

# The INTERTB RIFASHORT Trial

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# Outline

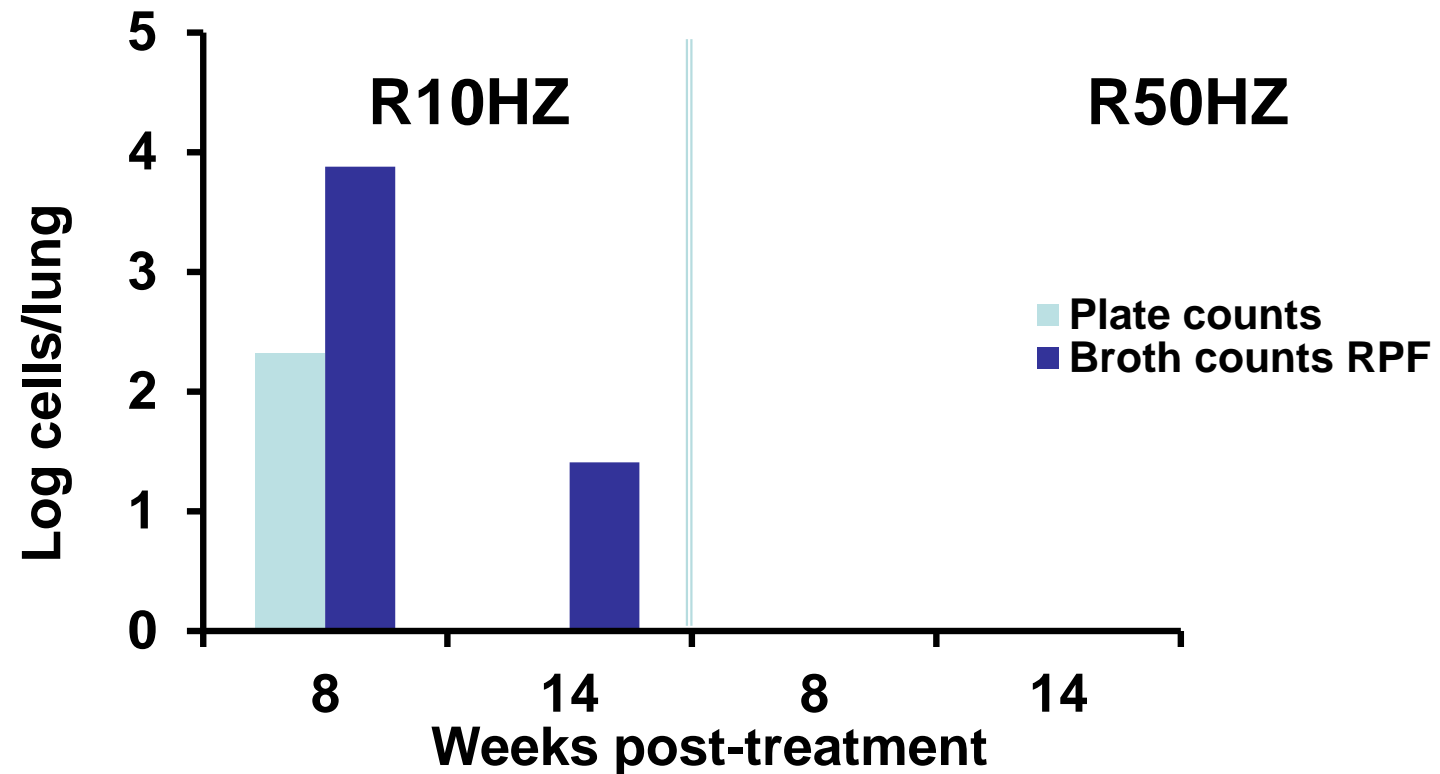
- ❖ Background
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- ❖ Current Status
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# RIFASHORT

AN INTERNATIONAL MULTICENTRE CONTROLLED CLINICAL TRIAL TO  
EVALUATE 1200mg AND 1800mg RIFAMPICIN DAILY IN THE REDUCTION  
OF TREATMENT DURATION FOR PULMONARY TUBERCULOSIS FROM 6  
MONTHS TO 4 MONTHS

