STREAM STAGE 2

Week 76 results and lessons learned

I.D. Rusen on behalf of the STREAM Trial Collaboration

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No conflicts of Interest to declare

Economic evaluation of shortened, bedaquiline-containing treatment regimens for rifampicin-resistant tuberculosis (STREAM stage 2): a within-trial analysis of a randomised controlled trial

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Summary
Background The STREAM stage 2 trial assessed two bedaquiline-containing regimens for rifampicin-resistant tuberculosis: a 9-month all-oral regimen and a 6-month regimen containing an injectable drug for the first 2 months. We did a within-trial economic evaluation of these regimens.

Evaluation of two short standardised regimens for the treatment of rifampicin-resistant tuberculosis (STREAM stage 2): an open-label, multicentre, randomised, non-inferiority trial

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Summary
Background The STREAM stage 1 trial showed that a 9-month regimen for the treatment of rifampicin-resistant tuberculosis was non-inferior to the 20-month 2011 WHO-recommended regimen. In STREAM stage 2, we aimed to compare two bedaquiline-containing regimens with the 9-month STREAM stage 1 regimen.

Outline

- STREAM background

- Stage 2 efficacy results

- Stage 2 safety results

- STREAM Trial lessons learned

STREAM Background

- STREAM Stage 1 was an open-label trial which began in July 2012 to compare the 'Bangladesh' regimen with the WHO recommended regimen and the non-inferiority results were published in the NEJM in 2019

- While STREAM Stage 1 was still recruiting the trial team was approached about including additional regimens containing the recently conditionally approved drug bedaquiline

- After extensive consultation the trial was modified to include two additional regimens in Stage 2 of the protocol: a fully oral regimen and a shorter/simpler regimen

STREAM Regimens

Long Regimen (20 months)	Control Regimen (9 months)	Oral Regimen (9 months)	Six-Month Regimen
WHO 2011 recommendation	Moxifloxacin	Levofloxacin	Levofloxacin
	Clofazimine	Clofazimine	Clofazimine
	Ethambutol	Ethambutol	-
	Pyrazinamide	Pyrazinamide	Pyrazinamide
	-	Bedaquiline	Bedaquiline
	Kanamycin*	-	Kanamycin**
	Isoniazid*	Isoniazid*	Isoniazid**
	Prothionamide*	Prothionamide*	-

* 16 week intensive phase   ** 8 week intensive phase

Stage 2 Implementation

- Eligible patients (infected with *Mycobacterium Tuberculosis* resistant to rifampicin but sensitive using line probe assays to fluoroquinolones and aminoglycosides) were enrolled from March, 2016 to January 2020 in Ethiopia, Georgia, India, Moldova, Mongolia, South Africa, Uganda

- Participants were followed up weekly to Week 4, 4-weekly until Week 52, 8-weekly until Week 84 and 12-weekly thereafter to Week 132

Major Protocol Amendments

- STREAM Stage 2 faced particular challenges in relation to changing global guidelines that resulted in several protocol amendments

- In 2018 the protocol was amended to drop two regimens:

    - Long regimen which was no longer relevant as countries adopted the standardised 9–12-month regimen following May 2016 Guidelines

    - The shortened Six-month regimen which was considered to be of lesser interest than the fully Oral regimen

- Approval/adoption of amendments varied across countries in terms of timing and ultimately implementation

