

Center for Tuberculosis



University of California San Francisco

A systematic review of estimand and endpoint definitions in recent phase III trials in DS-TB and DR-TB: Preliminary Results

INTER-TB Meeting, 16 Oct 2020

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TBTC Study 31/ ACTG A5349

Symposium at the 51st Union World Conference on Lung Health 21 October 2020, 10:30am US Eastern Time (80 minutes), SP-10

Symposium chairs: Susan Swindells, Nguyen Viet Nhung



- 1. The design and primary efficacy results of Study 31/A5349, Susan Dorman
- 2. Safety of high-dose rifapentine regimens, Ekaterina Kurbatova
- 3. Secondary efficacy and safety analyses of short regimen performance by disease phenotypes and patient subgroups, **Payam Nahid**
- 4. Perspectives on shortened TB regimens: local medical and community views, **Grace Muzanye**
- 5. Lessons learned and next steps, Richard Chaisson

Two poster presentations on adolescent sub-study

21 October 2020, 10am CET/4am ET EP02-115-21, Kim Hedges

EP02-116-21, Joan Mangan





- Endpoints
- Estimands
- Systematic review of Estimands and Endpoints:
 - Methods
 - Results
- Conclusions



What proportion of patients are cured with the 6-month standard regimen for DS-TB?

MITT = Modified Intention-To-Treat; PP = Per Protocol

99% - SHRZ/HR	Fox, 1981
95-99% - SHRZ/HR(Z)	FDA guidance for pulmonary TB trials, 2013
96% - SHR	EA/BMRC Study R 1972
95.1% (PP)	RIFAQUIN, Jindani et al. 2014
92%	NIRT, Jawahar et al. 2013
92% (PP)	REMoxTB, Gillespie et al. 2014
88.7% (PP)	OFLOTUB Phase III, Merle et al. 2014
85.6% (MITT)	RIFAQUIN, Jindani et al. 2014
84% (MITT)	REMoxTB, Gillespie et al. 2014
82.8% (MITT)	OFLOTUB Phase III, Merle et al. 2014

- What do we mean by 'cure'?
- When is it measured?
- What is the denominator (patient population)?
- How do we classify death or loss to follow-up?
- What about treatment changes for adverse events?

REMoxTB

Were considered not able to be assessed — no.		
Had reinfection with a different strain	1	7
Had a negative culture at 76 weeks but lost to follow-up thereafter	5	1
Were included in primary outcome analysis — no.	124	24
Outcome		
Attained favorable status — no. (%)†	99 (79.8)	193 (
Had an unfavorable outcome — no. (%)	25 (20.2)	52 (2
Determined on the basis of bacteriologic findings‡		
Had no negative cultures§	1	5
Had bacteriologic reversion during treatment period¶	4	13
Had bacteriologic relapse after treatment period and started ≥2 additional drug therapies	0	7
Had positive culture at last assessment**	2	1
Determined on the basis of criteria other than bacteriologic findings		
Had negative culture at last assessment but died during the treatment or follow-up period	5	9
Had treatment extended or changed after adverse event	3	4
Started ≥2 additional drug therapies owing to decision by the investigator††	3	2
Withdrew consent for treatment, was given a different regimen, or was lost to follow-up before 76 weeks	4	8
Had treatment extended or changed after poor adher- ence or loss to follow-up	0	2
Had negative culture at last assessment but was lost to follow-up before 76 weeks	3	1

Composite Primary Outcome

STREAM Favorable outcome - no. (%) Patients with outcome 467 (92) 436 (85) 419 (Culture-negative status at 18 mo 409 (80) 389 (76) 367 (Unable to produce sputum 2 (<1) 0 0 Unable to produce sputum at 49 (10) 31 (6) 35 (18 mo but culturenegative status earlier Missing data on L-J culture at 9 (2) 14 (3) 17 (18 mo and MGIT negative Unfavorable outcome - no. (%); Patients with outcome 78 (15) 43 (8) 105 (6-Mo treatment phase Nonviolent death 5(1) 6(1) 7 (Treatment failuret Culture-confirmed 3 (1) 4 (1) 1 (Not culture-confirmed 4(1) 1 (<1) 4 (Adverse reaction NA NA N Withdrawal of consent NA NA N Relocation NA NA N Other investigator decision NA NA N No completion of treatment NA NA N Follow-up Relapse after culture-negative 12 (2) 46 (9) 64 (status Retreated for tuberculosis 14 (3) 17 (3) 27 (Death from tuberculosis or 2 (<1) 0 0 respiratory distress No culture-negative status Ever 1(<1)1 (<1) 0 At last visit 2 (<1) 3 (1) 2 (

