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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**

Outline

- 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	1
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 adherence or loss to follow-up	0	2
Had negative culture at last assessment but was lost to follow-up before 76 weeks	3	1

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	0	2 (<1)	0
Unable to produce sputum at 18 mo but culture-negative status earlier	49 (10)	31 (6)	35 (
Missing data on L–J culture at 18 mo and MGIT negative	9 (2)	14 (3)	17 (
Unfavorable outcome — no. (%)†			
Patients with outcome	43 (8)	78 (15)	105 (
6-Mo treatment phase			
Nonviolent death	5 (1)	6 (1)	7 (
Treatment failure‡			
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 status	12 (2)	46 (9)	64 (
Retreated for tuberculosis	14 (3)	17 (3)	27 (
Death from tuberculosis or respiratory distress	2 (<1)	0	0
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 + optir 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 OBR (MITT), MGIT

Endpoint – no. (%)	Delamanid + optir 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)

Composite Primary Outcome

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.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

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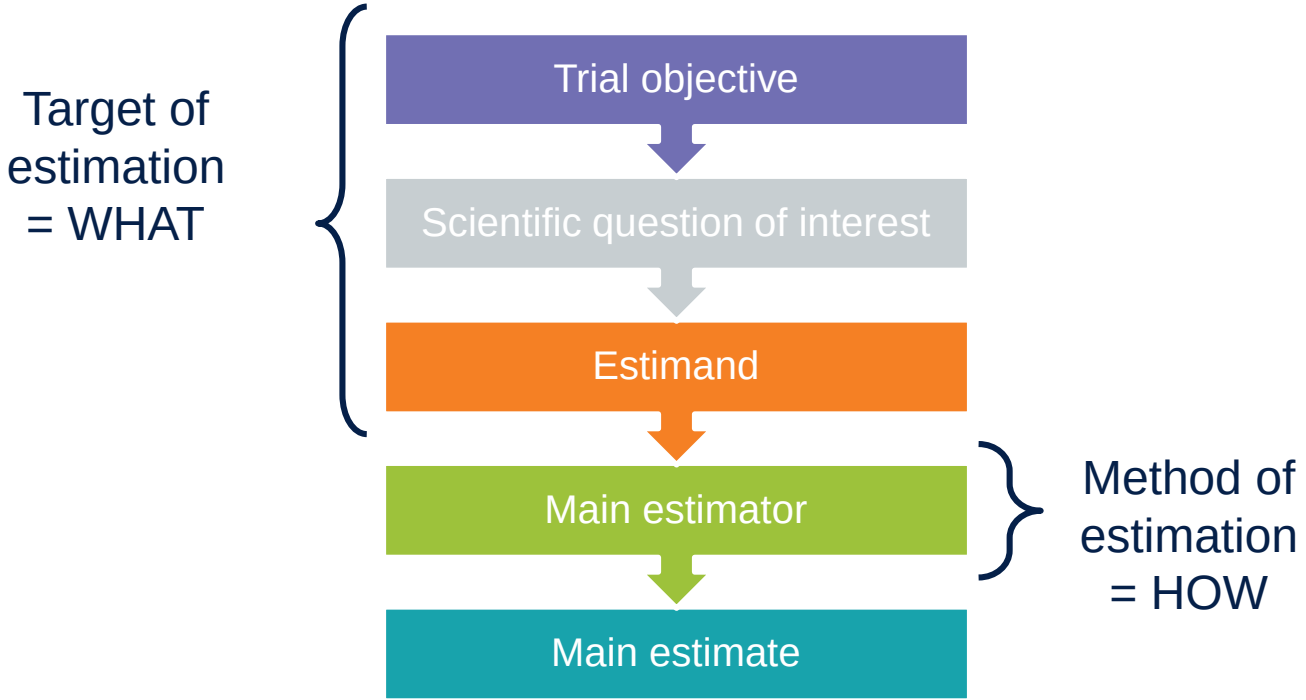
A new framework

ICH E9 (R1) Addendum: Estimand and sensitivity analyses



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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

