



World Health  
Organization

**END TB**



# Lessons Learned from Completed TB Trials and Implications for Future Trials



**GLOBAL TB  
PROGRAMME**

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Research for TB Elimination  
WHO, Geneva

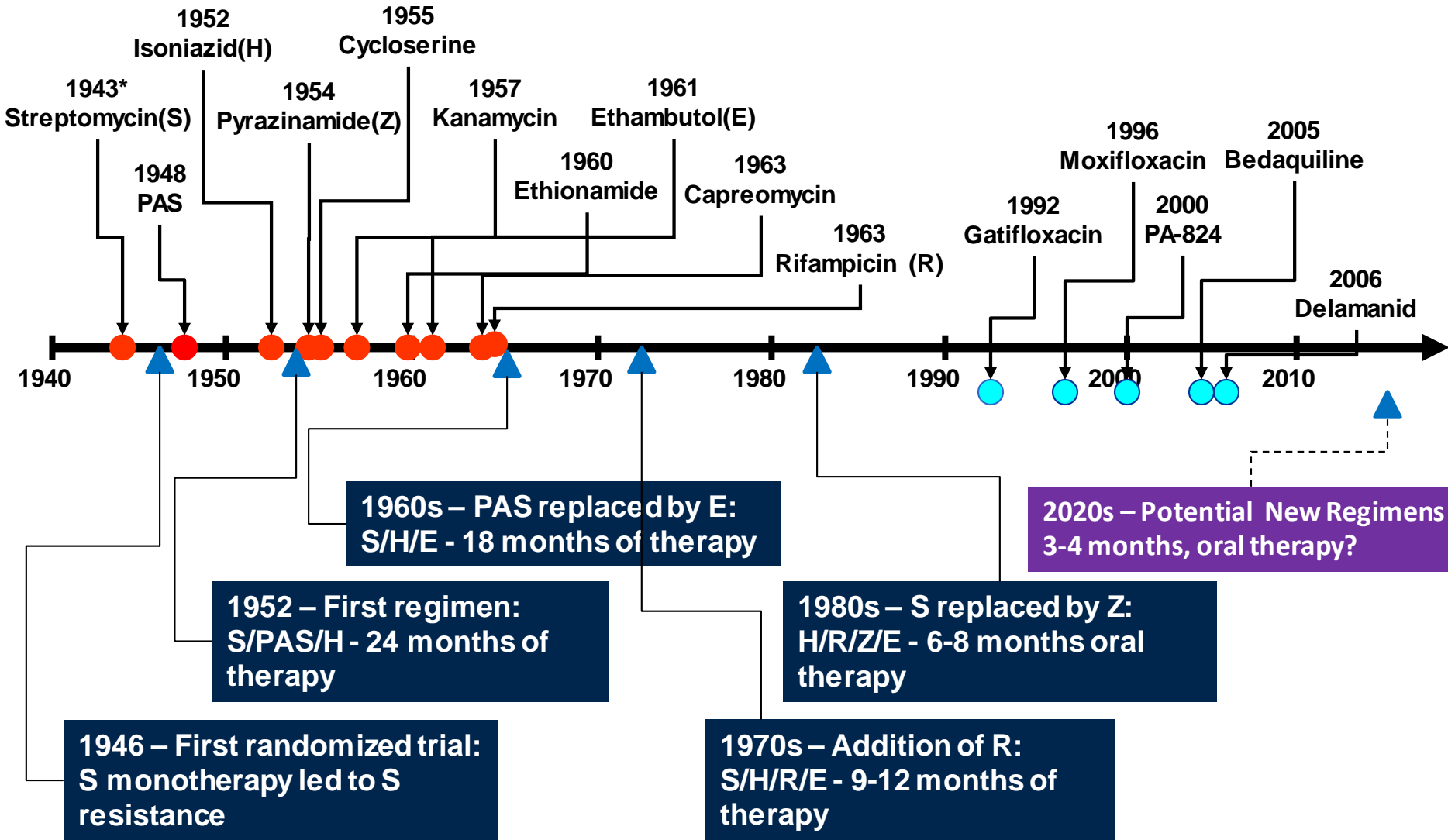
FDA  
17 July 2017

# Overview

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- Background
- Approaches to Trial design
- End-points considerations
- New trial designs
- Target Regimen Profiles for TB treatment
- Lessons learnt and suggestions for future studies

# New TB Drugs



## Development of Regimens

\* Year of first publication

Adapted from Ma Z et al. Lancet 2010

# Approaches to trial design

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- Classical path in DS TB
- Accelerated approval in MDR-TB
- The combination development path
- Unified path in DS and MDR-TB
- Uncontrolled trials

# Classical path in Drug Susceptible TB: *ReMox, OFLOTUB & Rifaquin*

- Single drug substitution in EHRZ control regimen
  - moxifloxacin for isoniazid or ethambutol
  - gatifloxacin for ethambutol
- Non-inferiority design
- Margin determined by limit of what could be expected to be achieved using reduced duration of control regimen
- Delta was set at 6% - "*reflect[ing] consultation with clinicians in high-burden countries and re-analysis of previous trials showing the effect of shortening treatment to 4 months without substituting a new drug.*" (Gillespie et al, NEJM, 2014)

# *The* NEW ENGLAND JOURNAL *of* MEDICINE

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## Four-Month Moxifloxacin-Based Regimens for Drug-Sensitive Tuberculosis

Stephen H. Gillespie, M.D., D.Sc., Angela M. Crook, Ph.D., Timothy D. McHugh, Ph.D., Carl M. Mendel, M.D.,