Delamanid C213 trial

5.2 Treatment Success or Failure at Month 30

Table S7 Treatment Success or Failure at Month 30 (MITT),				
Endpoint – no. (%)	Delamanid + optin background regi (N=226)			
Treatment Success*	173 (76.5)			
Treatment Failure	53 (23.5)			
Achieved 6-month SCC, then died	6 (2.7)			
Achieved 6-month SCC, discontinued and alive/unknown at Month 30	10 (4.4)			
Achieved 6-month SCC, discontinued, then died	0 (0,0)			
Achieved 6-month SCC, then had positive culture	9 (4.0)			
Died before 6 months	1 (0.4)			
Failed to achieve 6-month SCC and died after 6 months	3 (1·3)			
Discontinued before 6 months and alive/unknown at Month 30	9 (4.0)			
Discontinued before 6 months then died	1 (0.4)			
Failed to achieve 6-month SCC, discontinued, and alive/unknown at 30 months	2 (0.9)			
Failed to achieve 6-month SCC, discontinued, then died	1 (0.4)			
Failed to achieve 6-month SCC and completed 30 months	11 (4.9)			

*SCC by 6 months, completed trial to 30 months with sustained MITT=modified intent-to-treat, SCC=sputum culture conversi

5.3 End of Treatment Outcomes

Table S8 Treatment Outcome at End of Treatment with OBI (MITT), MGIT			
Endpoint – no. (%)	Delamanid + optin background regi (N=224)		
Favourable Outcome	182 (81.3)		
Cured	173 (77·2)		
Completed	9 (4.0)		
Unfavourable Outcome	42 (18.8)		
Failed	11 (4.9)		
Defaulted	22 (9.8)		
Died	9 (4.0)		

The composite efficacy outcome is not fit for purpose for TB phase III trials

- (1) At odds with best practice
 - Post-randomization exclusions without proper causal inference methodology
- (2) Variation between trials and sponsors
- (3) Inflation of Type I and II errors and consequent incorrect decisions in adaptive platform trials.
- (4) A barrier to identifying highly efficacious regimens
 - Events not related to TB increase variability and add 'noise'
- (5) At odds with policy makers and guideline developers
 - Not aligned with WHO expert guidelines development groups which rely on WHO programmatic outcomes definitions when considering evidence.
- (6) Mixes efficacy and safety
- (7) Impedes progress in prediction modelling and biomarker discovery
- (8) Regulatory guidance is changing
 - ICH E9 (R1) addendum: Estimands and Sensitivity Analyses (Nov 2019)

A new framework

ICH E9 (R1) Addendum: Estimand and sensitivity analyses

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

STATISTICAL PRINCIPLES FOR CLINICAL TRIALS E9

> Current Step 4 version dated 5 February 1998

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

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17 February 2020 EMA/CHMP/ICH/436221/2017 Committee for Medicinal Products for Human Use

ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials Step 5

Transmission to CHMP	July 2017
Adoption by CHMP for release for consultation	20 July 2017
Start of consultation	31 August 2017
End of consultation (deadline for comments)	28 February 2018
Final adoption by CHMP	30 January 2020
Date for coming into effect	30 July 2020





Pre-specifying the Estimand: Benefits

- ICH E9 (R1) framework provides a standardized language to help us articulate the treatment effect that we want to measure
- ITT vs MITT vs PP. What do we mean? Which is most important?
- Clear interpretation for different stakeholders that have different perspectives (different estimands for different purposes)
 - Regulators vs Guidelines developers vs Clinicians vs Patients
- Transparent definitions, achieves buy-in from TB community prior to analysis and presentation or results.
- Facilitates cross-trial analyses

Modernization of Phase III TB Clinical Trial Endpoints

 The aim of this project is to describe a primary efficacy outcome and estimand(s) that addresses the limitations of the currently used primary efficacy outcome.

Modernization of Phase III TB Clinical Trial Endpoints

- The primary efficacy outcome for a TB phase III trial should fulfil the following criteria:
 - Capture TB-related efficacy while not being unduly influenced by aspects of tolerability and safety;
 - Permit methods of analysis that include all randomized patients, in line with the intention-to-treat principle;
 - Be specific for bacteriological failure and relapse in order to:
 - Permit reliable decision-making in adaptive designs,
 - Identify when a regimen or strategy delivers 97-100% cure,
 - Allow for development of predictive models linking phase II and phase III endpoints to support development of biomarkers of treatment response
 - Be acceptable to regulators to permit licensure and to bodies issuing treatment guidelines;
 - Result from broad consensus across the TB clinical trials community to be used in future phase III trials to better facilitate evidence synthesis.