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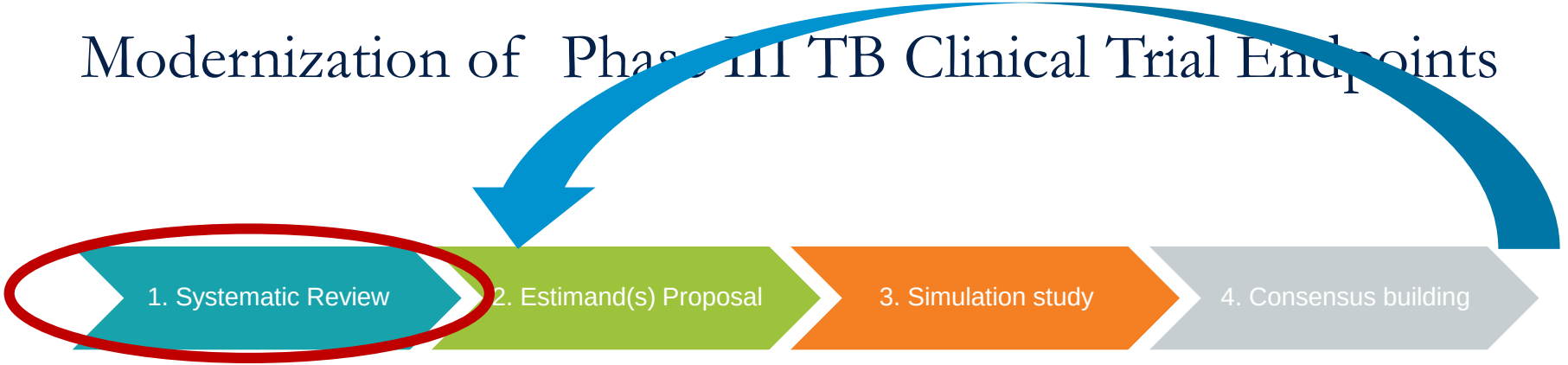
Modernization of Phase III TB Clinical Trial Endpoints

- 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 III TB Clinical Trial Endpoints



- 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

- Present proposals to relevant trialists and stakeholders for discussion, feedback, and consensus

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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)

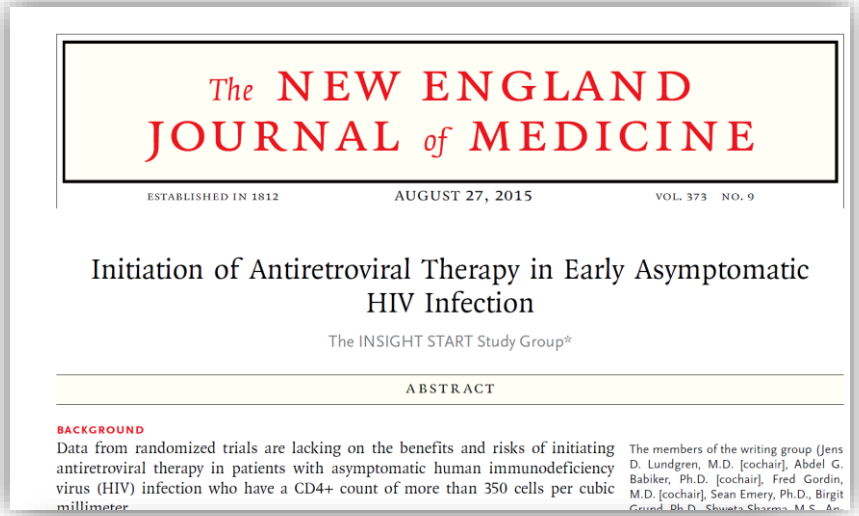
2. Standardization

- 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 herpes simplex virus infection and esophageal

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]



