and prevention, includes component B on treatment for all TB patients including those with MDR-TB, and component C which aims at managing co-morbidities such as HIV and hepatitis C. The observational study includes participants with such co-morbidities. The second pillar of the strategy, bold policies and supportive systems, includes a component targeting engaging the private sector as well as a component on rational drug use. The endTB project touches on both these components. The third and last pillar, intensified research and innovation, includes components on the development of new interventions as well as research to optimize implementation and impact. Again, this is at the very core of the endTB project: development of new regimens for MDR-TB and looking into how countries can use new medicines rationally and confidentially.
4. Globally, anti-microbial resistance is now recognised as an important health challenge. The endTB project is highly relevant in this context because of its focus on the introduction of new medicines and of the development of novel regimens for treatment of MDR-TB.

Effectiveness: rated medium to high

1. The outputs of the grant are consistent with the objectives and the outcome to establish best practices for the use of new TB medicines and novel regimens through generated and shared evidence. Obviously, it is too early to speculate on the results of O2; however, if one or more of the experimental arms show non-inferior treatment outcome with similar or – better - less toxicity, then future MDR-TB patients will benefit substantially.
2. Currently, the consortium executes the project within the budget. The grantee estimates a budget gap to optimally conduct an extension for O2, which the evaluators could not verify. However, the effectiveness is rated medium due to substantial delay in implementation of the project's O2 mainly because the activities plan was very ambitious while the protocol development and approval by all relevant authorities, including in the trial countries, took much longer than anticipated.
3. The grantee stated that the consortium responded to the WHO's public call for individual patient data on treatment of rifampicin and multidrug-resistant tuberculosis (MDR/RR-TB), which will be used to update the WHO treatment guidelines, stating that the consortium will provide data.

Efficiency: rated as medium

1. The national authorities are involved to varying extents at different stages of the project and their involvement seems to differ depending on the implementing partner in-country. In some countries, endTB project planning and implementation were done in close collaboration with the national stakeholders, primarily the national TB program, in other countries the national authorities did not seem very engaged, but were still informed about the implementation.
2. Grant implementation can benefit from improved financial management; the emphasis of the project is on field treatment and research activities rather than on the project management procedures.

3. Challenges are raised with the Unitaid Secretariat when the consortium deems it necessary, which does not seem to be often, the main challenge – planning for continuation of Output 2 activities remains unresolved and is a source of concern since the start of the grant.

Impact: rated as medium to high

1. The grantee reported on impact as outlined in the project plan and Log-Frame through indicator 'the number of patients who newly enrolled to receive a new TB drug as part of their MDR-TB regimen in an endTB country within the reporting period'. The latest data available – though not verified yet – are from the end of 2017. These data show an achievement much higher than the target, with a substantial improvement in 2017. Even more impact is expected from the potential policy recommendation based on the project's results when the data from O1 show good results and an acceptable safety profile, and when the O2 data become available in 2021 (on the assumption that the consortium will receive an extension), further impact is expected if the trial shows that the shorter regimens are not inferior to the current 20 months regimen, and less toxic.
2. Public health and economic impact can be measured in terms of gains the quality of life, Return on Investment, a qualitative assessment can be carried out, or it can be a combination of quantitative and a qualitative assessments. Investing in data collection for impact assessment now will facilitate post-implementation impact evaluation.

Transition and scalability: rated as medium

1. The new drugs have been integrated in the national clinical guidelines in most of the endTB countries, which contributes to the scale up of the use of the new drugs. In the majority of the countries endTB contributed significantly to the scale up by quick starting the importation of the new drugs, and providing clinicians with the training and practical experience of using the new drugs.
2. One activity that has in most countries been transitioned is the funding for the new drugs; commonly this funding is taken over by the GF.
3. Country operational plans (Appendix 1.5 of the project plan, 2014) outline transition and sustainability arrangements per endTB country. However, detailed transition and hand-over plans for the majority of the countries are not yet available.

Learning and risk mitigation: medium

1. Learning takes place within the consortium but there is no structured approach or a system using lessons learnt in the project cycle. Except for the events (presentations, meetings) on the results of Output 1 at the 2017 World TB Conference, there are no documented lessons learnt.
2. The programmatic and financial risks were identified in 2014 in a risk register. Over the course of grant implementation, a new Unitaid risk tool was developed. It is a tool for internal use which was applied for the first time in December 2017 and will be applied at least every six months. In addition, the endTB consortium updates a Risk Management Matrix every six months and submits it to Unitaid as part of routine reporting.

The evaluators consider it a substantial risk of already invested resources if the clinical trial under O2 is not allowed to continue. Continuation of O2 would require an extension of the current grant.

6. Recommendations

To Unitaid:

1. A decision on the future of the grant, specifically regarding O2, should be taken sooner rather than later. This is important because if continuation of O2 has implications on the trial design, the earlier decisions are made the better; and in addition, if such a design change were to occur, then continued enrolment may contribute to additional loss of investments.

2. For future grants, Unitaid may wish to take into consideration that grants including clinical trials, which require protocol approval of another entity, and that have a significant follow-up period, such as trials for MDR, need a substantial preparatory time before initiation of the trial. Such preparatory time should be included in the grant period. The importance of follow-up time for trials on MDR-TB is not only related to the duration of the treatment (current short regimen at least 9 months, often at least 20 months), but also that the trial should look into relapse rate for which more follow-up time is needed.