*The NEW ENGLAND JOURNAL of MEDICINE*

### ORIGINAL ARTICLE

## High-Dose Rifapentine with Moxifloxacin for Pulmonary Tuberculosis

Amina Jindani, F.R.C.P., Thomas S. Harrison, F.R.C.P., Andrew J. Nunn, M.Sc.,

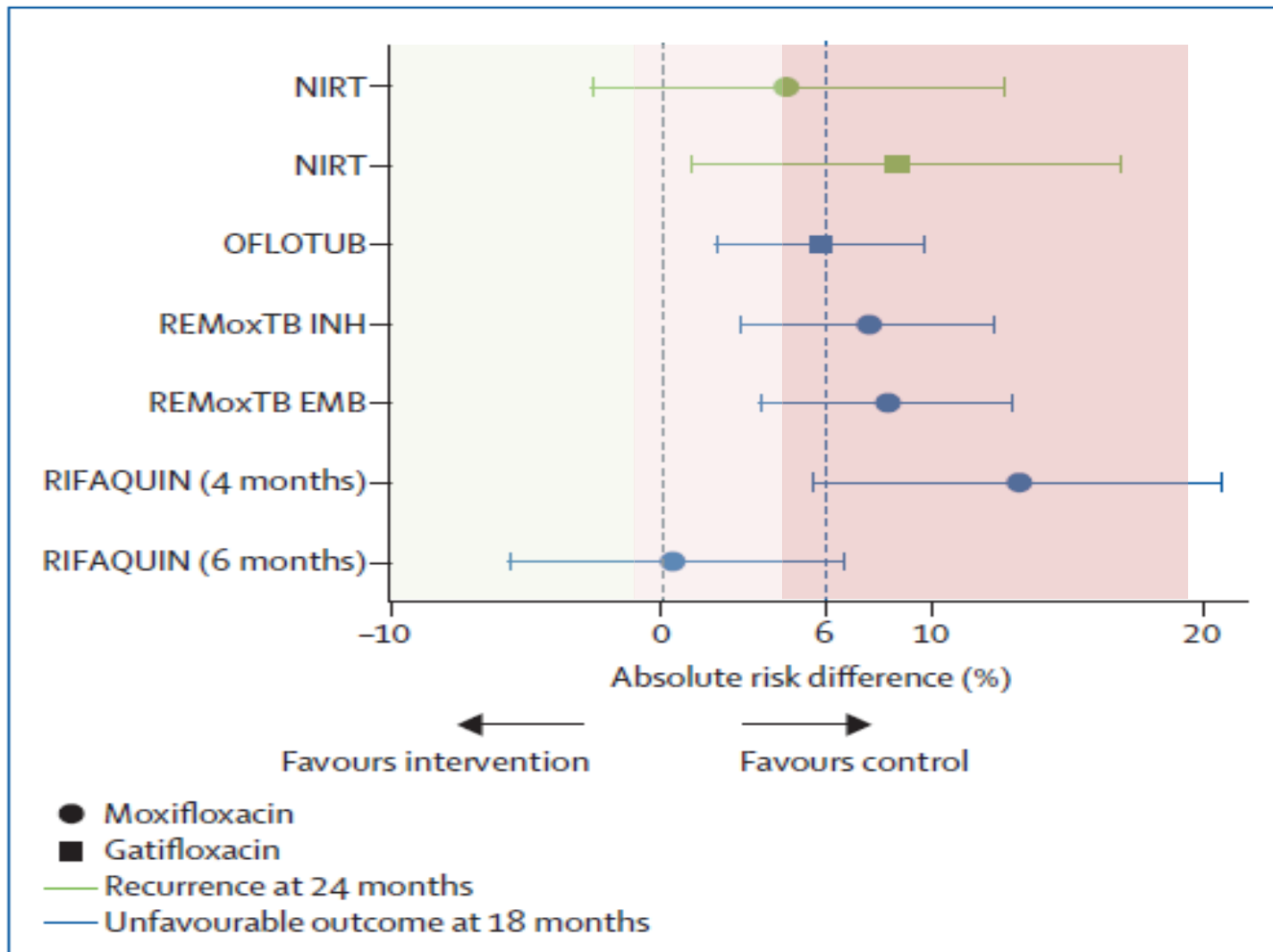
*The NEW ENGLAND JOURNAL of MEDICINE*

### ORIGINAL ARTICLE

## A Four-Month Gatifloxacin-Containing Regimen for Treating Tuberculosis

Corinne S. Merle, M.D., Katherine Fielding, Ph.D., Omou Bah Sow, M.D.,  
Martin Gninafon, M.D., Mame B. Lo, M.D., Thuli Mthiyane, M.Sc.,  
Joseph Odhiambo, M.D., Evans Amukoye, M.D., Boubacar Bah, M.D.,  
Ferdinand Kassa, M.D., Alimatou N'Diaye, M.D., Roxana Rustomjee, M.D.,  
Bouke C. de Jong, M.D., Ph.D., John Horton, M.D., Christian Perronne, M.D.,  
Charalambos Sismanidis, Ph.D., Olivier Lapujade, B.Sc.,  
Piero L. Olliaro, M.D., Ph.D., and Christian Lienhardt, M.D., Ph.D.,  
for the OFLOTUB/Gatifloxacin for Tuberculosis Project\*

# Proportion unfavourable at 18 months post-randomisation: difference from control (95% CI)



**Figure: Quinolone-containing regimens compared with standard treatment for tuberculosis**

<b>Trial regimen</b>	<b>Treatment duration</b>	<b>2 month culture negativity (%)</b>	<b>Relapse rates (%)</b>
2EHRZ/6HE (Study A)	8	86	12
2EHRZ/4HR (Study A)	6	83	6
2EHRZ/4HR (RIFAQUIN)	6	85	4
2EMRZ/4P1M1 (RIFAQUIN)	6	90	4
2EMRZ/2P2M2 (RIFAQUIN)	4	90	16
2EHRZ/4HR(OFLOTUB)	6	75	7
2GHRZ /2GRH (OFLOTUB)	4	75	15
2EHRZ/4HR (REMOX)	6	83	8
2MHRZ/2MHR (REMOX)	4	85	15
2EMRZ/2MR (REMOX)	4	87	20



# Re-analysis of Fluoroquinolone Clinical Trials (TB-ReFLECT) - Main findings

- Integrative analysis of 3 fluoroquinolone phase III TB clinical trials – N=3,039
- Failures both in Standard of care and Test arms were mostly associated with insufficient drug (rifampicin) levels (adherence)
- Longer duration of treatment beneficial
- Culture based predictors:
  - 4 month > 2 month
- Baseline covariates:
  - *"Hard to Treat"* patients with a higher risk of unfavorable outcome: HIV+, older, underweight, high initial smear, cavity at CXR.
- Evidence that different patient groups require different treatment duration
  - Concept of “one duration for all” needs re-examination
  - More aggressive regimens for 'hard-to-treat' patient categories

*R Savic, Union conference, Liverpool, 2016*

# Accelerated/conditional approval in MDR-TB

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- Comparison of **bedaquiline** + BR (background regimen) vs. placebo + BR in patients with MDR-TB

*Diacon et al, NEJM, 2014*

- Provisional approval from FDA obtained in December 2012 based on significant improvement in time to culture negativity