Trial Population

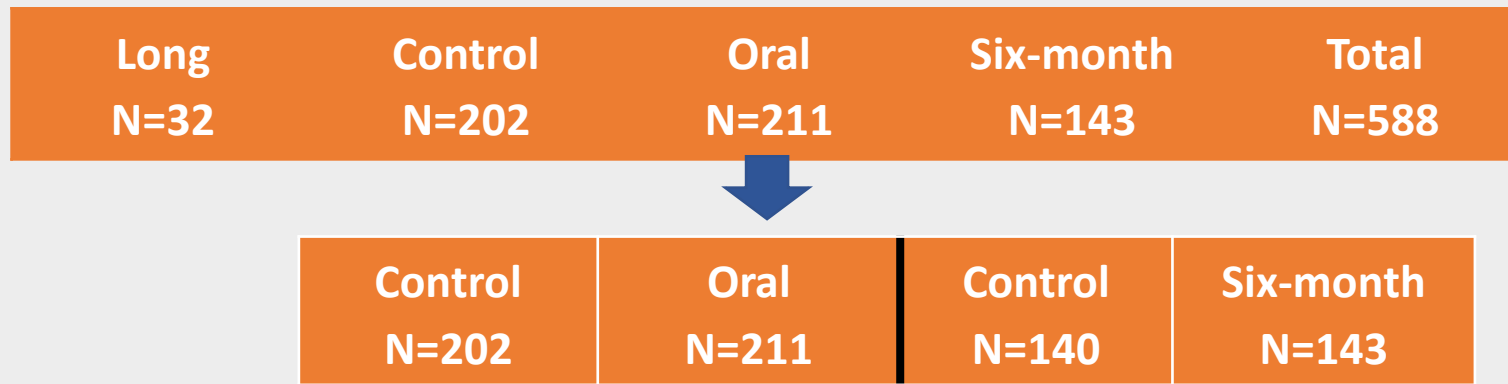| N (% of total randomised)	Control	Oral	Control	Six-month
Total Randomised	202	211	140	143
mITT population	187 (93%)	196 (93%)	127 (91%)	134 (94%)
mITT exclusion reasons				
Rifampicin-susceptible	5 (2%)	7 (3%)	5 (4%)	3 (2%)
XDR-TB	1 (<0.5%)	2 (1%)	0	1 (1%)
No positive culture at central lab	7 (3%)	6 (3%)	7 (5%)	5 (3%)
Randomised in error	2 (1%)	0	1 (1%)	0
PP population	166 (82%)	177 (84%)	110 (79%)	122 (85%)

Retention and self-reported adherence in all arms were good; at 76 weeks 95% of the mITT population were seen or were known to have died

Primary Endpoint

- Participants were assessed 76 weeks after enrolment

- Favourable outcome: last two cultures negative (latest in 76 week window) provided that an unfavourable outcome had not already been obtained

- Unfavourable outcome: a composite measure based on bacteriological or non-bacteriological reasons like change of treatment, loss to follow-up and death from any cause

Analysis

- Comparisons of the Control regimen and the Six-month regimen are restricted to participants that were randomised concurrently.

Long N=32	Control N=202	Oral N=211	Six-month N=143	Total N=588

Control N=202	Oral N=211	Control N=140	Six-month N=143

- All analyses are stratified by randomisation protocol, and primary comparisons also stratified by HIV status.

Favourable/Unfavourable Outcome

	Control	Oral	Control	Six-month
Total in MITT population	187	196	127	134
Total favourable	133 (71.1%)	162 (82.7%)	87 (68.5%)	122 (91.0%)
Total unfavourable	54 (28.9%)	34 (17.3%)	40 (31.5%)	12 (9.0%)
	-11.0% (-19.0%, -2.9%)			

Sensitivity Analysis	Difference (95% CI)	P-value
Adjusted for randomisation protocol and baseline smear, culture, age, HIV status, baseline isoniazid resistance, extent of opacity, and number of cavities	-10.3% (-18.8%, -1.7%)	p=0.019

Favourable/Unfavourable Outcome

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Total unfavourable	54 (28.9%)	34 (17.3%)	40 (31.5%)	12 (9.0%)
		-11.0% (-19.0%, -2.9%)	-22.2% (-31.2%, -13.1%)	

- The Six-month regimen had significantly fewer unfavourable outcomes compared to the concurrently randomised participants on the Oral regimen: a difference of 12.5% (95% CI 4.2%, 20.8%) p=0.002