# Background – Hu et Al

No RPF-dependent persisters after treatment with high dose rifampicin regimen



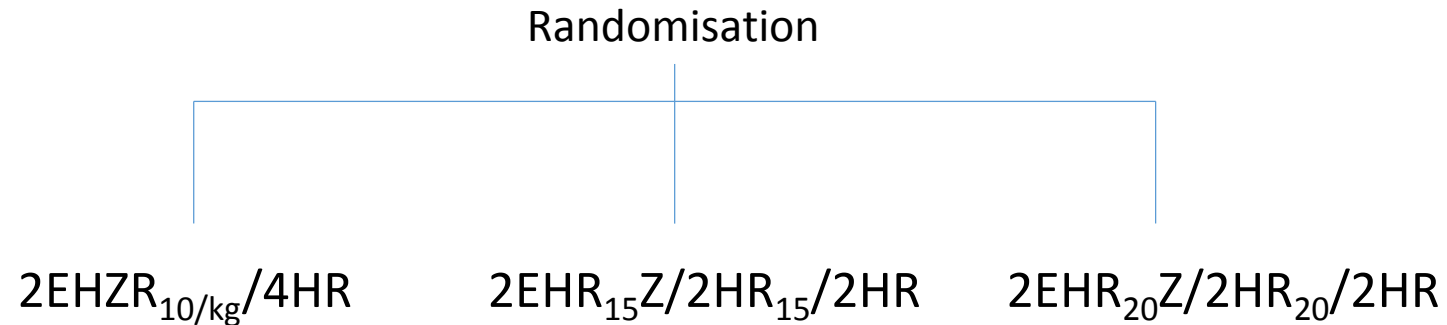
Hu Y, Liu A, Ortega-Muro F, Alameda-Martin L, Mitchison D and Coates A.

High-dose rifampicin kills persisters, shortens treatment duration, and reduces relapse rates *in vitro* and *in vivo*.

Frontiers in Microbiology. 2015.6:1-10.

# Background - RIFATOX

Phase II toxicity study  
(n=300 HIV-negative, microscopy-positive PTB patients)

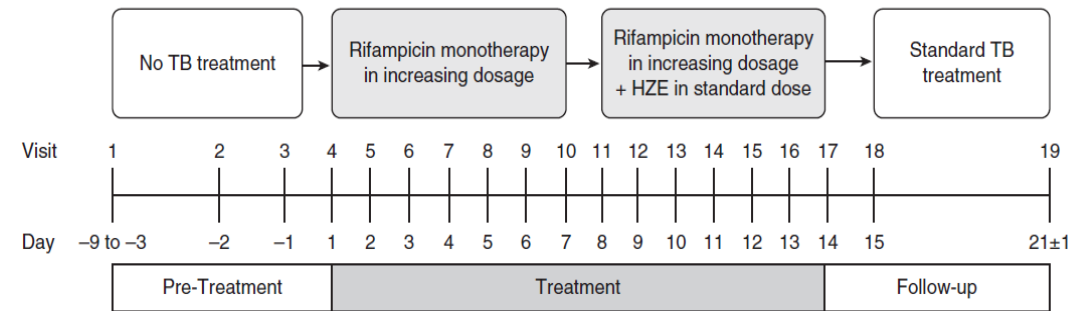


Patients followed-up  
to 16 weeks from  
randomisation

Results: No significant increase in adverse events occurred  
when rifampicin dose was increased

# Background - Boeree et al

- Open-label phase II multiple dose-ranging study
- Adults with newly diagnosed sputum-smear positive PTB
- Rifampicin monotherapy for 7d, followed by adding HZE for further 7d
- Similar numbers of grade 1 and 2 AEs between the five groups
- Five grade 3 AEs (two in 20mg/kg and one in 30mg/kg group). One possibly related to hepatotoxicity
- Rifampicin safe up to 35mg/kg