- Comparison of two different doses of **delamanid** vs. placebo in addition to an optimized BR based on WHO recommendations

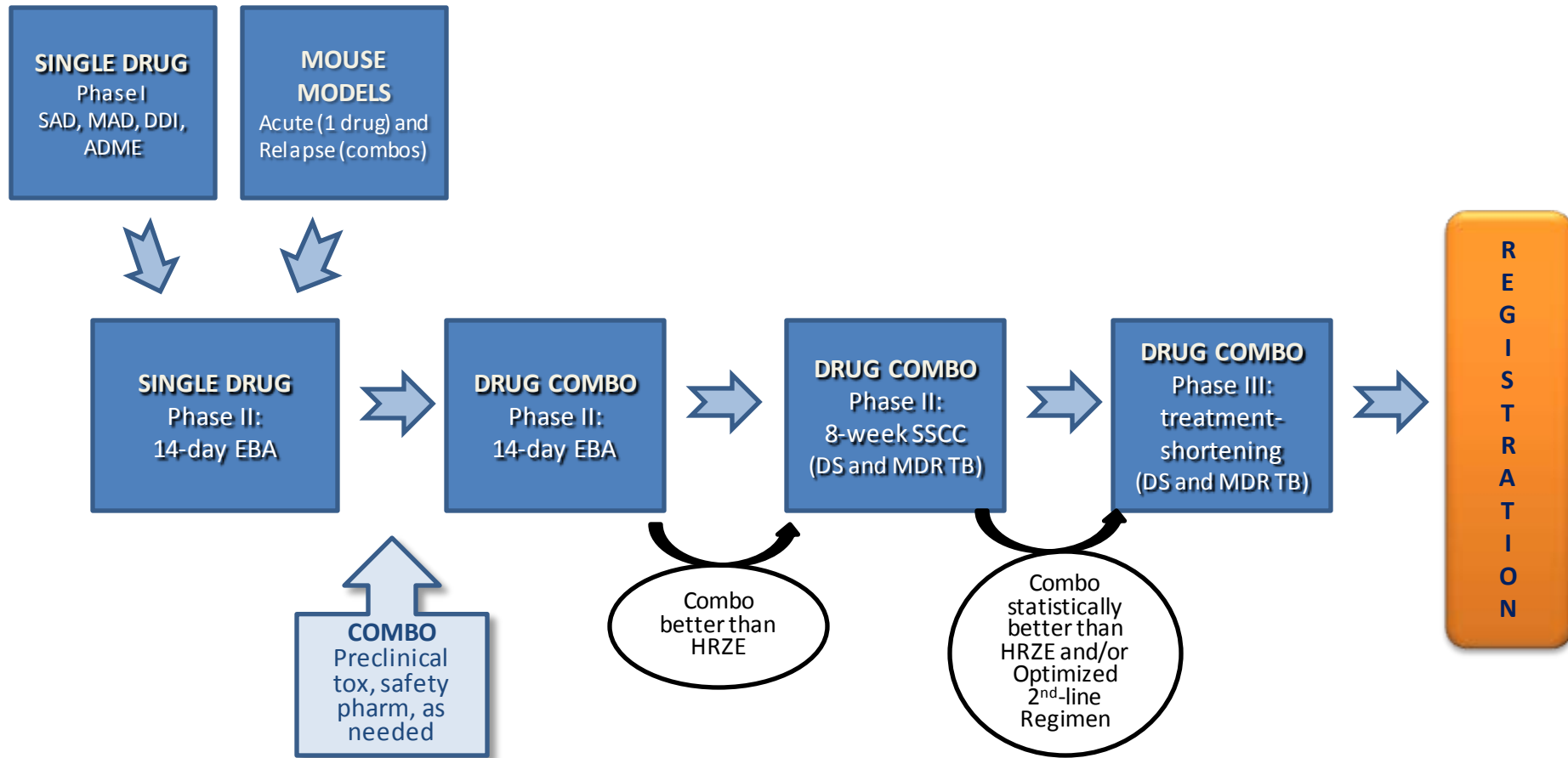
*Gler et al, NEJM, 2012*

# *But ....*

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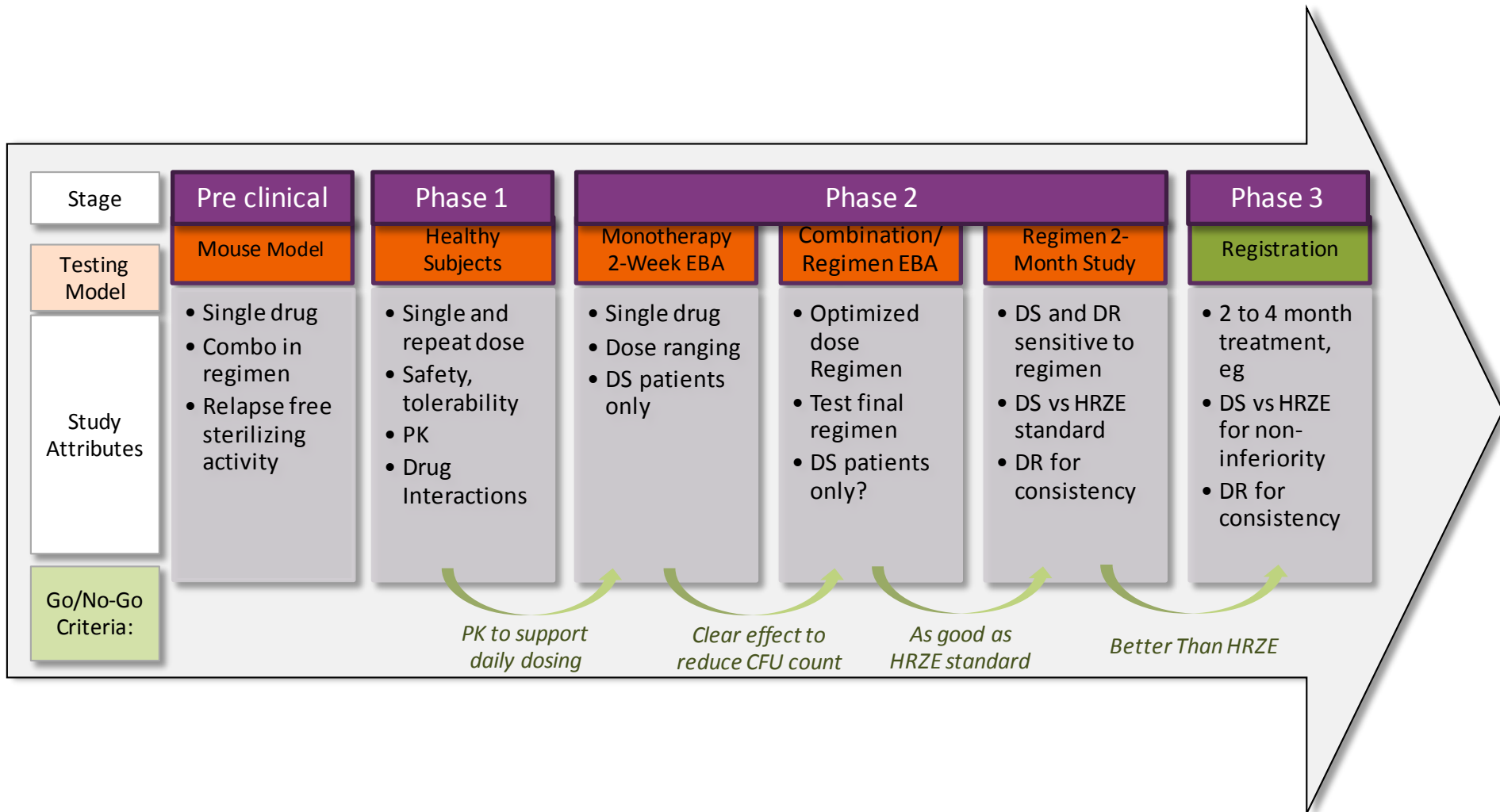
- While these two studies provided important information about the safety and efficacy of two new drugs, they did not provide any information about the best way these drugs could be used within a regimen.
- A series of new trials being funded to assess these and other drugs in different combinations