Bacteriological Reasons for Unfavourable

	Control	Oral	Control	Six-month
Determined on the basis of bacteriological findings	20 (37.0%)	8 (23.5%)	16 (40.0%)	3 (25.0%)
Died within 3 weeks of randomisation (culture positive)	1	2	1	0
Bacteriological reversion during treatment period	11	3	8	1
Restarted treatment for bacteriological recurrence	1	1	1	1
Changed treatment due to persistent positive cultures	5	0	4	1
Changed treatment due to tuberculosis empyema	0	1	0	0
Positive culture at week 76	2	1	2	0

Non-Bacteriological Reasons for Unfavourable

	Control	Oral	Control	Six-month
Determined on the basis of non-bacteriological findings	34 (63.0%)	26 (76.5%)	24 (60.0%)	9 (75.0%)
Died (culture negative)	1	3	0	2
Lost to follow up before 76 weeks (culture negative)	3	6	2	2
Treatment changed after adverse event	20	6	14	3
Started bedaquiline	6	0	5	0
Started kanamycin	0	6	0	0
Started linezolid	13	0	8	1
Started ≥2 drugs	1	0	1	2
Treatment extended for adverse event	4	3	3	1
Treatment extended due to investigator decision	1	1	1	0
Treatment changed for other reasons	2	2	1	1
Early withdrawal (up to week 4)	3	5	3	0

HIV Status

- 14% of trial population co-infected with HIV, the majority from South Africa and Uganda

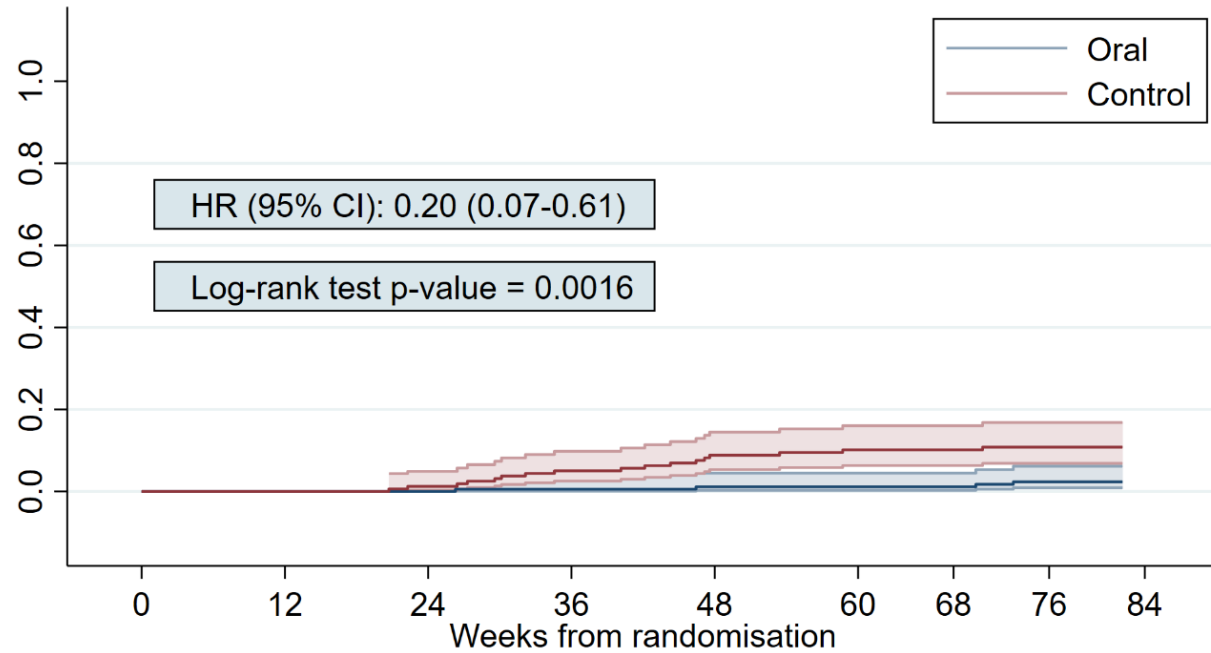|	Control	Oral
HIV infected: No. favourable (%)	9 (36.0%)	26 (86.3%)
HIV uninfected: No. favourable (%)	124 (76.5%)	136 (80.5%)