To Unitaid and the grantee:

3. To prevent further delays on O2, Unitaid should ask the grantee to present a clear enrolment plan which shows when trial enrolment will be completed taking into account the fact that Kyrgyzstan still did not start enrolling and that a new site needs to be prepared to replace Georgia.

4. Unitaid and the grantee should expedite resolving the data sharing issue such that data become available as soon as possible to influence PMDT guidelines and through these improve the care to patients with MDR-TB. This applies to both the data on pharmacovigilance as well as the other data from the observational study.

5. The impact framework outlines relationships between endTB outputs, outcomes and the two impact areas: public health impact and economic impact. The impact framework is linked to the endTB specific ToC. endTB consortium is encouraged to maintain the ToC co-developed during this evaluation and adjust it as the project progresses, the clinical trials landscape alters, and the assumptions and contextual drivers change. Maintaining an up-to-date ToC will assist the economic analysis of the impact. Unitaid should consider an in-depth economic analysis as soon as possible, starting with establishing the methodology, model and collecting the required data.

To the grantee:

6. The grantee should use the remaining grant time optimally to transition the experiences gained from the project to national programmes or other relevant stakeholders. This includes several aspects:
    a. Continue working on including the use of the new medicines in national guidelines where this inclusion has not yet occurred (Bangladesh, Haiti, Indonesia (Dlm only), Kazakhstan, Lesotho, Myanmar, Peru (Dlm only));

b. Adapt the EMR to be better usable for clinical decision making and for programmatic needs; this means – amongst others - that the system should allow missing variable (as a variable), be available to clinicians during their consultations and include alert (such as 'this patient is due for bacteriological examination'); and have downloadable reports that are aligned with (inter)national recording and reporting procedures. Currently the system is mostly used for project research purposes. National programmes should have access to their patient data without restriction (apart from the usual restrictions related to patient confidentiality.
c. Provide targeted TA in endTB countries, including TA to ensure sustainable financing and transition, preferably prioritizing the capacity building needs of the national and local staff. Develop a TA plan, based on the current gaps in capacity and foreseeing the knowledge and skills the in-country specialists will need in the near future to scale up the use of the new drugs.
d. Develop transition and hand-over plans in line with country operational plans as soon as possible, as the project nears its completion. Such plans have to be developed with a special attention to two countries (Peru and DPRK) where no funders of new drugs have been identified. In Bangladesh, Indonesia and Pakistan this should also include provisions on how to continue the activities in the private sector. The grantee should use their experience in the private sector to develop a model of care for use in the wider TB community.

7. The grantee should systematically analyse O1 data to identify any safety or effectiveness concerns related to the new medicines that would warrant more caution or even an interim analysis of O2. While at present there are no reasons to consider that the new medicines would have safety or effectiveness concerns, analysis of O1 data may reveal such concerns. If this occurs, the grantee should discuss with the scientific advisory committee if an interim analysis of O2 data is warranted. Furthermore, the grantee should explain very clearly how analysis of O1 is done, and by which subgroup to avoid overestimating the effect of the new medicines.

8. Have a more systematic approach to learning, and document lessons learnt. All consortium partners interviewed by the evaluators indicated great learning within the project, but lacked information on how this learning was systematically documented and how it influenced implementation or change of practices, also it was not clear if and how lessons learnt by one partner or from implementation in one country could benefit other partners and implementation sites. Documenting lessons learnt will help continue scaling up the use of the new drugs in endTB countries after the project completion and could benefit other (non-endTB) countries in new drugs' introduction and scale up.

9. The consortium needs to apply and follow its communication strategy in order to improve in-country visibility, communicate clearly about the objectives and the approaches of endTB with in-country stakeholders, including proactive and systematic communication with the WHO country offices. This will reduce ambiguity and increase transparency which will positively contribute to collaboration in-country.

The Output 2 sites need to develop their proactive communication and community engagement plans, also with the view of improving enrolment.

10. endTB are encouraged to use more structurally their approach to removing barriers and scaling up of new drugs in line with the six elements needed for introduction of new TB drugs, as per WHO Policy Implementation Package for New TB drugs[2]. One possibility is to collaborate with other global and/or in-country stakeholders to conduct a rapid assessment similar to the readiness assessment checklist of how well a country meets the minimum requirements for introduction of new TB drugs/regimens[2]. This may help identify and prioritize the remaining barriers and focus on a small number of high impact interventions to address them within the grant life-time. This applies especially to the countries that continue to experience problems with the new drugs importation. The transition and hand-over plans should be informed by this rapid assessment results.

Appendices

Appendix 1. References

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Appendix 2. Terms of Reference

TERMS OF REFERENCE

Partners In Health (PIH)
Expand New Drugs Markets for TB (endTB) Mid-Term Evaluation

PURPOSE OF THESE TERMS OF REFERENCE
These Terms of Reference (TOR) serve as an overall framework for the services to be provided under this project.

