STREAM Trial Update

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CPTR Meeting

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Washington, DC

Financial Disclosure

The Union receives funding from various sources to implement the STREAM Trial:

- Stage 1 – USAID (TREAT TB Cooperative Agreement)
  - MRC/DFID (MRC/DFID Concordat agreement)
- Stage 2 – USAID (TREAT TB Cooperative Agreement)
  - Janssen Pharmaceuticals

Results of the 9-month regimen in Bangladesh

	Published cohort (206 pts)	*Cohort update (515 pts)*
Cure	82.5%	81.2%
Completion	5.3%	3.3%
Default	5.8%	7.8%
Death	5.3%	5.6%
Failure	0.5%	1.4%
Relapse	0.5%	0.8%
Overall success rate:		Overall success rate:
87.9% (95% CI 82.7, 92.6)		84.5% (95% CI 0.81, 0.88)

Am J Respir Crit Care Med Vol 182. 684–692, 2010

Aung et all, IJTLD 18(10):1180–1187, 2014

A parallel approach to assessing the effectiveness of the Bangladesh regimen

Cohort studies

- Cameroon
- Benin
- Niger
- Swaziland
- Other African countries
- Uzbekistan

Randomised trial

- STREAM

STREAM Stage 1 study design

- STREAM is a randomised controlled trial of **non-inferiority design** currently being conducted in Ethiopia, South Africa, Vietnam and Mongolia
- The control regimen **(A)** is the locally used WHO recommended regimen in the participating countries
- The study regimen **(B)** is closely similar to the regimen used in Bangladesh with the exception that high dose moxifloxacin replaces high dose gatifloxacin

STREAM Study Population

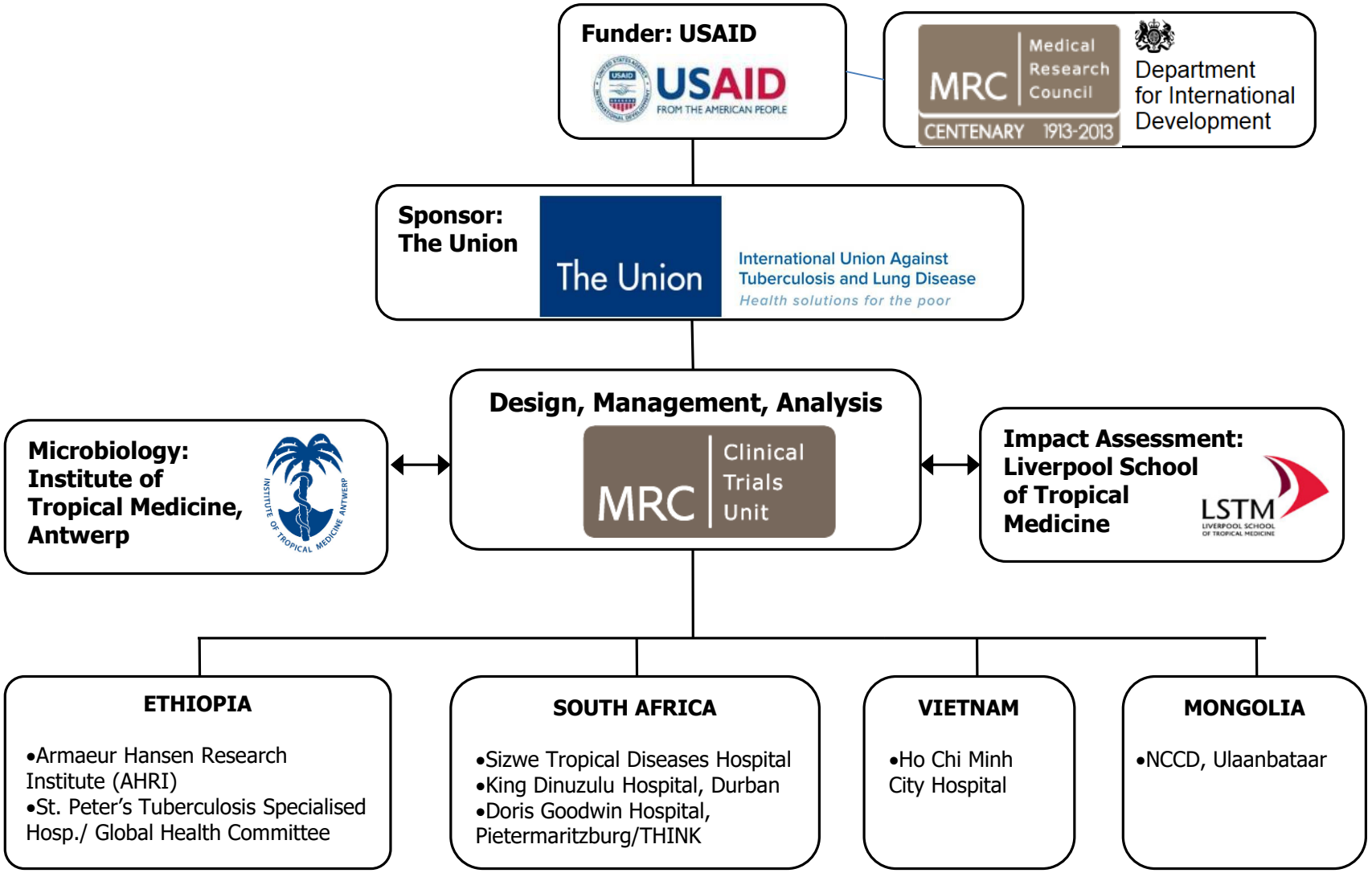
- Adults (18 years or older) who has given consent for treatment and follow-up
- Smear-positive pulmonary tuberculosis, or if HIV positive may be smear negative
- Evidence of initial resistance to rifampicin on line-probe assay, GeneXpert or other DST
- No evidence of initial resistance to fluoroquinolone or 2nd-line injectables on line-probe assay
- No pre-existent QT prolongation >500msec
- If pre-menopausal woman, not pregnant or breast feeding and agrees to use effective barrier contraception/IUCD during treatment