- Control regimen performed less well in the people living with HIV, but the Oral regimen performed well in both groups
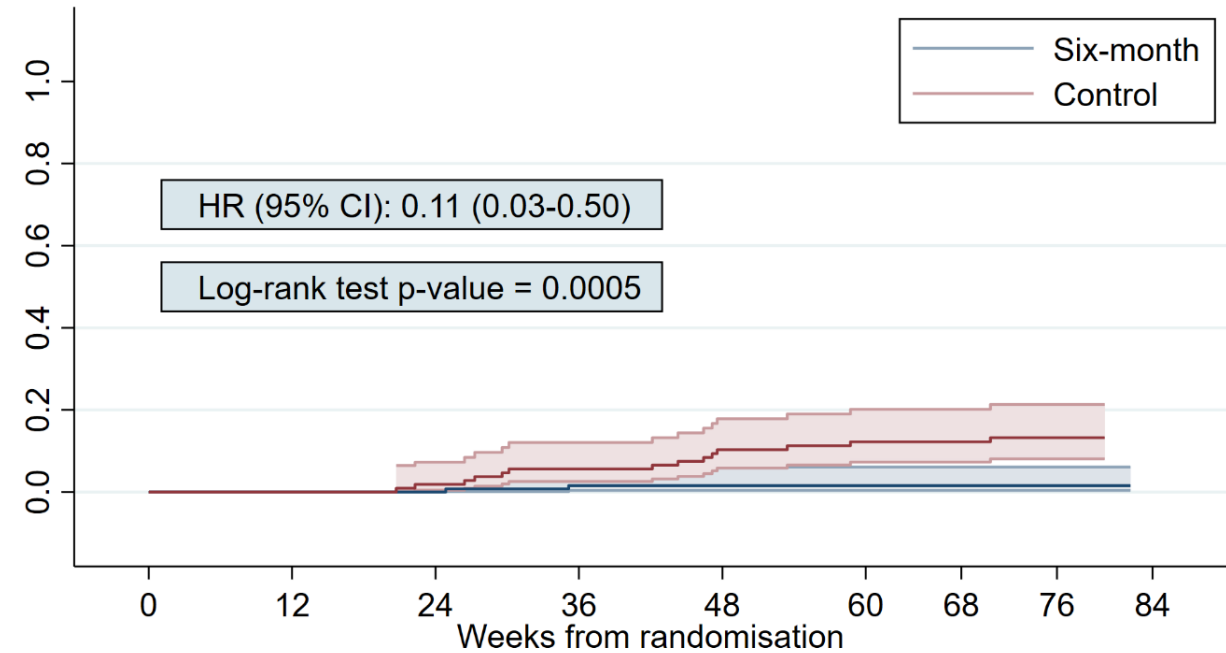
Secondary Endpoint: Failure or Recurrence

- Data up to the time of an unfavourable outcome used to classify individuals according to the likelihood that they were failing or recurring at the time

- 5-point scale: definite, probable, possible, unlikely, highly unlikely

- Independent clinical review of classification

- "Definite" and "probable" FoR events combined for the analysis

- Participants not classified as experiencing a definite or probable FoR event censored at the point they met the primary outcome criteria for unfavourable or week 76

Time to Failure or Recurrence

Acquired Resistance

Drug	Control	Oral	Control	Six-month
Total unfavourable for bacteriological reason	20	8	16	3
DST result unavailable	1	1	1	0
DST results	19	7	15	3
Acquired resistance by drug				
Bedaquiline + clofazimine	0	1	0	0
Clofazimine	1	1	1	0
Fluoroquinolones	1	1	1	3
Fluoroquinolones + clofazimine	0	1	0	0
Kanamycin	2	0	0	0
Pyrazinamide	1	0	1	0
Any resistance	5	4	3	3
% of total in mITT	5 (2.7%) /187	4 (2.0%) /196	3 (2.4%) /127	3 (2.2%) /134

Summary of Main Efficacy Findings

- Stage 2 results showed that the efficacy of both the Oral regimen and the Six-month regimen are not only non-inferior but are superior to the Control regimen.