Rifampicin ranged from 10mg/kg (control), 20, 25, 30 to 35mg/kg

# Background - Boeree et al (2016)

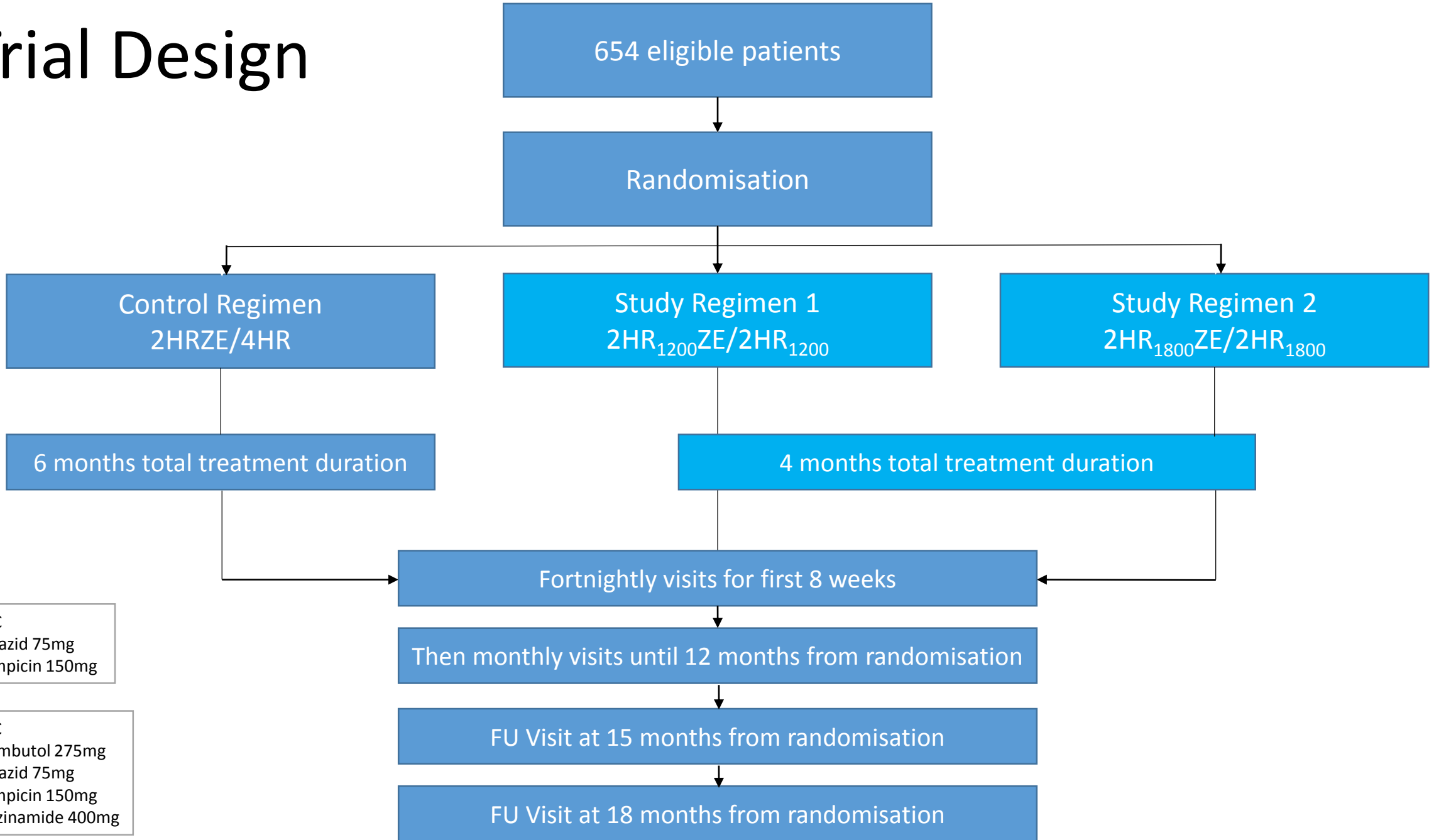
- Open-label multi-arm multi-stage trial, adults with newly diagnosed rifampicin-sensitive PTB
- High-dose rifampicin arms: 35mg/kg+HZE; 20mg/kg+QHZ; 20mg/kg+MHZ, given for 12w
- Primary outcome: time to culture conversion within 12w, using mITT pop
  
- Time to culture conversion faster in 35mg/kg rifampicin group vs control
- No safety concerns – grade 3-5 AEs similar by arm

# RIFASHORT – Trial Overview

- International, 3 arm, Phase III, open label non-inferiority trial
- Xpert MTB positive / rifampicin susceptible, HIV negative, pulmonary TB patients
- Aims:
  - to determine whether an increase in the daily dose of rifampicin **to 1200mg or 1800mg** would result in more rapid sterilisation of the lungs and allow a reduction of treatment **duration to 4 months**
  - To assess whether the increased doses will result in an increase in **severe (grade 3 or 4) adverse events** and/or any **serious adverse events**



# Trial Design



2FDC  
Isoniazid 75mg  
Rifampicin 150mg

4FDC  
Ethambutol 275mg  
Isoniazid 75mg  
Rifampicin 150mg  
Pyrazinamide 400mg

# RIFASHORT Global Team

**Mbarara, Uganda**

PI: Dr Daniel Atwine

**Lima, Peru**

PI: Dr Eduardo Ticona

**Santa Cruz, Bolivia**

PI: Ilona Westermann-Patino

**Gaborone, Botswana**

PI: Dr Tefera Agizew

**SGUL/LSHTM**

Co-ordinating  
Team, London, UK

**Datafax, Data management**

Kampala, Uganda

**Potential NEW SITES**

- **Conakry, GUINEA**
- **Kathmandu, NEPAL**
- **Mexico City, MEXICO**
- **Monterrey, MEXICO**