DESIRED TIMEFRAME
Requested start date: 8 January 2018
Completion date: 23 March 2018

1. Background

In 2015, there were an estimated 10.4 million Tuberculosis (TB) cases and 1.4 million deaths[11]. Of the estimated 580 000 new drug-resistant TB cases, only 132 000 cases were detected (a slight increase from 122,000 cases in 2014) and 125,000 enrolled on Multi-Drug Resistant (MDR) TB treatment (up from 110,000 in 2014). Of those treated about half (52%) were cured with many who were lost to follow-up or died[12].

MDR-TB is caused by bacteria that do not respond to isoniazid and rifampicin – the two most potent anti-TB medicines. MDR-TB patients require treatment with second-line treatment regimens that are more complex to administer, of longer duration, more costly and with more harmful side effects than those used to treat patients that are not resistant.

In May 2014, a global strategy to prevent, care for and control TB was endorsed and adopted by the World Health Assembly. The Strategy marks a critical shift from controlling to eliminating TB by 2035 and rests on three pillars that describe the pathway to elimination: (1) integrated and patient-centred TB care and prevention; (2) bold policies and supportive systems and (3) intensified research and innovation.

The “Expand New Drugs Markets for TB” grant (henceforth “endTB grant”) was approved by the Unitaid Executive Board in May 2014 for $60.3 million for a period of four years from April 2015 to March 2019. The grant is being implemented by Partners In Health (PIH) together with Médecins Sans Frontières (MSF) and Interactive Research & Development (IRD) as consortium partners. The grant uses the first TB drugs developed in almost 50 years (bedaquiline (Bdq) and delamanid (Dlm)) to help improve treatment outcomes for MDR-TB in 17 countries. Key outputs of the endTB project include an observational study of the use of new MDR-TB drugs (Bdq and Dlm) in eligible MDR-TB patients and a clinical trial to find simpler, less toxic, more effective ways to treat MDR-TB. Evidence generated from

[11] There were an additional 400,000 deaths in people living with HIV but these are attributed to HIV and not to tuberculosis infected patients
[12] http://www.who.int/tb/challenges/mdr/mdr_tb_factsheet.pdf

both these outputs is considered key to addressing the challenges in treating patients with drug-resistant TB.

1.1 Treatment guidelines

In 2013 and prior to the start of the endTB grant, WHO issued interim policy guidance on the conditional use of Bdq[13] and Dlm[14] for a duration of six months only due to the low quality of evidence. In 2016, WHO issued an update to the treatment guidelines[15] for drug-resistant TB with no change to the 2013 interim guidance on Bdq and Dlm. The only change was the reclassification of the drugs to Group D2 (add-on agents, not core to the MDR-TB regimen). In addition, the 2016 update now includes a shorter 9 – 12 month MDR-TB treatment regimen (as compared to an 18 to 20 months regimen) under specific conditions[16].

2. Goal, outcome and outputs of the endTB Grant

Goal: The overall project goal is to increase uptake of new TB drugs as part of treatment regimens that are more effective and less toxic.
Outcome: Establish best practices for use of new TB medicines and novel regimens through generated and shared evidence.

The goal and outcome of the endTB grant are planned to be achieved through the realisation of four outputs and the following supporting activities within each:

Output 1: Treatment with new TB drugs (Bdq and Dlm) and close monitoring of a large cohort of patients in early adopter sites

- Procurement of new companion TB drugs
- Prepare an operational research protocol and conduct an observational study
- Evaluate MDR-TB patients for eligibility for new TB drugs
- Initiate and monitor MDR-TB treatment with new drugs
- Establish an endTB care management system/open source electronic medical record (EMR) and a pharmacovigilance system
- Develop a model of care for private sector pulmonologists in Bangladesh, Indonesia and Pakistan

Output 2: Simplification of MDR-TB treatment around a few priority regimens

- Prepare the trial protocol for an innovative evaluation of novel regimens
- Procure specific commodities for the trial
- Prepare sites for participation in regimen development
- Implement a clinical trial of several novel regimens
- Analyse data from the new regimen trial

Output 3: Reduction of country-level barriers to scale-up use of new TB drugs in all

[13] http://apps.who.int/iris/bitstream/10665/84879/1/9789241505482_eng.pdf
[14] http://apps.who.int/iris/bitstream/10665/137334/1/WHO_HTM_TB_2014.23_eng.pdf
[15] http://apps.who.int/iris/bitstream/10665/250125/1/9789241549639-eng.pdf?ua=1
[16] In patients who are Rifampicin resistant and Isoniazid resistant and who were not previously treated with second line drugs and who are not resistant / or are highly unlikely to be resistant to fluoroquinolones and second line injectable agents.

endTB countries

- Facilitate importation of new and companion drugs in endTB countries
- Adapt national TB guidelines in all endTB countries to include new TB drugs
- Improve transparency and accountability of TB programs, both national and NGO, as they relate to access to new TB drugs
- Provide technical assistance to ensure sustainable financing and transition of new TB drugs and regimens in endTB countries

Output 4: Provision of supportive structures to facilitate the sharing of knowledge and dissemination of evidence that support development of the WHO PMDT guidelines of new TB drugs

- Disseminate endTB clinical and programmatic findings globally
- Collaborate with other groups implementing uptake of new TB drugs and novel regimens
- Disseminate market intelligence information for new TB drugs and key companion TB drugs