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 27, 2015 VOL. 373 NO. 9

Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

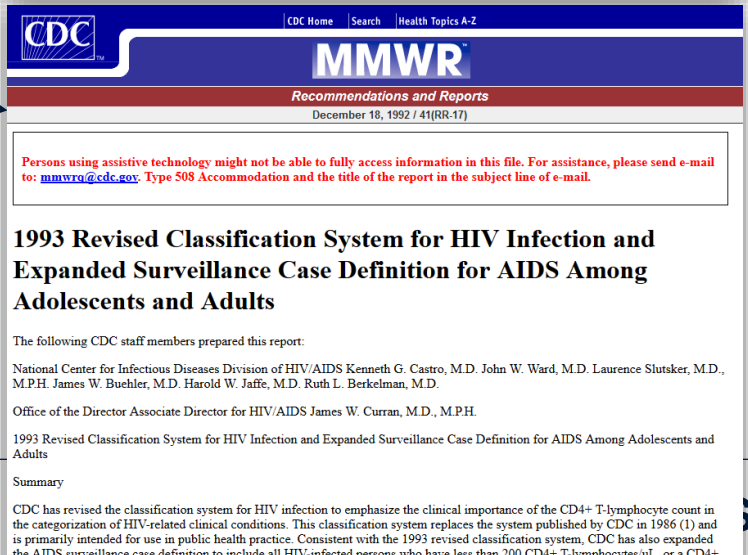
The INSIGHT START Study Group*

ABSTRACT

BACKGROUND

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., Shweta Sharma, M.S., An-



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MMWR

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: mmwrq@cdc.gov. 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 HIV infection to emphasize the clinical importance of the CD4+ T-lymphocyte count in the categorization of HIV-related clinical conditions. This classification system replaces the 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

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

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

PROSPERO 2020 CRD42020197993

- Objectives of systematic review:
  1. 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

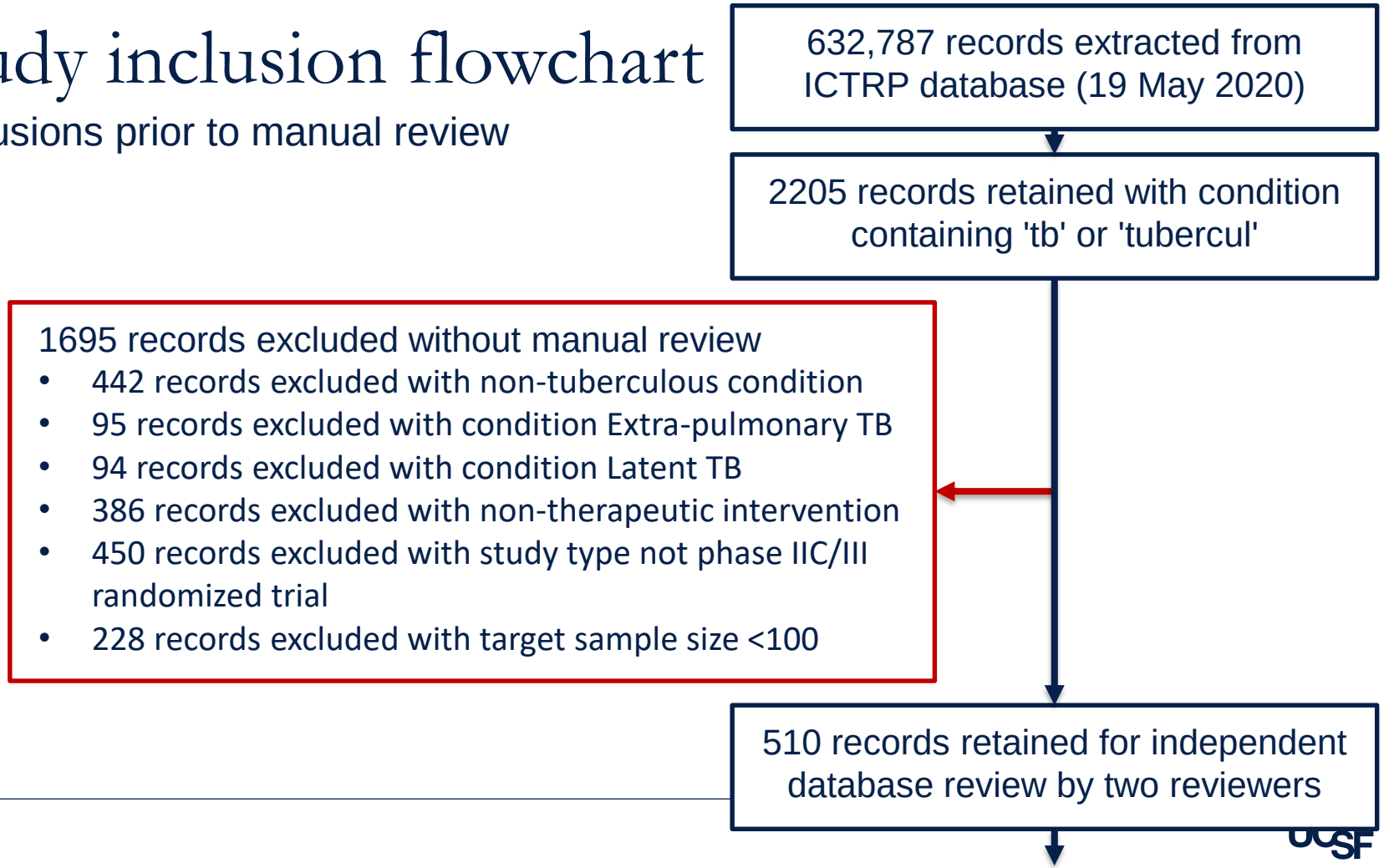
WHO International Clinical Trials Registry Platform (ICTRP)