Stage 1: current status

- Enrolment to Stage 1 commenced: July 2012
- Sites: Ethiopia (2), South Africa (3), Vietnam and Mongolia
- 424 of initial target of 400 patients enrolled
- Intake closed: June 30th 2015
- Retention rates are high to date

- Primary endpoint at 30 months
- Last patient visit: Q4 2017
- Results from Stage 1 expected: Q1/2 2018

STREAM Stage 1 Partners



STREAM Stage 2

- In 2013 following the provisional licensing of bedaquiline The Union was asked to consider:
  - is it possible to include additional regimens to the STREAM trial in its present form?
  - if so, what would be the appropriate regimen(s) to evaluate?
- After extensive discussions between the study partners and other experts it was agreed that the primary interest to patients and programmes would be:
  - A fully oral regimen and/or
  - A shorter/simpler regimen

STREAM Stage 2 regimens

In STREAM Stage 2 patients will be randomised to one of four regimens:

A: the locally used WHO approved MDR-TB regimen

B: the modified 9-month Bangladesh regimen studied in Stage 1

C: a fully oral 9-month regimen

D: a six-month regimen

Both regimens C and D contain bedaquiline throughout

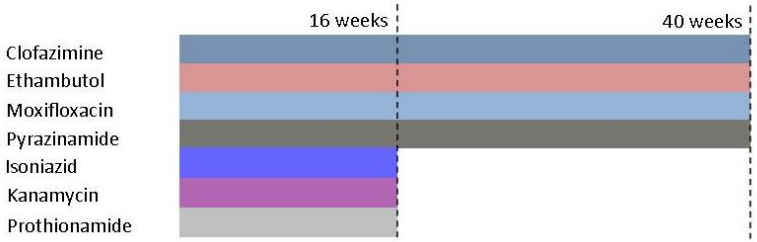
Regimens for Stage 2

Regimen A

Locally used WHO-approved MDR-TB regimen

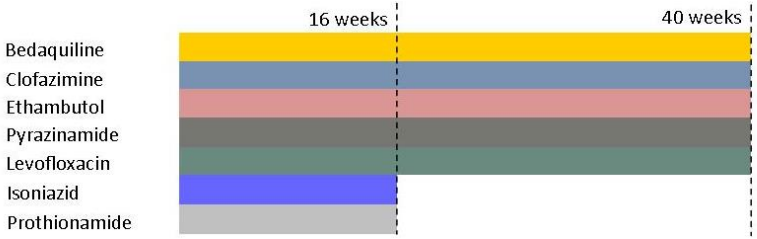
Regimen B

(Stage 1 study regimen)



Regimen C

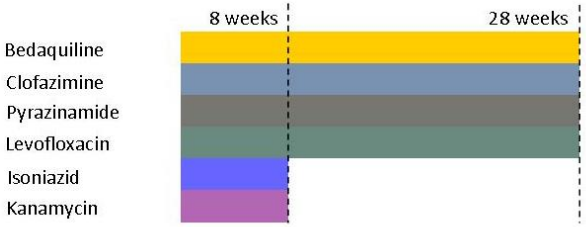
(modified Stage 1 study regimen, all oral)



- **Bedaquiline added**
- **Moxifloxacin replaced by levofloxacin**
- **Kanamycin dropped**

Regimen D

(modified Stage 1 study regimen, shortened)



- **Bedaquiline added**
- **Moxifloxacin replaced by levofloxacin**
- **Prothionamide dropped**
- **Ethambutol dropped**

STREAM Stage 2

Primary objectives:

- To assess whether the proportion of patients with a favourable efficacy outcome on Regimen C, **the fully oral regimen**, is as effective as Regimen B at 76 weeks (18 months)
- To assess whether the proportion of patients with a favourable efficacy outcome on Regimen D, **the 6-month regimen**, is as effective as Regimen B at 76 weeks (18 months)

Parallel regulatory objective:

- To assess whether the proportion of patients with a favourable efficacy outcome on Regimen C, **the fully oral regimen**, is superior to Regimen B at 76 weeks (18 months)

STREAM Stage 2 planned timeline

- FPI took place in March, 2016
- Plan to complete enrolment to Stage 2 in 24 to 30 months
- Last patient enrolled Q3 of 2018
- Last patient reaches 18 months post-randomisation Q1 of 2020
- Last patient completes long term follow-up Q1 of 2021

Additional STREAM Stage 2 Activities

- As in STREAM Stage 1, a health economics component evaluating patient and health system costs will take place at some Stage 2 sites

- A strengthened community engagement component will be supported in Stage 2 building upon initial Stage 1 efforts

Thank you for your attention

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On behalf of the STREAM Trial Management Group