2.1 Additional project information

The observational study (Output 1) is being conducted in 17 countries, with PIH responsible for six of them (Lesotho, Peru, DPRK, Ethiopia, Haiti and Kazakhstan), MSF for six (Kenya, Georgia, Armenia, Kyrgyzstan, Myanmar and Belarus), and IRD for five (Pakistan, Indonesia, Bangladesh, Viet Nam and South Africa). The first patients have been enrolled shortly after grant signature in April 2015 in several MSF countries (Georgia, Armenia, Belarus), but the majority of the countries started enrolment much later due to 1) delays in procurement, delivery and registration of new TB drugs (Dlm is still available in only 12 out of the 17 countries), 2) prolonged ethical approvals in countries, and 3) lower than anticipated number of eligible MDR- TB patients in several countries (e.g. Kenya and Indonesia). As a result of these circumstances, only a third of the target cohort (946 patients out of the 2700 target) has been enrolled in the study by the end of 2016.

The clinical trial (output 2) is being conducted in 6 endTB countries – Georgia, Peru, Lesotho, Kazakhstan, Kyrgyzstan and South Africa. The trial was initially expected to start in late 2015, but its launch was significantly delayed due to 1) delays in procurement, delivery and registration of new TB drugs, 2) prolonged ethical approvals in countries and 3) addition of a control arm in the clinical trial. The first patients were enrolled in the clinical trial in Georgia in February 2017, and in Peru and Kazakhstan in July 2017.

3. Objectives of the activity

Provide Unitaid with a detailed assessment of the **programmatic progress** of endTB grant towards increased uptake of new TB drugs as part of treatment regimens that are more effective and less toxic; and with recommendations to Unitaid and PIH to improve the grant implementation.

In addition, evaluators will be expected to construct a grant-specific **theory of change** in the context of the global WHO endTB strategy and Unitaid's new strategy (2017 – 2021)

and to develop an **impact framework** (covering both direct and indirect impact) with a suggested methodology and key assumptions to measure impact.

4. Scope of work

The evaluator is expected to perform an evaluation of the endTB grant according to the Organisation for Economic Co-operation and Development's (OECD) Development Assistance Committee (DAC) standard evaluation criteria of grant relevance, effectiveness, efficiency, impact, transition and scalability and lessons learned (refer to Annex 1) as well as its progress against the objectives and deliverables in the endTB project plan and logical framework.

While the endTB grant cuts across two strategic periods (2013-2016 and 2017-2021), it will conclude under the umbrella of the new Strategy (2017 -2021). The evaluator should therefore

contextualise the grant against the new Strategy (and set of Key Performance Indicators) noting that both strategies form a continuum of Unitaid's mandate.

All Strategic KPIs are in scope for this evaluation: for KPI 1.1, 1.2, 1.3[17], the evaluator is expected to provide a framework and methodology of potential impact under plausible assumptions,

while stating any limitation to the estimates. For KPI 4[18], the evaluator should evaluate whether the following critical access barriers have been addressed:

Demand and adoption: Countries, programmes, providers (e.g. healthcare providers, retailers) and end users rapidly introduce and adopt the most cost-effective products within their local context.

Innovation and availability: There is a robust pipeline of new products, regimens or formulations intended to improve clinical efficacy, reduce cost, or better meet the needs of end users, providers or supply chain managers. It means that new and/or superior, evidence- supported, adapted products are commercially available and ready for rapid introduction in low and lower-middle income countries.

5. Target respondents

Target respondents would include (but are not limited to) the following:

- The lead grantee (PIH in Boston) and consortium members (MSF, IRD)
- In-country organisations/stakeholders in select project countries (including but not limited to policy makers / key decision makers at the county level, officials (high and mid-level including national TB programme managers) at relevant Ministries
- Wider stakeholder group indirectly involved with the endTB grant such as funders, technical bodies (WHO, KNCV-Tuberculosis Foundation) experts/resource persons, TB implementing agencies (e.g. GDF, EGPAF, CHAI, MSF), civil society groups such as Treatment Action Group, etc.
- Relevant staff at the Unitaid Secretariat

[17] http://icai.independent.gov.uk/tag/assessment-framework/

[18] https://unitaid.eu/news-blog/unitaids-new-strategy-will-focus-reducing-inequities-health-access/

6. Methodology, place of work and frequency of interaction

The grant evaluation methodology will involve a combination of document reviews and key informant interviews with the relevant stakeholders. Evaluators will undertake reviews of the grant using the grant documents such as:

1. Grant Agreement and all Annexes including the project plan and logical framework
2. Inception report, annual and semi-annual reports
3. Memorandums of Understanding
4. Relevant reports and presentations
5. Relevant memos and communication with lead grantee

The evaluators will work remotely and will be required to travel to two of the project countries (Georgia and Indonesia). This will be in addition to the visit to the headquarters of the grantee, PIH, in Boston. Evaluators will be expected to meet with the Unitaid team in Geneva for the purpose of the evaluation prior to the first draft and for presentation of the final findings. In addition, the Unitaid focal point for the evaluation will have weekly to bi-weekly updates with evaluators.

