The endTB Project: Output 1
Introduction of New Treatments

UNITAID

Partners In Health (PIH)

Médecins sans Frontières (MSF)

Interactive Research & Development (IRD)

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February 17, 2015

Project Overview

Public health problem: MDR-TB treatment is long, toxic, and not very effective

Typical Daily Pill Burden for MDR-TB/HIV Co-infected Patient >60kg: **17 Tablets, 3 Capsules, 2 Sachets, and 1 Intramuscular Injection** (Excluding Ancillary Drugs for Adverse Effects)

Morning dose	Evening dose
Pyrazinamide (500mg): 4 tablets Kanamycin (1-g vial): 1 g IM Levofloxacin (500 mg): 2 tablets Ethionamide (250 mg): 1 tablet Cycloserine (250 mg): 1 capsule PAS (4-g sachet): 1 sachet	Ethionamide (250 mg): 2 tablets Cycloserine (250 mg): 2 capsules PAS (4-g sachet): 1 sachet Pyridoxine (50 mg): 4 tablets
AZT/3TC combination: 1 tablet Cotrimoxazole: 1 tablet	AZT/3TC combination: 1 tablet EFV (600 mg): 1 tablet
Total pill burden in morning: 9 tablets, 1 capsule, 1 sachet and 1 intramuscular injection	Total pill burden in evening: 8 tablets, 2 capsules, 1 sachet.

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Project Overview

Market problem: new TB drugs exist but are not getting to patients in low- and middle-income countries.

- Manufacturers are focused on bringing **single** TB drugs to market, and less interested in producing effective **regimens**.
- Most TB clinical trials do not focus on MDR-TB, take years to be finished, and have do not guarantee a more effective MDR-TB regimen.
- Current market incentivizes selling new TB drugs in high-income, developed countries.

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endTB Objectives

Overall Goal: Increased uptake of new TB drugs as part of treatment regimens that are more effective and less toxic.
Market and Public Health Outcomes: Evidence and best practices about the use of new TB drugs and novel regimens.
Outputs and Activities: 4 Outputs, with specific Activities

Timeline: Grant signing March 1, 2015. Treatment to begin almost immediately.

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endTB - Outputs

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

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

Output 3: Reduce country-level barriers to scale-up use of new TB drugs in all endTB countries.

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

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what will Output 1 do?

Output 1: Establish an evidence base for broader use of appropriate, new MDR-TB drugs by enrolling a total of 3200 patients in 17 countries on new drugs and regimens.

endTB will expand access to new TB drugs and substantially advance the evidence base for the safety and efficacy of MDR-TB regimens containing bedaquiline or delamanid.

Patient enrollment	2600
Sites	17
Countries	Peru, Lesotho, Kazakhstan, Kenya, Georgia, Armenia, Kyrgyzstan, Swaziland, India, Myanmar, Belarus, Pakistan, Indonesia, Bangladesh, Democratic People's Republic of Korea (DPRK), Nepal,and Ethiopia
endTB implementing partners	PIH, MSF, IRD, EBF, NATA
Regimens used	Designed by field clinicians, with guidance from endTB (also see Appendix 1.11); in general, any regimen that complies with WHO recommendations is allowed
Research component	Observational research on efficacy and safety of regimens constructed according to current guidance

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Number of Output 1 patients to be enrolled by site

Site	*endTB implementer*	*Number to be enrolled in Output 1*
Peru	PIH	420
Lesotho	PIH	150
Kazakhstan	PIH	573
Ethiopia	PIH	30
Kenya	MSF-OCP	26
Georgia	MSF-OCP	220
Armenia	MSF-OCP	96
Kyrgyzstan	MSF-OCG	75
Swaziland	MSF-OCA	40
India	MSF-OCA	40
Myanmar	MSF-OCA	40
Belarus	MSF-OCA	30
Pakistan	IRD	284
Indonesia	IRD	94
Bangladesh	IRD	252
DPRK	EBF	150
Nepal	NATA	80
Total		**2600**

Output 1 Activity	Description
Activity 1.1	Procurement of new and companion TB drugs for Output 1.
Activity 1.2	Prepare and conduct an operational research protocol for an observational study of Output 1 patients.
Activity 1.3	Evaluate MDR-TB patients for eligibility for new TB drugs.
Activity 1.4	Initiate and monitor MDR-TB treatment with new drugs.
Activity 1.5	Establish an endTB care management system/open-source electronic medical record (EMR).
Activity 1.6	Develop a model of care for private sector pulmonologists in Bangladesh, Indonesia, and Pakistan.

Activity 1.1: Procurement of new and companion TB drugs for Output 1.

- EndTB procurement will focus on five WHO Group 5 drugs: **Bdq, Dlm, Lzd, Cfz and Imp/Cln**.
- Bdq and Dlm are considered to be "new TB drugs" as they have recently been approved for MDR-TB treatment by an SRA

EndTB will negotiate directly with manufacturers to ensure a secure and equitable pricing model for new TB drugs. Pooling across sites and reliable quantification will help to leverage price reductions at the manufacturer level.

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Activity 1.2: Prepare and conduct an operational research protocol for an observational study of Output 1 patients.

For the 2600 Output 1 patients, endTB will collect and analyze individual patient data on treatment outcomes and adverse events.