# Combination development pathway for the treatment of TB



SAD: Single ascending dose; MAD: Multiple ascending dose; DDI: Drug-drug interaction; ADME: Absorption, Distribution, Metabolism, and Excretion; EBA: Early Bactericidal Activity; SSCC: Serial Sputum Colony Count; Combo: combination

# Unified Path in Drug Sensitive/Drug Resistant Regimen Development



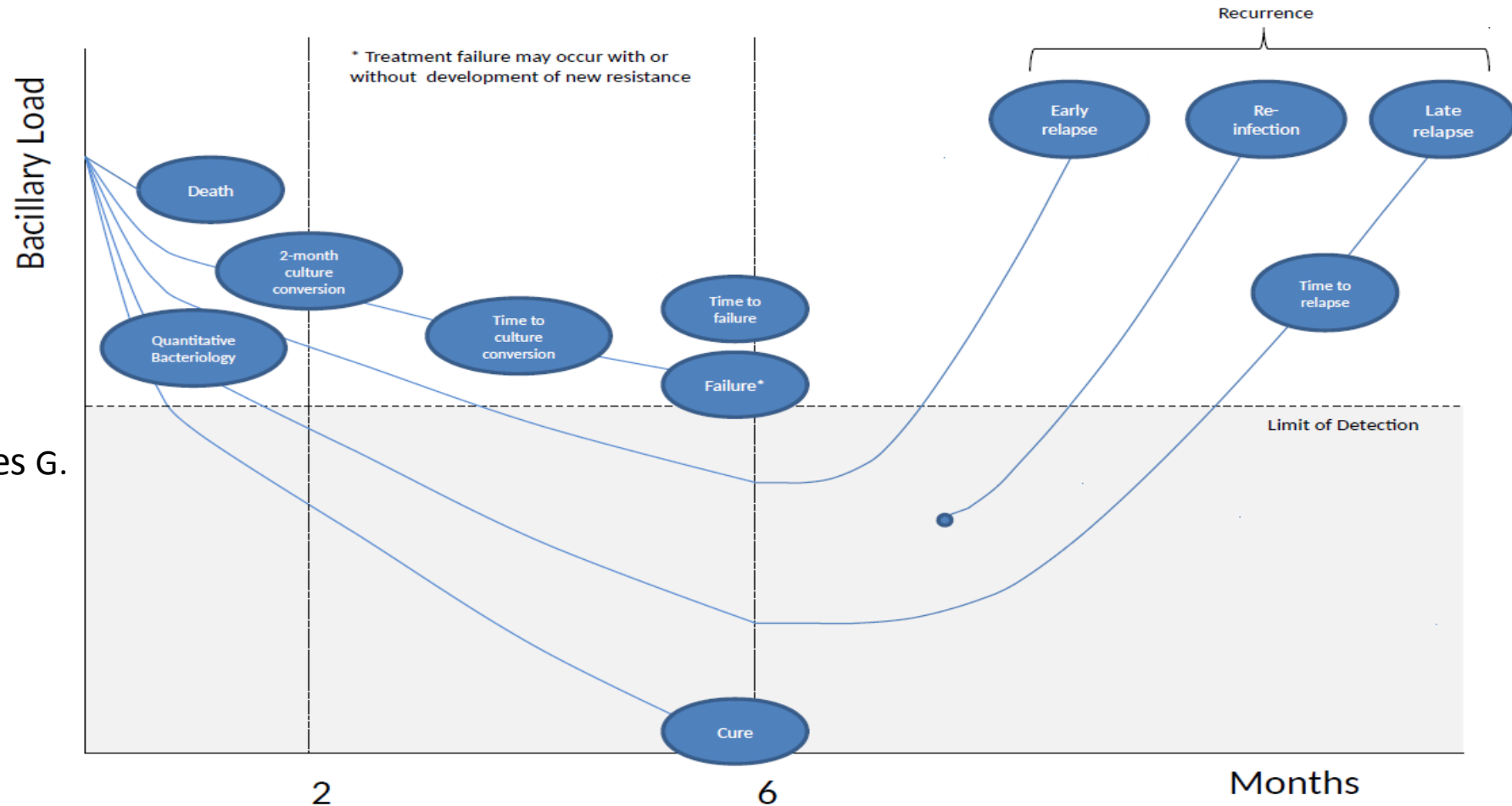
# Unified path in DS and MDR-TB: 8 week SSCC Study of B-Pa-Z-M (NC005)

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- Patients with newly diagnosed DS- or MDR-TB, sensitive to moxifloxacin
  - DS:** randomised comparison of bedaquiline, pretonamid & pyrazinamide vs. EHRZ
  - MDR-TB:** uncontrolled, same drugs plus moxifloxacin
- Phase II results in MDR-TB cohort suggested that there was evidence of substantial additional benefit from addition of moxifloxacin – an indirect comparison
- Next step? A phase III using four drug MDR-TB regimen?