Modernization of Phase 111 TB Clinical Trial End pints

1. Systematic Review

2. Estimand(s) Proposal

• Review endpoint definitions across phase III trials and identify areas of agreement and areas of disagreement. •Use estimand framework to provide standardized endpoint definitions, and associated methods of analysis

- •Ensure consistency with broad definitions in regulatory guidelines
- •May need multiple estimands for different stakeholders (regulatory vs programmatic, DS-TB vs DR-TB)

- Analyses to explore impact of estimand(s) proposal on trial operation characteristics
- •Phase III, Phase IIC platform trials, Adaptive trial designs

- 4. Consensus building
- •Present proposals to relevant trialists and stakeholders for discussion, feedback, and consensus



Modernization of Phase III TB Clinical Trial Endpoints

Two goals

1. Specification

- Pre-specification of all aspects of estimand (including intercurrent events)
- Transparency
- Trial design and conduct matches estimand (e.g. whether or not to follow patients withdrawn from treatment)

2. Standardization

- Evidence-based best practice standards that all phase III trials can adopt.
- Facilitates cross-trial analyses.



An example from the INSIGHT START trial

The primary end point was a composite outcome that included two major components. The first was any serious AIDS-related event, which included death from AIDS or any AIDS-defining event (as outlined in the 1993 expanded surveillance document of the Centers for Disease Control and Prevention),³¹ with the exception of nonfatal horness simplex views infection and ecopherceal

An end-point review committee whose members were unaware of study-group assignments reviewed all reported serious AIDS-related and serious non–AIDS-related events and deaths using preestablished criteria.³² Events that the committee considered to be confirmed or probable were counted as end points.^{33,34}

Insight Start Study Group, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med. 2015;373(9):795-807.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

AUGUST 27, 2015

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Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group*

ABSTRACT

BACKGROUND

DC

Data from randomized trials are lacking on the benefits and risks of initiating antiretroviral therapy in patients with asymptomatic human immunodeficiency virus (HIV) infection who have a CD4+ count of more than 350 cells per cubic millimeter

The members of the writing group (Jens D. Lundgren, M.D. [cochair], Abdel G. Babiker, Ph.D. [cochair], Fred Gordin, M.D. [cochair], Sean Emery, Ph.D., Birgit Grund Ph.D. Shueta Sharma, M.S. An-

CDC Home Search Health Topics A-Z



Recommendations and Reports December 18, 1992 / 41(RR-17)

Persons using assistive technology might not be able to fully access information in this file. For assistance, please send e-mail to: <u>mmwrq@cdc.gov</u>. Type 508 Accommodation and the title of the report in the subject line of e-mail.

1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults

The following CDC staff members prepared this report:

National Center for Infectious Diseases Division of HIV/AIDS Kenneth G. Castro, M.D. John W. Ward, M.D. Laurence Slutsker, M.D., M.P.H. James W. Buehler, M.D. Harold W. Jaffe, M.D. Ruth L. Berkelman, M.D.

Office of the Director Associate Director for HIV/AIDS James W. Curran, M.D., M.P.H.

1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults

Summary

CDC has revised the classification system for HU infection to emphasize the clinical importance of the CD+T-Tymphocry the count in the categorization of HU-related clinical conditions. This classification system published by CDC in 1986 (1) and is primarily intended for use in public health practice. Consistent with the 1993 revised classification system, CDC has also expanded the AIDS groundlance case definition to include all HU-infered corrane tube have lass the normalization and the arc of CD4.

Primary efficacy outcomes of TB Phase IIC and Phase III clinical trials: A systematic review PROSPERO 2020 CRD42020197993

- Objectives of systematic review:
 - Catalogue primary long-term efficacy outcome definitions (including analysis populations and primary objectives) from recent phase IIC and III trials for new regimens for drug susceptible (DS) and drug resistant (DR) Tuberculosis.
 - 2. Conduct a thematic analysis on primary efficacy outcomes to identify areas of consensus and disagreement that can be used to develop consensus estimands for phase IIC and III TB therapeutics trials.

Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020197993



Inclusion and exclusion criteria for Trials PICOS framework

- Participants:
 - Adults and/or children infected with pulmonary TB that are enrolled in TB clinical trials.
- Interventions:
 - Combination regimens using new or repurposed drugs for the treatment of patients with DS or DR TB.
- Comparator:
 - Standard of care according to WHO guidelines or placebo plus optimized background regimen.

Inclusion and exclusion criteria for Trials PICOS framework

• Outcome:

- Long-term durable cure including data both during and after treatment
- Studies with no outcome data on post-treatment follow-up (for relapse) will be excluded.
- Studies:
 - Trials of new regimens that have been designed to advance a drug or regimen for regulatory approval, and have impact by informed guidelines
 - Only trials with registry entries or translations in English will be included.
 - Any trials with a total sample size of less than 100 will be excluded



Study inclusion

WHO International Clinical Trials Registry Platform (ICTRP)

- Since July 2005, ICMJE journals only consider registered trials.
- ICTRP is comprehensive database of global clinical trial registries
- ASCII text file download (3.5GB) for interrogation (May 2020)
- ICTRP contains trials registered from May 1994.



Study inclusion

WHO International Clinical Trials Registry Platform (ICTRP)

Data providers for ICTRP

- Australian New Zealand Clinical Trials Registry (ANZCTR)
- 2. Brazilian Clinical Trials Registry (ReBec)
- 3. Chinese Clinical Trial Register (ChiCTR)
- 4. Clinical Research Information Service (CRiS), Republic of Korea
- 5. <u>ClinicalTrials.gov</u>
- 6. Clinical Trials Registry India (CTRI)
- 7. Cuban Public Registry of Clinical Trials (RPCEC)
- 8. EU Clinical Trials Register (EU-CTR)

- 9. German Clinical Trials Register (DRKS)
- 10. Iranian Registry of Clinical Trials (IRCT)
- 11. ISRCTN
- 12. Japan Primary Registries Network (JPRN)
- 13. Pan African Clinical Trial Registry (PACTR)
- 14. Peruvian Clinical Trials Registry (REPEC)
- 15. Sri Lanka Clinical Trials Registry (SLCTR)
- 16. Thai Clinical Trials Register (TCTR)
- 17. The Netherlands National Trial Register (NTR)