7. Qualification and skills

Evaluators will have prior experience in designing and leading evaluations, data analysis skills, and technical competence in the field of TB treatment

Specific expertise in the following areas is required:

1. Experience in conducting evaluations of grants in the TB field and familiarity with WHO guidelines on TB care
2. Experience with operational research, clinical studies and procurement
3. Experience with assessment of public health and market impact
4. Experience in Monitoring & Evaluation in the public health sector;
5. Proficiency in English; proficiency in Russian an advantage

8. Deliverables

The contractor should submit the following deliverables by the dates determined for each evaluation (NB **This reflects the latest updates/changes in dates**):	**Time (in brackets revised dates based on discussion 8 January)**
1. An Inception report outlining the process for the evaluation including a proposed methodology / approach to the review, a work plan and timeline and a list of interviewees	8th – 19th January (submission inception report 19th January)
2. A first draft evaluation report for review and comments by Unitaid. This includes a virtual presentation of the draft findings to the Unitaid Secretariat.	19th February – 2nd March (submission first draft report by 2nd March, presentation (in person or virtual) on 7th March)
3. A Second Draft evaluation shared with Unitaid and the grantee	5th-16th March (submission second draft report by 16th March)
4. Presentation at Unitaid premises on the final evaluation report	week of 19th March (presentation final findings 29th March)
5. Final evaluation report	week of 19th March (submission final report 31st March)

The evaluation report will be available to the public on the Unitaid website https://unitaid.eu/project/end-tb-project/#en. Note: Unitaid reserves the right to redact sensitive or confidential information from the evaluation report prior to its publication.

ANNEX 1: Unitaid's Evaluation Framework

Relevance
1. Are the outcome(s) and impact(s) of the grant aligned with Unitaid's overall mission to contribute to catalyse access to TB care in resource limited settings? Is the grant relevant to and contribute to Unitaid's strategy (2017- 2021)?
Effectiveness
1. Are the outputs of the grant consistent with the objectives and expected outcomes as described in the project plan? If changes have been made, has the Unitaid Secretariat been involved in discussions and decision making on the changes? 2. Have the outputs and activities in the logframe for the evaluation period been achieved within the timeframe and budget specified in the initial project plan? 3. What are the main factors influencing (or preventing) the achievement or non-achievement
Efficiency
1. Has the grantee ensured project planning, implementation and assessment in collaboration with the national authorities? Can the grant implementer and their partners demonstrate that national authorities were aware and participating in grant activities at the national level? 2. How cost efficient and cost effective was grant implementation? 3. How was the consortium management? Was this effective arrangement? 4. Were challenges raised with the Unitaid Secretariat in a timely manner and did the Secretariat participate in resolving these challenges?
Impact
1. Has the grantee been able to report on impact as originally framed in the project plan and Log-Frame? If not, has the grant impact been measured in another way? 2. Where relevant, can the grantee attribute Unitaid's financial support for medicines, diagnostics or preventive products purchased to beneficiary country? If not, what, in your assessment, is the reason? 3. What is the potential impact and value for money of Unitaid's investment in this project? 4. Would you consider this project a game-changer i.e. succeeded in unlocking access barriers?
Transition and scalability
To what extent will the benefits of this grant continue after donor funding ceases? 2. To what extent have the new drugs been integrated in the national treatment guidelines 3. To what extent have grant activities been transitioned to the NTPs (includes patient care, EMR) 4. To what extent have the grant activities / new approach / product been scaled up and what were the contributing or limiting factors?
Learning & Risk mitigation:
1. Have lessons learnt thus far been documented and widely disseminated by grantees and Unitaid? How was this information shared within the consortium? 2. Did the grantee consider the impact on project activities of changes to the MDR TB treatment guidelines and put into place mitigation measures? Likewise, did the grantee communicate learnings from this grant that could potentially contribute to the current guidance available on MDR TD treatment 3. Were programmatic and financial risks identified and tracked sufficiently in advance and mitigation actions mapped out over the course of grant implementation?

Appendix 3. List of people interviewed for the evaluation

Organisation / country	Name	Position	Communicated by/through
Damien Foundation Belgium	Tine Demeulenaere	Medical Advisor	by e-mail
Damien Foundation Belgium	Nimer Ortuno Gutierrez	Medical Advisor	by e-mail
GDF	Dr. Brian Kaiser	formerly Unitaid, involved this project	Skype
Georgia	Sylvia Goossens	Head of Mission	in-person
Georgia	Marielle Connan	Project Coordinator Output1	in-person
Georgia	Tinatin Kotrikadze	Medical Coordinator	in-person
Georgia	Dali Zhizhilashvilli	Mission Pharmacy Manager	in-person
Georgia	Valérie Marecual	Project Coordinator Output2	in-person
Georgia	Rebekah Varela	Finance/HR coordinator	in-person
Georgia	Dr. Zaza Avaliani	Director National Center for TB and Lung Diseases (NCTLD)	in-person
Georgia	Dr. Nana Kiria	Deputy director/chief doctor NCTLD	in-person
Georgia	Nestan Tukvadze	Head of Research Unit NCTLD	in-person
Georgia	Nino Lomtadze	Head of surveillance and strategic planning department, coordinator of the GF program at the sub-recipient level	in-person
Georgia	Dr. Marika Eristavi	Phtisiologist O2 NCTLD	in-person
Georgia	Nino Kiria	Study coordinator O2 NCTLD	in-person
Georgia	Mariam Bichiashvilli	Assistant study coordinator O2 NCTLD	in-person
Georgia	Lasha Darchia	Database manager O2 NCTLD	in-person
Georgia	Nikoloz Nasidze	Patients Union - Board member, TB People - director	in-person
Georgia	David Alkhazashvili	Patients Union - member, TB People - member	in-person
Georgia	Giorgi Kuchukhidze	National Centre for Disease Control, program manager GF TB program in Georgia	in-person
Georgia	Anano Gegeshidze	Medical Doctor O1	in-person
Georgia	Narine Danielyan	Medical Activity Manager O1	in-person
Georgia	Ledi Bichikashvili	Database Supervisor O1	in-person
Georgia	Mariam Ekizashvili	Data entry operator O1	in-person
Georgia	Tamar Maglakelidze	Data Entry Processiong Officer O1	in-person
Georgia	Nino Chumburidze	Research associate O1	in-person