- Both regimens were significantly less likely to result in treatment failure or recurrence compared to the Control regimen.

- Very low levels of acquired resistance seen in all arms

- In an exploratory analysis, the Six-month regimen had a better efficacy outcome than the Oral regimen

Summary of Safety Events to Week 76

	Control	Oral	Control	Six-month
Total randomised	202	211	140	143
Total in safety analysis population	202	211	140	143
Participants with SAE	35 (17%)	38 (19%)	26 (19%)	27 (19%)
Participants with treatment related SAE	7 (3%)	4 (2%)	6 (4%)	6 (4%)
Participants with any Grade 3-4 AE	108 (53%)	106 (50%)	75 (54%)	79 (55%)
Death	5 (2.5%)	7 (3.3%)	2 (1.4%)	2 (1.4%)

Independent Review of Deaths to Week 76

Death Review Cause of Death	Control (n=202)	Oral (n=211)	Control (n=140)	Six-month (n=143)
Cardiac – Arrhythmic * (Possible sudden cardiac death)	1	1	1	-
Cardiac - Structural (e.g. ischaemic heart disease)	-	1	-	-
HIV-related	1	-	1	-
Tuberculosis	1	3	-	1
Other**	2	2	-	1
Total	**5**	**7**	**2**	**2**

* In neither was there evidence of severe QTcF prolongation
** 2 cancer deaths, 1 pneumonia, 1 hypoglycaemia in a diabetic patient,
1 hypothermia secondary to alcohol intoxication

Selected Hepatic, Cardiac and Hearing Events

System organ class/SMQ	Control (n=202)	Oral (n=211)	Control (n=140)	Six-month (n=143)
QTcF over 500ms	12 (6%)	7 (3%)	8 (6%)	4 (3%)
ALT > 5xULN	19 (9%)	20 (10%)	12 (9%)	12 (8%)
AST > 5xULN	25 (12%)	28 (13%)	13 (9%)	10 (7%)
Grade 3 or 4 Hearing loss in either ear (Brock criteria)	18 (9%)	4 (2%)	11 (8%)	6 (4%)

Summary of Main Safety Findings

- Safety profiles of the regimens were generally very similar

- Small number of deaths with no clear pattern by regimen

- Grade 3 or 4 adverse events common in all regimens

- QT prolongation was the most frequent severe adverse event but QTcF ≥ 500ms observed in only a small proportion; no torsades de pointes

- Severe hearing loss reduced in the Oral regimen

Lessons Learned

- STREAM was the largest MDR-TB trial ever conducted with over 1000 participants recruited over two stages

- Several efforts to capture the challenges, successes and lessons to guide future trials of STREAM's size and complexity