The aim is to greatly increase the evidence around the use of new TB drugs.

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Activity 1.3: Evaluate MDR-TB patients for eligibility for new TB drugs.

- This activity establishes a system to evaluate patients in the endTB catchment areas about whether the patient could benefit from a new TB drugs in their MDR regimen, which new TB drug, and if companion Group 5 drugs are needed.

- Specific indications for screening and initiating new TB drugs for each country are provided in *endTB's Guide for New TB Drugs*"

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Activity 1.4: Initiate and monitor MDR-TB treatment with new drugs.

The target number of patients for each site was determined by considering several factors:

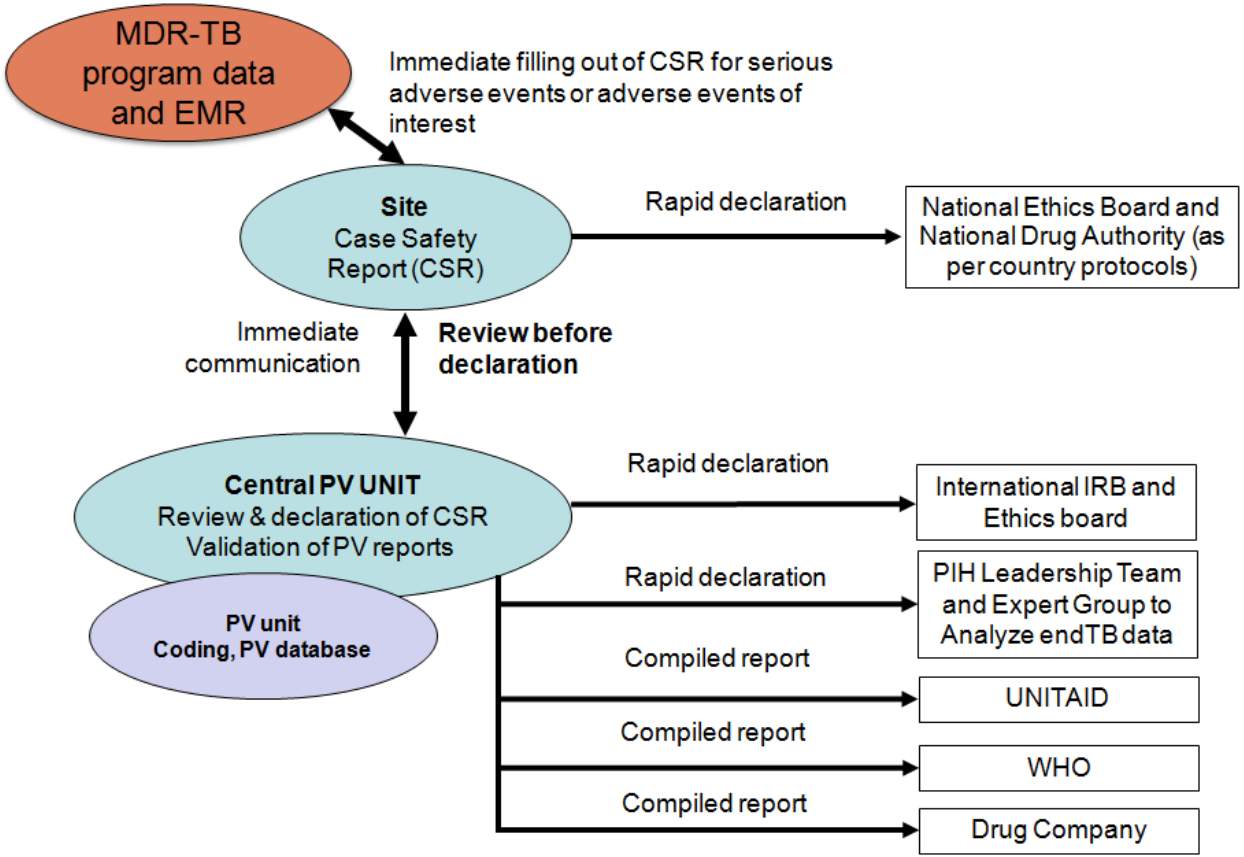
- Epidemiologically, it was estimated that approximately 30% of the MDR-TB burden in each catchment area will have an indication for a new TB drug.
- The programmatic capacity at each site to enroll and closely monitor patients was also considered.

The adverse event screening schedule will be quite intense and will be designed to detect rare adverse events that might have been missed in small clinical trials.

Activity 1.5: Establish an endTB care management system/open-source electronic medical record (EMR).

- Pharmacovigilance and operational research are key components of Output 1.
  - PV focuses on adverse drug reactions, which are defined as any response to a drug which is noxious and unintended, including lack of efficacy.
  - Pharmacovigilance is a proactive, medically driven safety risk management system.
- The EMR will serve as a tool for entry of standardized clinical data for patients treated through Output 1.

endTB Pharmacovigilance system



Activity 1.6: Develop a model of care for private sector pulmonologists in Bangladesh, Indonesia, and Pakistan.

- Densely populated Asian megacities like Dhaka, Jakarta and Karachi have a thriving and unregulated market of private health providers, including specialist pulmonologists.
- IRD will introduce new TB drugs and regimens through an innovative public-private initiative in Bangladesh, Indonesia and Pakistan.

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