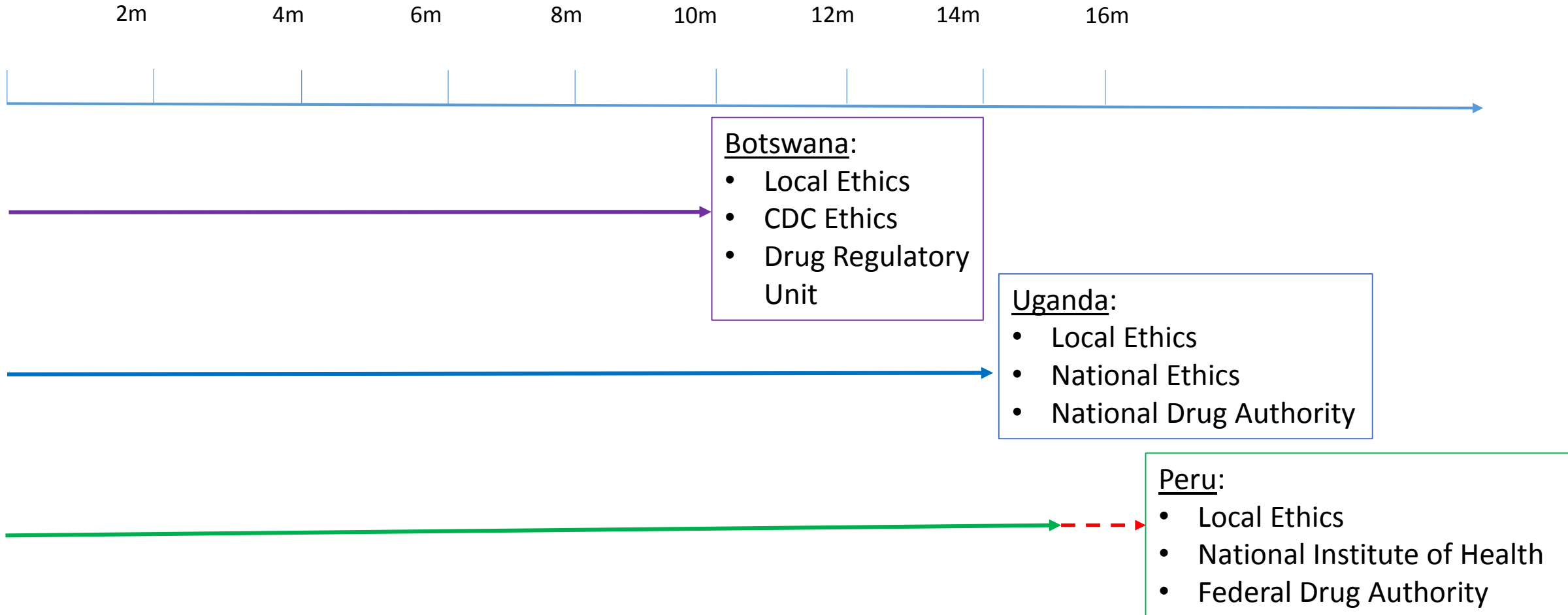
# Overall Status Update

- First site opened: 31<sup>st</sup> Jan 2017
- First patient recruited: 1<sup>st</sup> Feb 2017
- 2 sites now open
- Total recruitment to date: **81 patients randomised**
  
- Persister sub-study:
  - First site opened 9<sup>th</sup> June 2017
  - Recruitment to date: 30 patients
  - 1 site open

# Challenges

- Approval timelines
- Bolivia
- Drug supply timelines

# Approvals



# Bolivia

- 2 sites planned in Santa Cruz, previously part of RIFATOX
- Application made December 2016
- Early 2017 – refusal from Ministry of Health
- Internal political issues

# New sites

## Guinea & Nepal

- Sites with high TB incidence and low HIV prevalence
- Previous trials experience
- Reasonable cost

## Current Status

- Ethical approval received – Guinea
- Conditional approval received – Nepal
- Expect to open Jan/Feb 2018

# Additional New sites

## **Mexico City & Monterrey, Mexico**

- Access to large TB population, low HIV prevalence
- New collaborations
- 1 site experienced / 1 site new to trials
- Reasonable cost with potential additional funding available from Mexican Health system

## **Current Status**

- Ethics submission in progress
- Expected start Mar/Apr 2018





# Acknowledgements



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