Indonesia	Dr. Cut Yulia Indah Sari, Sp.P	Pulmonologist RS Islam	in person
Indonesia	Dr. Kemala Sari, Sp.P	Pulmonologist RS Islam	in person
Indonesia	Dr. Fauziah Asnely Putri, MPH	Site Manager	in person
Indonesia	Dr. Erlina Burhan, M.Sc., Sp.P(K)	Senior Pulmonologist RS Persahabatan	in person
Indonesia	Dr. Setiawan Jati Laksono	TB Officer WHO Indonesia	in person
Indonesia	Dr. Yusie Permata, MIH	KNCV Technical officer PMDT	in person
Indonesia	Dr. Bey Sonata	KNCV Director of Technical Services	in person
Indonesia	Dr. Asik Surya, MPPM	NTP Manager	in person
Indonesia	Dr. Endang Lukitosari, MPH	NTP Focal Point PMDT	in person
Indonesia	Aisyiyah	Patient organisation	cancelled last minute
Indonesia	GF Indonesia Country team		reached out, no response
Indonesia	Dr. Aga Krisnanda	Medical Officer Site	in person
Indonesia	Ms. Putri Lenggogeni	Data Officer Site	in person
Indonesia	Ms. Budi Rahmawati	Nurse Site	in person
IRD	Dr. Uzma Khan	focal point for IRD endTB	Skype
KNCV Kyrgyzstan	Bakyt Myrzaliev	Country Director Kyrgyzstan	Skype
KNCV Netherlands	Gunta Dravniece	PMDT consultant	Skype
KNCV Netherlands	Fraser Wares	PMDT consultant	Skype
KNCV Netherlands	Agnes Gebhard	Senior consultant	Skype
KNCV Netherlands	Mayra Arias	Team coordinator, Access to care team	Skype
MOH Lesotho	Dr. Llang Maama	NTP manager	Skype
MSF	Dr. Francis Varaine	MSF TB Working Group Coordinator, MSF endTB Leader	Skype
MSF	Dr. Sandra Collin	MSF endTB Focal Point	Skype
MSF Kyrgyzstan	Dr Arnol Saniev	clinical trial study coordinator	Skype
Other	Bernard Fourie	Unitaid Proposal Review Committee	in-person
Otsuka	Masanori Kawasaki	Associate director, TB projects	in-person
Otsuka	Agus Dwiyanto	Marketing director Indonesia	in-person
Otsuka	Jeffrey Hafkin	Director, TB products unit	in-person

Otsuka	Yoesrianto Tahir	Business and scientific development manager, TB project	in-person
Pakistan	Dr. Abdul Ghafoor	Technical Advisor PMDT to NTP Pakistan	Skype
Peru-PIH	Leonid Lecca García	Executive Director PIH Peru	Skype
Peru-PIH	Carmen Contreras	Director of Interventions PIH Peru	Skype
Peru-PIH	Lurdus Cruzado	SES PIH Peru	Skype
Peru-PIH	Sara Perea	SES PIH Peru	Skype
Peru	Dr. Sánchez	Pulmonologist form Sergio Bernales Hospital (MoH)	Skype
PiH	Ms. Meredith Cain	endTB Project manager	in person
PiH	Dr. Michael Rich	endTB project co-Leader	in person
PiH	Dr. KJ Seung	endTB project co-Leader /co-Principal Investigator (Output 1)	Skype
PiH	Dr. Carole Mitnick	endTB co-Principal Investigator (Output 2)	in person
PIH	Ms. Emily Durrant	Finance manager	
PIH	Dr. Abera Leta	PIH Lesotho	Skype
TAG	Lindsay McKenna		Skype
Union	Valérie Schwoebel	Union	Skype
Union	ALberto Piubello	MDR-TB Coordinator - Consultant	by e-mail
Unitaid	Ms. Janet Ginnard	Team Lead – Strategy	Conference call
Unitaid	Mr. Philippe Dunetton	Deputy Executive Director	Conference call
Unitaid	Mr. Draurio Barreira	TB Strategy Manager (Strategy)	Conference call
Unitaid	Ms. Eva Nathanson	Team lead (TB- Operations)	Conference call
Unitaid	Mr. Ross Leach	VFM Manager (Results)	Conference call
Unitaid	Ms. Deepti Mishra	Impact Officer (Results)	Conference call
Unitaid	Mr. Vincent Bretin	Team Lead Results	Conference call
Unitaid	Mr. Ademola Osigbesan	Supply and Procurement Officer (Operations)	received answers by email
Unitaid	Mr. Ganesh Ramachandran	Finance Manager (Finance)	Conference call
USAID	Mr. Mukadi Ya Diul	Medical Officer Infectious Disease Office/Tuberculosis Division	Phone
WHO	Dr. Fuad Mirzayev	WHO GTP	Phone
WHO	Dr. Karin Weyer	WHO GTP	Phone