Data providers for ICTRP

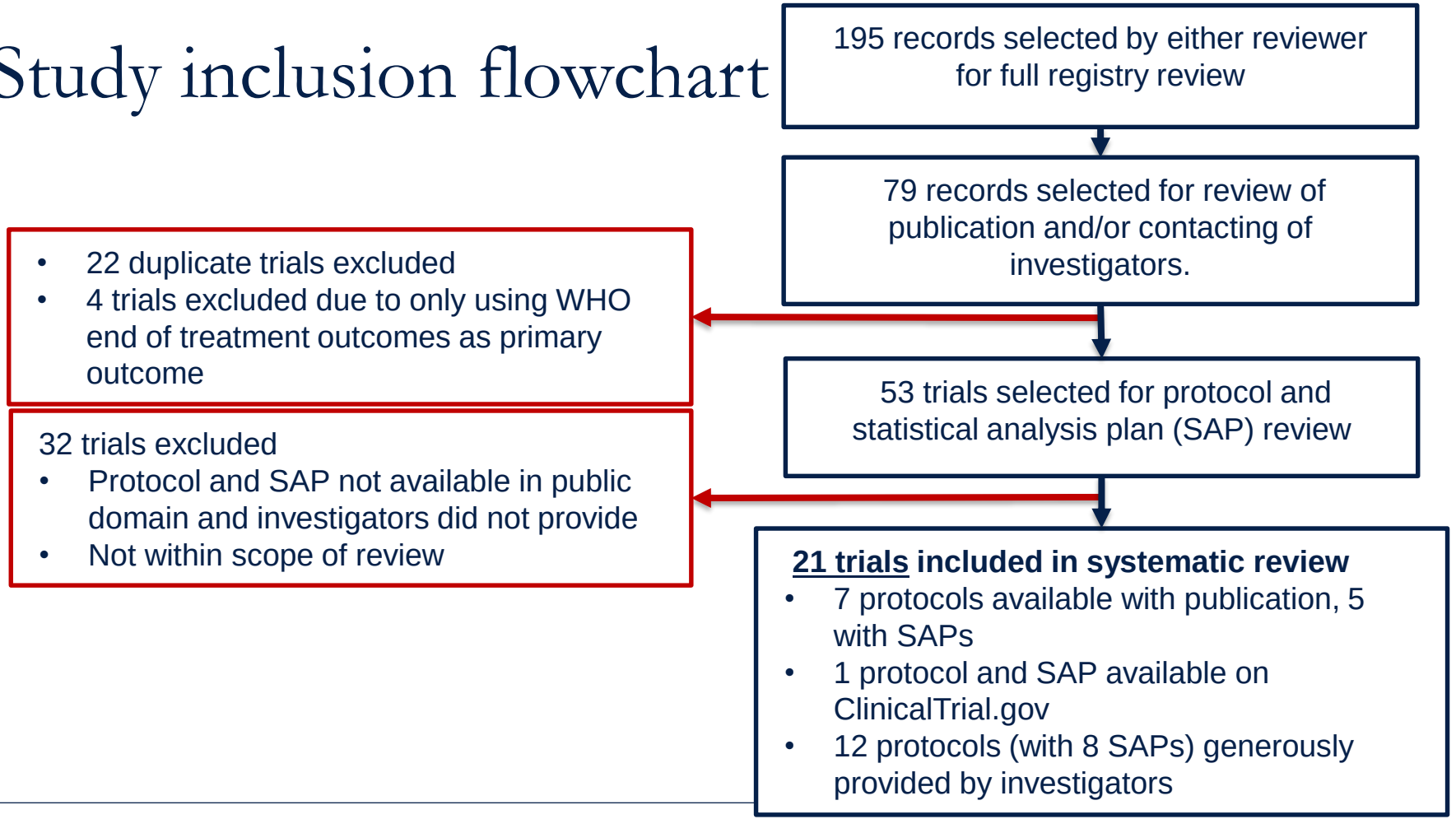
1. Australian New Zealand Clinical Trials Registry (ANZCTR)
2. Brazilian Clinical Trials Registry (ReBec)
3. **Chinese Clinical Trial Register (ChiCTR)**
4. Clinical Research Information Service (CRiS), Republic of Korea
5. **ClinicalTrials.gov**
6. **Clinical Trials Registry - India (CTRI)**
7. Cuban 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)