# Efficacy endpoints

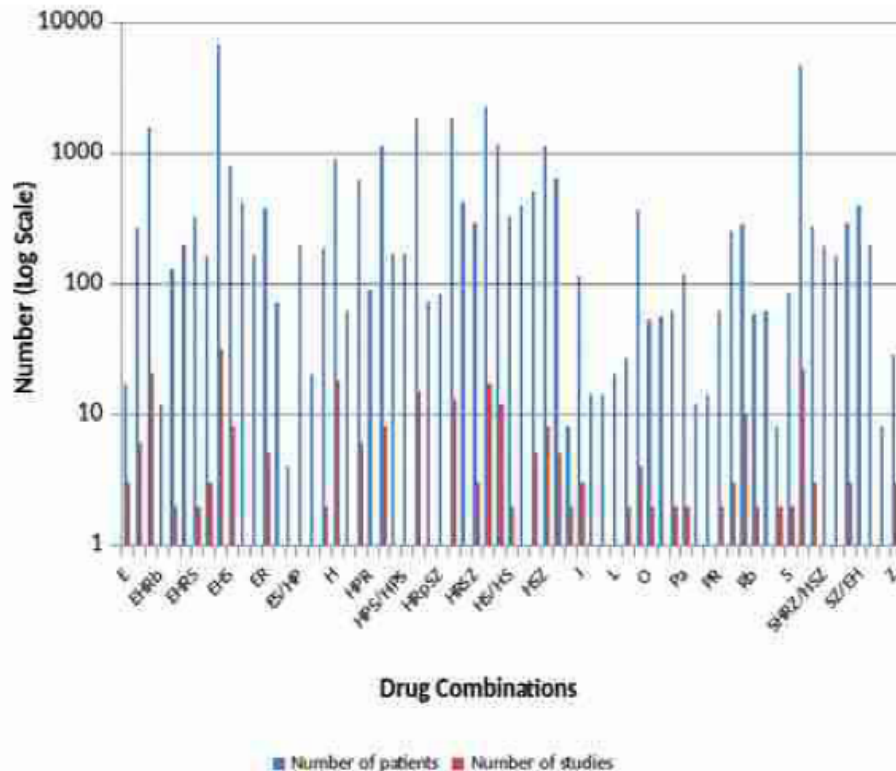
## Quantitative basis of efficacy endpoints



Davies G.  
2017

# Phase II studies

N=37,173 67 drugs/combinations



133 trials with Phase IIA/B Outcomes

96 Phase III trials with intermediate outcomes

EBA<sub>0-2</sub> and 8w CC most commonly reported endpoints

Inconsistent reporting of other EBA endpoints (EBA<sub>0-7</sub>, EBA<sub>0-14</sub>) and alternative approaches

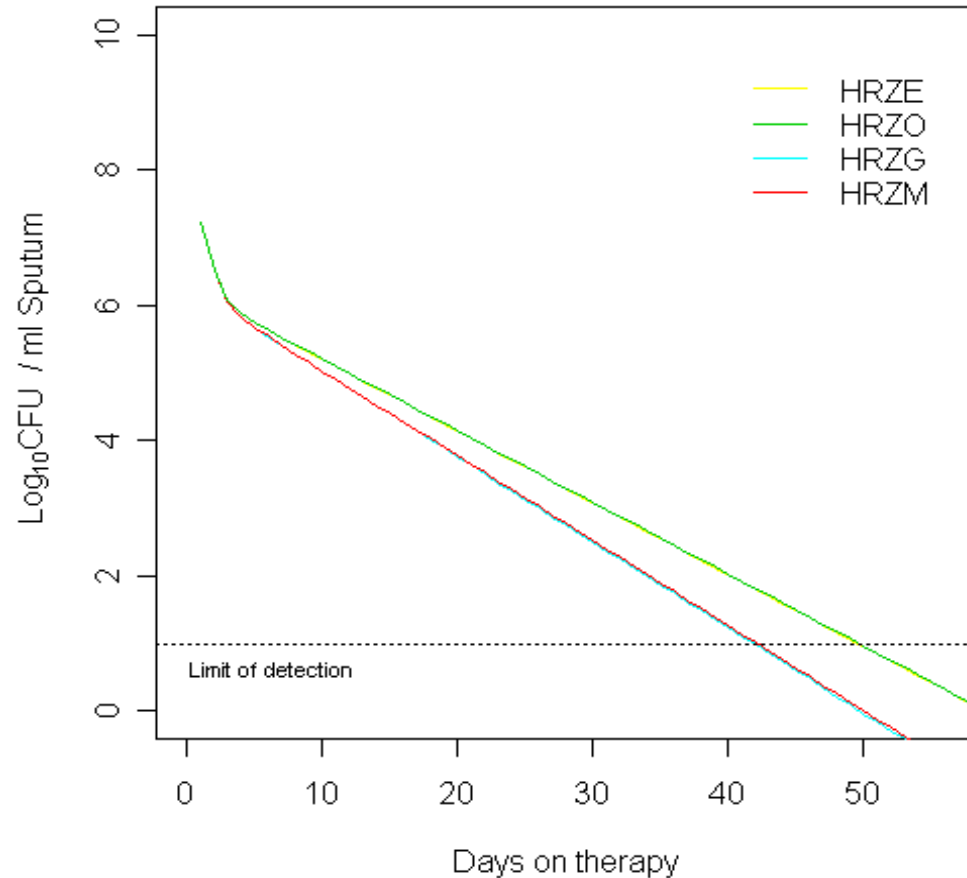
Only 3 regimens with EBA over >2 days and 8w CC data