Appendix 4. Interview guide

General information collected:
- Name and position of interviewee, length of time working in present role
- Date of interview
- Country (if relevant)

Implementing partners:
1. What is your role in the endTB project? How long have you been involved in the implementation?
2. What have been the challenges in implementing the grant? How were the challenges overcome, who was involved and how was change implemented? What are the current challenges?
3. Has the endTB project changed MDR-TB care and prevention in the country? If yes, how? Have guidelines been changed or is that planned for? What is important knowledge for the country to (initiate) the change of the guidelines? Who is usually involved, what is the process?
4. What is the main source of funding in the country for TB (or more specifically MDR-TB)? Do you foresee any challenges with continuation of the funding once the endTB project ends? Is there a transition plan or plans to work on a transition plan? What are potential other sources of support (including financial)?
5. What has been an important lesson learnt from the endTB project? Why was it important?
6. If you had the possibility to change the implementation, how would you change it and why?
7. Anything that you want to share with us that we have not yet discussed?
8. Would you like to ask us any questions?

(Country) NTP and other stakeholders:
1. What is your role in MDR-TB care and prevention?
2. How did you learn about the endTB project? How are you kept informed on its progress?
3. What are the main barriers in MDR-TB care and prevention? Have these changed over time in the last 5-7 years? How?
4. How has the endTB project influenced MDR-TB care and prevention in the country? Have the guidelines been changed or is that planned for? What is important knowledge for the country to (initiate) the change of the guidelines? Who is usually involved, what is the process, how long does it take? Can the change in MDR-TB care precede the formal change in the guidelines? What would be necessary for that to take place?
5. What is the main source of funding in the country for TB (or more specifically MDR-TB)? Do you foresee any challenges with continuation of the funding once the endTB project ends? Is there a transition plan or plans to work on a transition plan? What are potential other sources of support (including financial)?
6. What it needed in this country to bring MDR-TB care to a higher level of quality? Is this reflected in any plans? Is funding available, and do you need partners to assist in implementation?
7. If you could decide on a next project regarding MDR-TB care and prevention, what would you do?
8. Anything that you want to share with us that we have not yet discussed?
9. Would you like to ask us any questions?

Participants of the studies (observational or RCT):
1. What is your diagnosis? What drugs do you take? Do you know how long your treatment is going to take?
2. How often do you visit the clinic? How do you find visiting the clinic (are there any challenges: remoteness, transportation costs, leaving work/children, facilities at the clinic, attitude of staff)? How do you overcome these challenges? Is there anyone who helps you? Who is it and how do they help?
3. What do you do when you come for your clinic appointment? / What happens during the clinic appointment?

4. Have you signed any documents beforehand to be part of the study? Did you get a copy of this document?
5. What do you know about this study? / Why is this study conducted? How do you know?
6. Were you informed about the possible side effects of the treatment? Did you have sufficient time and possibilities to ask questions?
7. Are there any difficulties for you in relation to the treatment of this disease? What do you experience?
8. What do you think is necessary for patients to be able to take treatment for this disease (MDR-TB) and to finish it?
9. How does this disease and its treatment impact your daily life? Have you encountered difficulties with your family, employment (if applicable), in your community? If yes, what difficulties did you encounter, how have you dealt with these? Did the project support you? How?
10. Anything that you want to share with us that we have not yet discussed?
11. Would you like to ask us any questions?

Appendix 5. Numbers enrolled in Output 1

Country	Enrolment (unique patients) in Observational Cohort (through 31Dec17)	Enrolment (unique patients) in Full Cohort (through 31Dec17)	% of full cohort that is also enrolled in the observational study
Armenia	107	111	96%
Bangladesh	208	208	100%
Belarus	76	80	95%
DPRK	32	32	100%
Ethiopia	38	42	90%
Georgia	298	349	85%
Haiti	7	13	54%
Indonesia	29	29	100%
Kazakhstan	371	375	99%
Kenya	4	4	100%
Kyrgyzstan	10	10	100%
Lesotho	160	161	99%
Myanmar	42	42	100%
Pakistan	218	218	100%
Peru	136	160	85%
South Africa	14	14	100%
Viet Nam	Enrolment not yet started at time of the evaluation		
	1,750	1,848	95%

Note:
Participants in the full cohort gave permission to receive the new medicines and to PV monitoring.
Participants of the observational study form a subset of the full cohort and they gave permission to enrol in the observational study with their data analysed.