PRACTICAL RECOMMENDATIONS
FROM THE STREAM CLINICAL TRIAL

Implementing Clincial Trials

USAID FROM THE AMERICAN PEOPLE

Vital Strategies
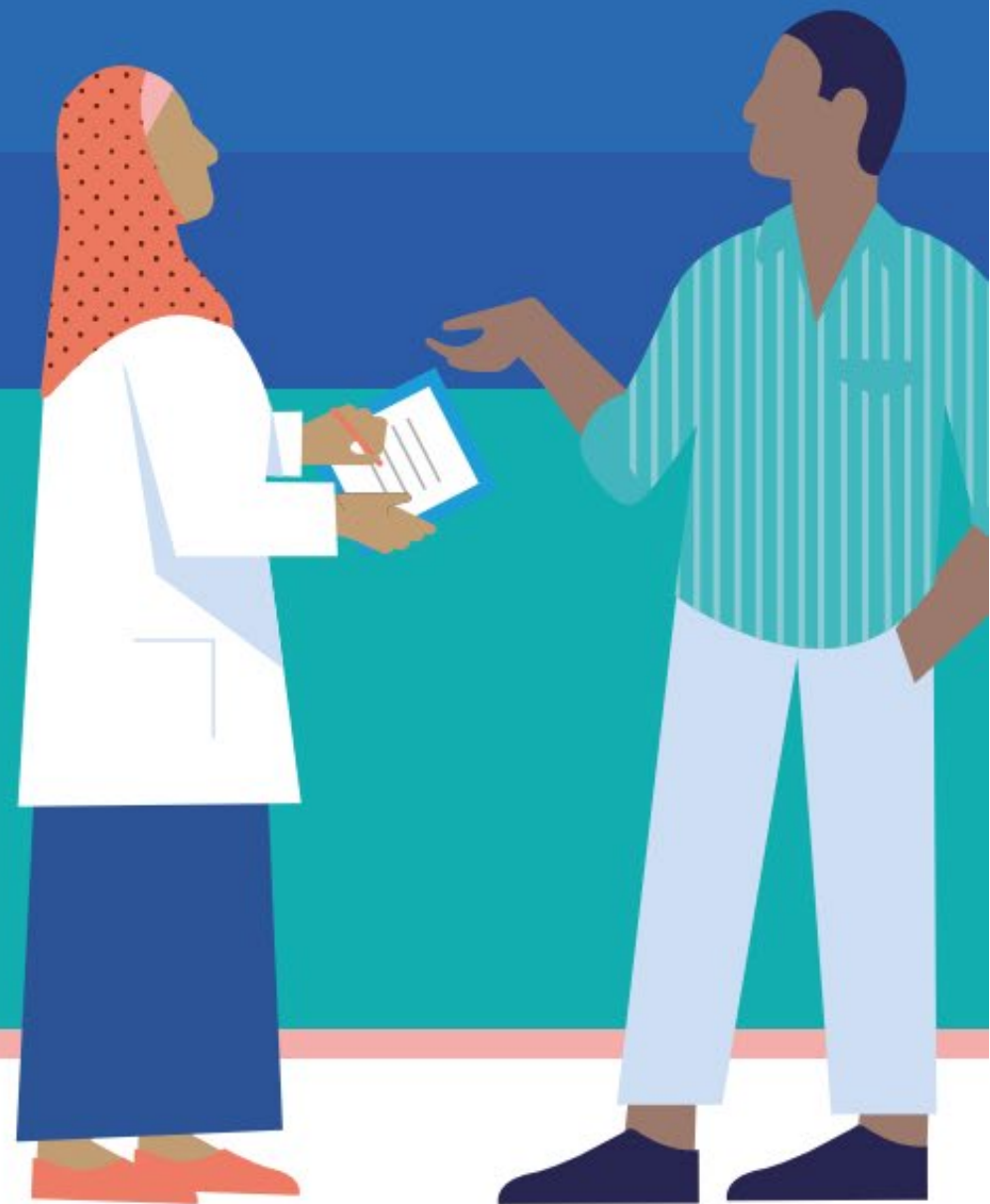
The Union

Trials

Implementation challenges and lessons learned from the STREAM clinical trial—a survey of trial sites

Leena N. Patel[1][*] , Meera Gurumurthy[2], Gay Bronson[1], Karen Sanders[3] and I. D. Rusen[1]

Abstract

Background Design and implementation of multi-country clinical trials for multidrug-resistant tuberculosis (MDR-TB) are complex for several reasons, including trial duration, varying levels of experience and infrastructure across settings, and different regulatory requirements. STREAM was an MDR-TB clinical trial that recruited over 1000 participants. We documented challenges and best practices/lessons learned from the site perspective to improve implementation of future trials.

TOGETHER, WE'RE DISCOVERING BETTER WAYS TO CURE TB

THANK YOU