Preliminary Results

EXTENSION OF TREATMENT																
Extension of treatment			Excluded from PP													
									Unfavorable							
Ongoing requirement for TB tx after end of FU	BACTERIOLOGICAL FAILURE								(96 wks)							
Still on tx at 108 wks, but not declared a tx failure	Patients not culture negati	ve status at time of endp	point													
Extension beyond protocol except for reinfection	Failure to achieve SCC by e	nd of follow-up				Unfavorable (mITT)										
Extension byond protocol except for pregnancy	Failure at end of tx					Unfavorable [m]TT1	Unfavorable ,									
Extension beyond protocol excent for missed dos	Last positive culture not fo	llowed by at least 2(-) re	SUIT LOST TO FOLLOW	-UP BEFORE END OF	TREATMENT											
Extension of treatment for other than unfavorable	absence of evidence of cc2	Icalled "treatment failun	elu							mITT: Unfavo	rable;					
RESTART TREATMENT	why?l		Lost to FU before	end of tx					Unfavorable	excluded from	PP (6 Unfav	orable [mITT]		_		
Restart of treatment except for reinfection	Last culture(-) betw. Wks 6	5-73 & no other post-bl re	Lost fo FU after w	k16 but before wk24				Unfavorable*								
Restart of treatment except for pregnancy	Last culture(-) betw. Wks 6	5-73 & penultimate cultur	re(+ LOST TO FOLLOW	-UP POST-TREATMEN	NT											
Restart of the because of unfavorable outcome with	contamination & b/r/c unf	avorable	Lost to FU if parti	cipant's scheduled fo	llow-up ends at wk73 (study DEATH Iduring tr	eatment]			1						
confirmation	No culture result within 9	wks of endpoint & most re	ece and participant d	oes not complete sch	neduled final visit.	DEATH DUE TO TE	3				-					
Le on b/r/c grounds	b/r/c		Lost to FU if parti	cipant's scheduled fo	llow-up ends at wk73 (study Death during tx (du	e to TB)		Unfavorable*	Unfavorable	Unfavorable**	Infavorable [mITT & P	PP]		Unfavorable	
Restart of tx because of unfavorable outcome wit	Culture result within 9 wks	of endpoint(+) due to cc	& n and staff can't ge	t info or contact parti	icipant for >14 consecut	ive wi Due to TB + anothe	r disease		Unfavorable*							
confirmation.	culture (+)		the scheduled fir	nal study visit.		DEATH DUE TO A	NY CAUSE			1		-	1			
	No culture result within 9	vks of endpoint & most re	ece Able to produce	sputum at end of FU,	but both specimens are	e missi Death from any cau	ise during treatment									
Restart of any MDR-TB tx after tx end but before e-	absence of cross contamin	ation	contaminated, ca	n't be brought back f	or repeat cultures, prov	rided 1 Death with docume	ented evidence not due to	TB			Unassessable		1			
CHANGE TREATMENT	Culture result within 9 wks	of endpoint(+) due to cro	oss not already been	classified as unfavor	able & provided that th	eir las Non-TB death (accid	dent, trauma, suicide, OI)		Unfavorable	Censored	Chassessable			Unassessable		
Replacement or addition of >1 drugs in experime	most recent culture (-) & b,	r/c unfavorable	followed by at le	ast 2 (-) cultures		Suicide			Unfavorable	Censored		Unfavorable (mITT & P	PPInfavorable (mITT & PF	Unassessable		
Replacement or addition of >1 drugs in control are	No culture result within 9	wks of endpoint & no oth	er p After cure, lost d	uring FU & one cultur	e(+) based on most rec	ent re DEATH, EXCEPT F	OR									
Replacement or addition of 22 drugs in control an	culture result		After cure, lost to	FU, moved away an	d one culture(+) based o	on mo Any death but accid	lent/trauma/violent cause	e during treatment	_		Unfavorable?	Infavorable (mITT & P	PFInfavorable (mITT & PF	Unfavorable		
confirmation	No culture result within 9	wks of endpoint & most re	ece culture			DEATH [during fo	llow-up]									
i.e. on b/r/s grounds	to cross contamination		After cure, lost to	FU, moved away an	d one culture(-) based o	on mo: DEATH DUE TO TE	8		Unformable	Unformation		Information for ITT 0.0		Understelle	lister and la	Information bits from 00
Change of ty because of unfavorable outcome with	No culture result within 9	wks of endpoint & most re	ece culture or contan	ninated		Death from confirm	ed/suggested possible to	failure or relapse (MOV	D UP)	Unravorable			winavorable (mitti & Pr	Unfavorable	Unravorable	ouravorable (wk ap
change of its because of unravorable outcome wi	b/r/c		Lost during FU &	culture(-) based on n	nost recent result (or co	ntami Patient completed	ATT but died due to TB du	ring 12mos of follow-up	MO Unfavorable							
Change of the except single drug replacement	Culture result within 9wks	of endpoint(+) due to cro	Lost after end of	tx, with last culture(-)	After cure, death du	uring FU & one culture (+) I	based on most recent								
change of tx except single drug replacement	no other post-baseline cu	ture result	Lost to FU after 6	m tx with negative la	st 🛛 culture	culture results	deventes 8 alarah (mish ani	danag of T0 an annual of			Unfavorable					
change of tx except for guideline change	Culture result within 9 wks	of endpoint(+) due to cro	Lost after end of	tx, if classified as unf	avorable	DEATH DUE TO A		idence of TB as cause of	-	1	Uniavorable					
Modify treatment for other than unfoverable room	most recent culture(+) due	to cross contamination	Lost after end of	tx, if patient did not	have culture(-) status	Death from any cau	ise during follow-up			1			1		[
Nodify deathent for other than dinavorable resp	culture result within 9 wks	of enapoint(+) due to cro	Lost after end of	tx, if patient culture(isolated+) not followed	by 2(After cure, death du	uring FU and one culture (-	-) based on most recent								
DISCONTINUE TREATIVIENT	"Browiewsky slassified as u	r/c unassessable	7 days apart			culture results (or c	contaminated)				End point committ	tee				
Discontinue tx (intervention group) due to need t	then eligible for re-evolution	tion at wk72	Lost after end of	tx, but not for above	three reasons	DEATH THAT IS S	PECIFICALLY NOT RELAT	TED TO TB		1			1		1	
regimen (adding at least one drug)	>1 culture(+) in last month	of ty one of which is at I	Lost after comple	ting tx & can't be tra	ced until the end of FU	(108w Death during FU w/	no evidence of failure or no evidence of failure or	relapse of 18 relapse of TB last culture	(J)			Unassessable		Unassessable		
Non-response to tx, started on new tx	$\geq 2(a)$ during last 2 mos of	ty period (mos 4-6)	or at censure)			Death where paties	nt had a study visit at or a	fter wk48, was not on tx a	and					010000000		
	2 2(+) wks 65-73	a period (mos 4 o)			<u></u>	had no evidence of	ongoing TB activity when	last seen, and where car	use							
	Lack of conversion by end	of intensive phase				of Depth during Filler	no evidence of failure or	relance of TR Jact culture	()			-	+			Unassessable
	Reversion in continuation	phase after conversion to	o negative			& last (+) result foll	lowed by at least 2(-) cult	ures at different visits (at	1	1			1			
	Continuation					leat 7 days apart) a	ind who haven't been clas	ssified as unfavorable.								
						DEATH, MISCELLA	ANEOUS									
						Death from a differ	ent strain					linassessable				