Appendix 6. Output 1 results available for WHO 2018 revision and at end of the grant (March 2019)

A) For the WHO 2018 revision

			Available results for the 2018 WHO PMDT revision - Full cohort				Available results for the 2018 WHO PMDT revision - Observational study			
Country	**Enrolment Full Cohort (up to Q22017)**	**Enrolment Observational Cohort (up to Q22017)**	**6 month outcomes available**	**12 month outcomes available**	**24 month outcomes available**	**30 month available (includes 6 mo post end Rx FU)**	**6 month outcomes available**	**12 month outcomes available**	**24 month outcomes available**	**30 month available (includes 6 mo post end Rx FU)**
Armenia	110	84	110	88	23	18	84	67	18	14
Bangladesh	113	90	113	43	0	0	86	33	0	0
Belarus	54	51	54	50	12	6	41	38	9	5
DPRK	22	10	22	17	0	0	17	13	0	0
Ethiopia	32	30	32	14	0	0	24	11	0	0
Georgia	349	298	349	303	146	89	267	232	112	68
Haiti	0	0	0	0	0	0	0	0	0	0
Indonesia	7	7	7	1	0	0	5	1	0	0
Kazakhstan	278	275	278	214	0	0	212	164	0	0
Kenya	6	4	6	4	1	0	5	3	1	0
Kyrgyzstan	6	6	6	0	0	0	5	0	0	0
Lesotho	99	98	99	64	15	0	76	49	11	0
Myanmar	20	20	20	18	0	0	15	14	0	0
Pakistan	143	105	143	59	0	0	109	45	0	0
Peru	113	96	113	60	0	0	86	46	0	0
South Africa	16	14	14	16	0	0	12	0	0	0
Total endTB	1,368	1,190	1,368	935	197	113	1,046	715	151	86

Note: Viet Nam had not yet started enrolling participants in Q2 2017

B) For the end-of-grant period

			Available results at end of grant period (31 March 2019) - Full cohort				Available results at end of grant period (31 March 2019) - Observational study			
Country	**Enrolment Full Cohort end of Sept 2018**	**Enrolment Observational Cohort end of Sept 20187**	**6 month outcomes available**	**12 month outcomes available**	**24 month outcomes available**	**30 month available (includes 6 mo post end Rx FU)**	**6 month outcomes available**	**12 month outcomes available**	**24 month outcomes available**	**30 month available (includes 6 mo post end Rx FU)**
Armenia	140	107	140	140	97	88	107	107	74	67
Bangladesh	277	221	277	242	87	43	212	185	66	33
Belarus	90	86	90	90	51	50	69	69	39	38
DPRK	99	46	99	39	18	17	76	30	14	13
Ethiopia	79	75	79	53	24	14	60	41	18	11
Georgia	349	298	349	349	338	303	267	267	258	232
Haiti	65	35	65	31	0	0	50	24	0	0
Indonesia	49	47	49	39	3	1	37	30	2	1
Kazakhstan	551	545	551	421	251	214	421	322	192	164
Kenya	6	4	6	6	5	4	5	5	4	3
Kyrgyzstan	28	28	28	16	0	0	21	12	0	0
Lesotho	221	220	221	181	81	64	169	138	62	49
Myanmar	51	51	51	45	18	18	39	34	14	14
Pakistan	262	193	262	262	96	59	200	200	73	45
Peru	247	210	247	189	84	60	189	144	64	46
South Africa	39	34	39	28	0	0	30	21	0	0
Viet Nam*	35	35	35	10	0	0	27	8	0	0
Total endTB	2,588	2,234	2,588	2,141	1,153	935	1,978	1,636	881	715

*assuming 100% will enrol in the observational study

Appendix 7. Regimen Trials for DR-TB

(courtesy of PIH)

Cheat Sheet to Regimen Trials for DR-TB planned, underway or recently completed in November 2017

Trial	Phase	Population			Efficacy			Toxicity	Shorten	All Oral	Compatible w/ART
		S	M	X	S	M	X				
Completed											
STREAM I†	3	✓✓#			Inconclusive			ALT, poss QTc	Inconclusive		17.5% vs. 8% death$^{\Delta}$
Otsuka (213)€	3	✓✓			Not superior			Not worse			11/12 HIV+, conv ≤ 6 mos.$^{\Delta}$
Underway or planned											
DELIBERATE	2	✓✓#						✓✓‡	✓		✓*$^{\Delta}$
endTB	**3**	✓✓			✓✓			✓	✓	✓	✓*
endTB-Q	**3**			✓			✓✓	✓	✓	✓	✓*
NC-008	2	✓¶§	✓#¶		✓¶§	✓#¶		✓	✓	✓	✓*$^{\Delta}$
NeXT	3	✓✓			✓✓			✓	✓	✓	✓*
NiX-TB	3		✓¶			✓¶		✓¶	✓	✓	✓*$^{\Delta}$
STREAM II	3	✓✓#			✓✓#			✓	✓	✓	✓*$^{\Delta}$
TB-PRACTECAL	2/3	✓✓			✓✓			✓	✓	✓	✓*

S ≈ "simple" MDR (without resistance to second-line drugs)≈50%
† = Preliminary
✓ =reported
✓ = planned to inform
✓✓= powered for
§ =and drug-susceptible TB
€ =not testing regimen

M ≈ MDR + resistance to 2nd-line drugs, not FQ≈30%
X ≈ MDR + resistance to FQ ≈ 20%
= excludes MDR with resistance to second-line injectables
¶ = uncontrolled
‡ = QT prolongation with DLM or BDQ vs. DLM & BDQ
* = requires manageable change in ART.
Δ = Limits on HIV-coinfected population (CD4, delay to ART initiation)