Davies G.  
2017

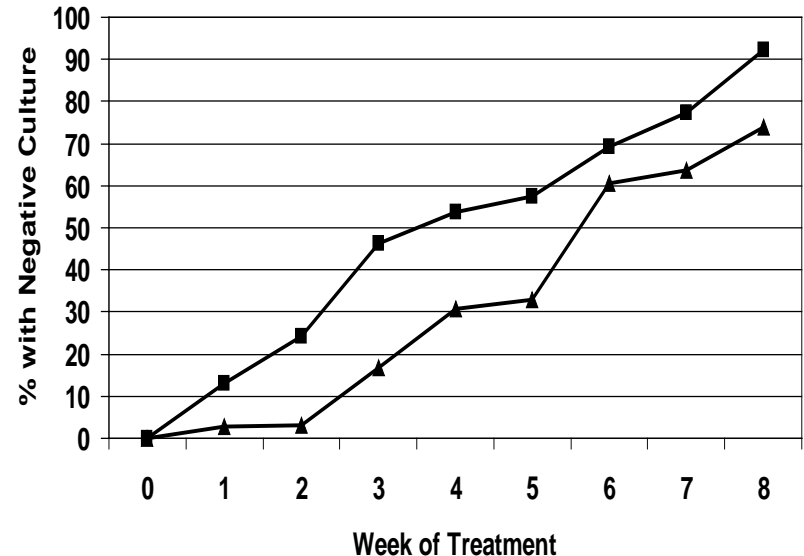


# Effects of replacing ethambutol with moxi- or gatifloxacin in the first-line therapy of TB

OFLOTUB Phase II-SSCC Study

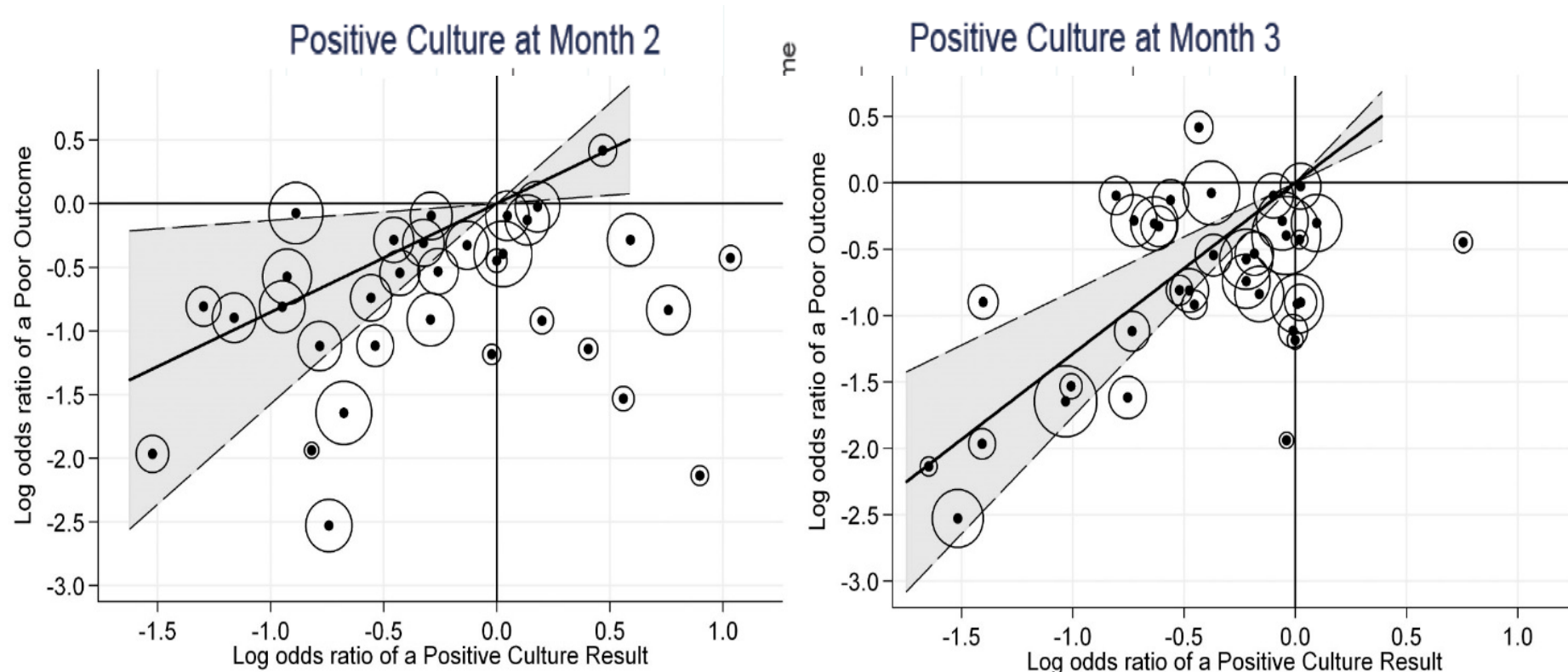


Brazil/JHU Orphan Drug Study



	0/74	9/69 (13.0%)	17/70 (24.3%)	31/67 (46.3%)	37/69 (53.6%)	35/61 (57.4%)	45/65 (69.2%)	48/62 (77.4%)	59/64 (92.2%)
Moxi									
EMB	0/72	2/68 (2.9%)	2/66 (3.0%)	11/66 (16.7%)	20/65 (30.8%)	21/64 (32.8%)	40/66 (60.6%)	42/66 (63.6%)	45/61 (73.8%)
% Diff	0	10.1	21.3	29.6	22.8	24.6	8.6	13.8	18.4
95% CI	-	(1.2, 19.0)	(10.4, 32.1)	(14.7, 44.6)	(6.6, 39.1)	(7.6, 41.5)	(-7.6, 24.9)	(-1.8, 29.4)	(5.6, 31.3)

# M2 Culture Conversion : Trial level surrogacy ?



**Analysis of culture results as surrogate endpoints across all trials.**

15 BMRC trials 6974 participants 37 treatment comparisons

# Longitudinal endpoints

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- Independent of sampling time-points
- No need for future ad hoc re-evaluation
- Unrestricted scale of measurement
- Greater statistical power
- Well-adapted to cumulative meta-analysis
- Little trial level evaluation due to design and reporting

# 'Time-to-event' endpoints



	Control	Q	20RQ	20RM	35R
Included in analysis	123	58	56	63	63
Median time	62 days	63 days	66 days	55 days	48 days
Adj. HR <sup>1</sup> (95% CI)		0.85 (0.57 - 1.27)	0.76 (0.50 - 1.17)	1.42 (0.98 - 2.05)	<b>1.78</b> <b>(1.22 - 2.58)</b>
		p=0.42	p=0.21	p=0.07	<b>p=0.003</b>