Characteristics of included studies

Total of 21 trials included in review

- 19 registered on ClinicalTrials.gov (and other registries), 1 on ISRCTN, 1 on CTRI (India)
- All trials registered between 2003 and 2020
 - 16 (76%) registered since 2010
- Drug resistance:
 - 9 trials in DR-TB, 12 trials in DS-TB
- Location of study sites:
 - 4 only in African sites, 5 only in Asian sites, 12 in both African and Asian sites
 - 8 trials included European sites, 6 trials included sites in the Americas
- 6 trials included participants younger than 18

Results

- All trials had broadly the same objective:
 - To investigate whether a novel treatment regimen had noninferior or superior efficacy in terms of a long-term durable cure extending through post-treatment follow-up
- All trials classified patient outcomes in two or three groups:
 - 1. Favorable / Successful
 - 2. Unfavorable / Unsuccessful
 - 3. Not Assessable / Unassessable / Excluded from analysis



Favorable Outcomes

- Most consistently defined across protocols of all outcomes
- Variation:
 - Number of cultures:
 - 'Culture negative' (8 trials)
 - Two negative cultures (9 trials)
 - Three negative cultures (2 trials)
 - Spacing
 - Different days ≥28 days apart

- Additional ways a favorable outcome could be achieved:
 - Failure to produce sputum at end of follow-up
 - Failure ever to produce sputum (2 trials) [without clinical symptoms]
 - Contaminated or unevaluable culture at end of follow-up (2 trials)
 - Exogenous reinfection (1 trial)



Unfavorable / Not Assessable

Numbers of protocols/SAPs describing outcome

	OUTCOME TIMING		
OUTCOME TYPE	During/at end of treatment	At end of follow-up	
Unfavorable Outcomes			
Biologically defined			
Never convert to culture positive		1	
Do not have negative status,			
inconsistent qualifications		6	
Persistently positive after specified			
time		1	
Clinical failure at end, regardless of			
culture		5	
Recurrence: Relapse, varying		10	
quanneations		10	
different strain†		2	
Death			
Any cause	4	6	
TB-related	7	12	
Death from extra-pulmonary TB	1		
Not TB-related [†] , with exception of:			
Accident, violence, trauma	7	7	
Suicide†	6	6	

	OUTCOME TIMING			
OUTCOME TYPE	During/at end of treatment	At end of follow- up		
Treatment issues				
Extension, with varying exceptions	10			
Restart, with varying exceptions		8		
Change treatment, with varying exceptions	5			
Change one drug, with varying exceptions	3	3		
Change more than one drug	4	4		
Discontinue treatment, with exceptions†	7			
Incomplete, with varying qualifications	5			
Off-protocol drugs†	3	3		
Not Assessable Outcomes				
Death				
Not due to TB†	4	3		
Suicide†	3			
Accident, violence, trauma†	8			
Death from a different TB strain		1		
Died with last culture negative		5		
Reinfected with a different strain†		10		
Discontinue treatment, with exceptions†		7		
Off-protocol drugs†		1		
Left study with last culture negative†		5		



Conclusions

- Protocols and SAPs sometimes included lack of sufficient detail
 - Precise implementation left up to statistician / programmer implementing SAP at time of final analysis?
- Little consensus in granular detail of endpoint definitions
- Some areas of agreement across protocols indicating some consensus among TB community
 - Multiple negative cultures needed for a Favorable outcome
 - Mortality not always unfavorable
- Findings will inform proposals for Estimand(s) and Endpoint definitions



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 - Johnson Lyimo, MD, MPH
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 - Rada Savic, PhD
 - Payam Nahid, MD, MPH
- Bill & Melinda Gates Foundation for project funding
- Sponsors of trials that generously provided protocols and statistical analysis plans (SAPs).





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BILL& MELINDA GATES foundation