Study inclusion flowchart

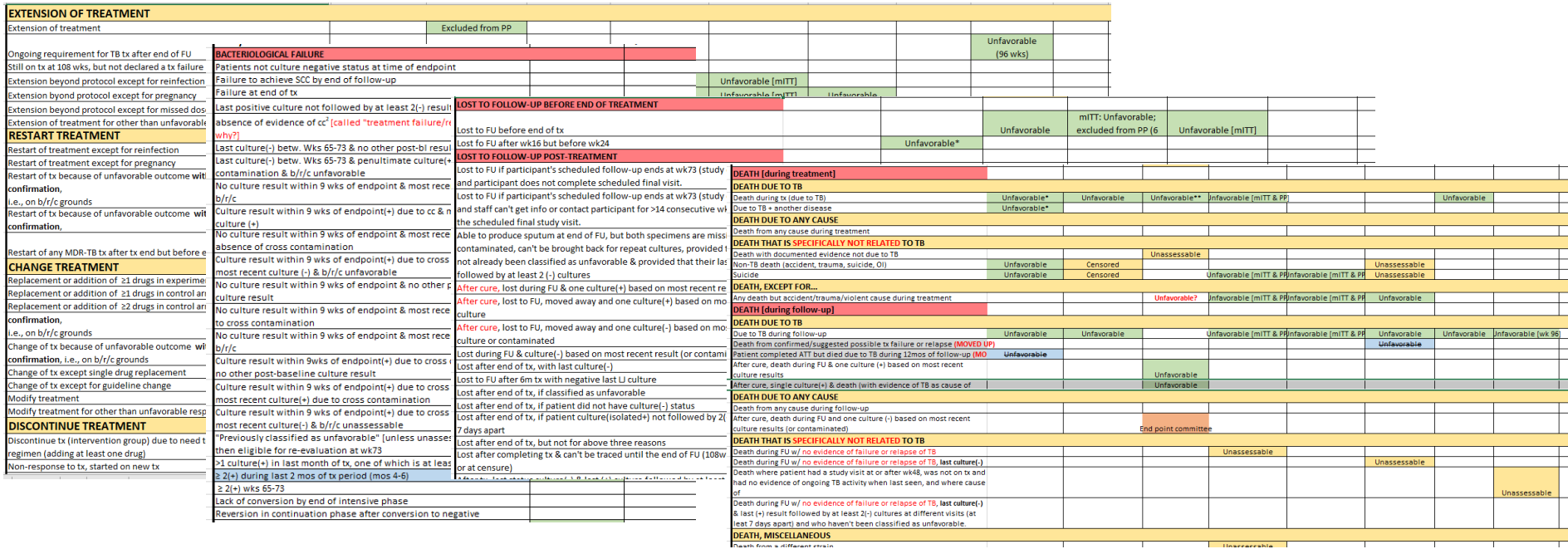
Exclusions prior to manual review



Study inclusion flowchart



Preliminary Results



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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 non-inferior 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 TYPE	OUTCOME TIMING	
	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 qualifications		18
Recurrence: Reinfection with a 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 TYPE	OUTCOME TIMING	
	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

† Considered as unfavorable by some protocols, not assessable by others.

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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

Acknowledgements

- UCSF Center for Tuberculosis:
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  - Nancy Hills, PhD
  - 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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