Boeree MJ,  
Hoelscher M  
CROI 2015 Abstract  
95 LB

# Need for real-time assessment of efficacy in TB regimen development trials

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## *Major issue:*

- Lack of direct readout of response (amount of TB organisms killed) severely limits the measure of treatment effect
- Lack of a predictive quantitative relationship between Phase 2 readout (organisms killed) and Phase 3 readout (cure)
  - *unclear how to translate culture conversion outcomes*
- Need for new biomarkers for quantitative measurement of bacterial load in sputum

# Multi-Arm Multi-Stage (MAMS) Phase II/III

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- Multi-arm phase II/III trials, originally developed in oncology, with planned interim analyses
- The final analysis is done on the definitive endpoint
- Usual Phase III bacteriological endpoint of failure or relapse
- An intermediate endpoint used to compare each experimental arm with the common control at interim analyses
- Arms dropped if insufficient evidence of benefit using pre-specified critical values or hurdles

# MAMS in TB

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- Feasibility of MAMS design in TB demonstrated (Panacea trial)
- Arms without evidence of sufficient efficacy dropped early thereby reducing the sample size
- Slight risk of dropping an effective regimen

## ***But...***

- Logistically challenging
- Culture results slow and not a good predictor
- Need for better and real time biomarkers measured earlier in treatment
- Would limited data on relapse assist our decision making process?

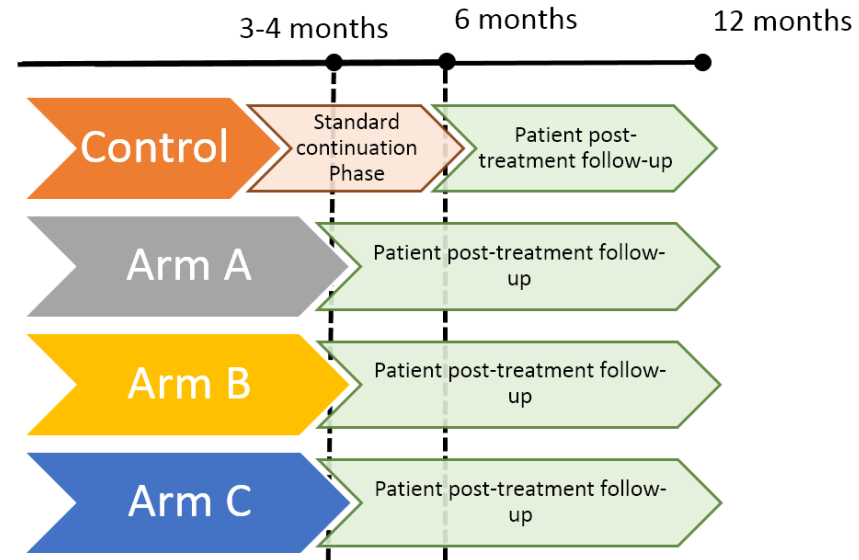
# Accelerating development: Phase IIC STEP design



- Studying the intended duration in Phase II
- Generating richer data prior for more informed Phase III go/no-go decision making
- Richer data for accelerated/conditional approval?



# Accelerating development: Phase IIC STEP design



- sample size similar to Phase IIb study
- novel regimen(s) given for intended duration, 3 or 4m
- patients followed for 12 months post randomisation
- composite failure/relapse endpoint data collected

# Uncontrolled confirmatory trials: Ebola

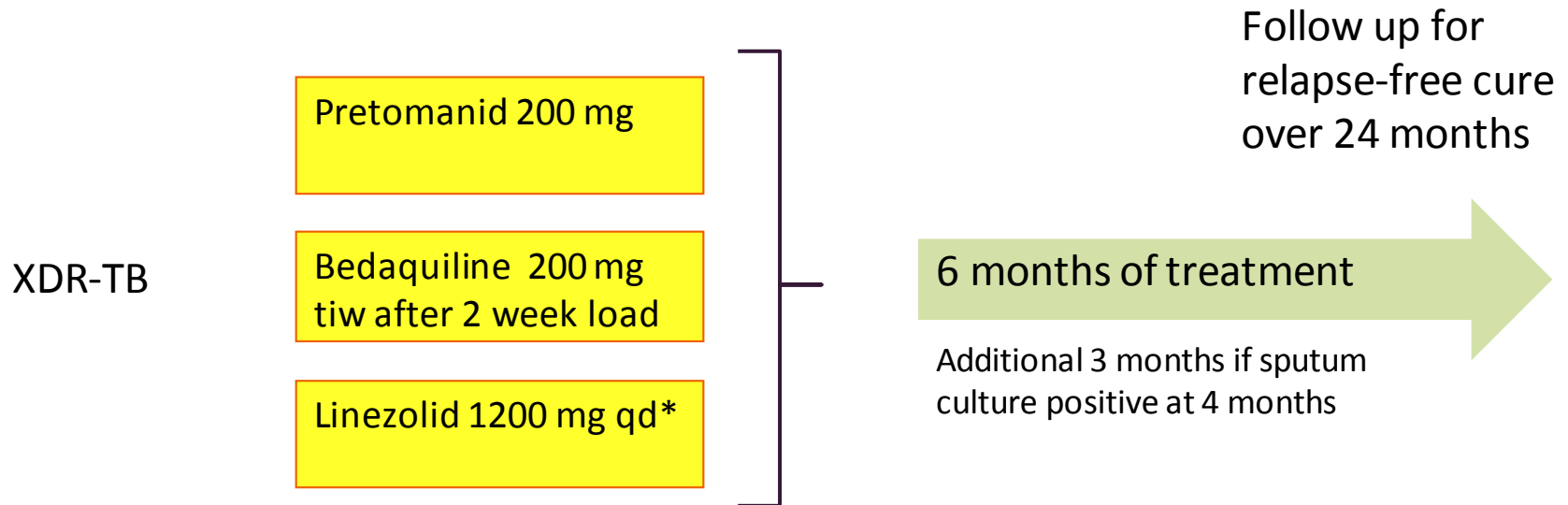
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- Trials of new treatments for Ebola:
  - *“When conventional care means such a high probability of death [70%], it is problematic to insist on randomising patients to it when the intervention arm holds out at least the possibility of benefit. **Ethical arguments are not the same for all levels of risk.**”*
  - *“Equipoise is a useful principle, but it can break down when conventional care offers little benefit and mortality is extremely high.”*

Adebamowo C., Bah-Sow O, Binka F, et al. Randomised controlled trials for Ebola: practical and ethical issues. Lancet 2014

# Nix-TB Trial in XDR-TB

Patients with XDR-TB or Who Have Failed MDR-TB Treatment



\*Amended from  
600 mg bid strategy

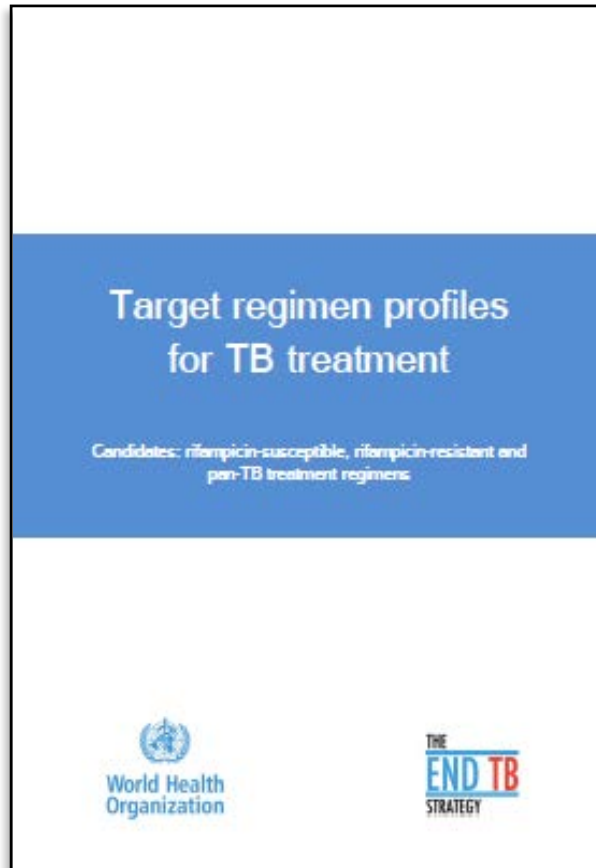
Sites: Sizwe and Brooklyn Chest, South Africa

# Particular considerations for uncontrolled confirmatory trials

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- Do the arguments for uncontrolled trials apply in XDR-TB? MDR-TB? DS-TB?
- How comparable is the trial patient population with that of the historical control?
- Historical case fatality rates are irrelevant if current study patients receive better supportive care - are there other appropriate historical controls?
- What would be the efficacy of the standard of care if given with “study’s level of supportive care”?

# Developing TPPs for TB Treatment: *starting with the goal in mind...*



- **Objective**

To align the targets and specifications that developers should meet for the performance of new TB treatment regimens with the needs of end-users.

- **Target audience**

Pharmaceutical industry, research institutions, product development partnerships, donors, NGOs and CSOs.

[http://www.who.int/tb/areas-of-work/treatment/new\\_drugs/en/](http://www.who.int/tb/areas-of-work/treatment/new_drugs/en/)

# Target Regimen Profiles for TB Treatment

- **Three Target Regimen Profiles:**
  - Rifampicin-susceptible
  - Rifampicin-resistant
  - Pan-TB regimen
- **All Target Regimen Profiles explicitly describe:**
  - *clinical indication* of the treatment (e.g. DS-TB; DR-TB; all forms of TB)
  - *critical endpoints* to be obtained and their measurement (e.g. non relapsing cure within 2/4/6/9 months of starting treatment)
  - *target population* (children, adults, PLHIV, ...)
  - *treatment characteristics*: e.g.. expected duration; frequency and route of administration (e.g. daily, fully oral); formulation (dispersible tabs; FDCs;...)
  - likely set of users.

[http://www.who.int/tb/areas-of-work/treatment/new\\_drugs/en/](http://www.who.int/tb/areas-of-work/treatment/new_drugs/en/)

# Lessons learnt:

## 1- Treatment implications

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- Most impactful intervention is ensuring adequate dosing and adherence to treatment
- Importance of rifamycins as backbone of shortened therapy re-emphasized
  - Role of high dose ?
- Patients with high bacterial burdens and experiencing slow decline in bacterial burdens over the initial 4–8 weeks of treatment constitute a subset most likely to relapse.
  - Evidence that different patient groups may require different treatment duration
  - 'Hard to treat patients' to be considered as specific population for longer treatment duration and/or higher doses ?
  - Specific drug combination ?
- Implications for Phase 2/3 trials : need for initial patient stratification ?
- Ensure appropriate representation to allow robust subgroup analysis.

# Lessons learnt :

## 2 - Design of future regimens

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- An increasing number of potential regimens are being assessed - need to be able to review multiple regimens together
- Culture conversion limited value for predicting long term outcome - high need of quantitative assays of bacterial burden over time
- Alternative designs enable more rapid differentiation between multiple candidate regimens but logistical constraints remain
- Uncontrolled studies may have a place early in development
- Choice of the non-inferiority margin needs careful consideration, as does the risk of bio-creep



# Lessons learnt :

## 2 - Design of future regimens (contd)

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- PK/PD analyses are critical
  - using drug exposure to understand intermediate endpoints in addition to dose selection is key
  - examining the relation between dose and treatment duration for efficacy endpoints
- PK/PD data should be incorporated to build integrative PK/PD models that could reveal further opportunities for regimen optimization (incl. safety) and improve trial design.

# Lessons learnt :

## 3. Standardization of trial data collection

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- Consistency in collecting clinical data across the trials is needed to expedite integrated learning
- Culture results are relevant risk factors, but not capable of predicting individual relapse
- Definition of Phase III clinical trial endpoint should be at minimum recurrence/relapse
- MITT and PP definition need re-examination (impact of adherence)
- Incorporation of PK data and detailed adherence histories
- C-DISC
- Safety data key

# WHO needs for Guideline development

- WHO guidelines based on *best available evidence*
  - GRADE approach for evidence assessment across questions and outcomes
  - Criteria for moving from evidence to recommendations
- Main aspect: *what is the best available evidence that can be brought about that ultimately benefits patients ?*
- Need for clearly and rationally justified approaches (choice of drug combination, design, conduct, end-points, analyses);
- Based on the premise that TB drug R&D focus is shifting towards developing and testing *TB regimens* (rather than individual drugs), a set of targets is proposed, for three types of indications: RS-TB, RR-TB and Pan-TB;
- Need to further strengthen dialogue between regulators and policy-makers

# Acknowledgements

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***Thank you for  
your attention !***

