

# Examining the efficacy of the short MDR-TB regimen: alternative analyses from the STREAM trial

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# STREAM Randomized Controlled Trial (Nunn *et al.*, NEJM, 2019)

- Main (efficacy) finding:
  - The **Short 9-11 month injectable-containing regimen** was non-inferior to the **Long 20+ month WHO regimen** with respect to the primary efficacy outcome.
- HIV-adjusted difference between regimens
  - Modified ITT: 1.0% (95% CI -7.5%, **9.5%**)
  - Per protocol: -0.7% (95% CI -10.5%, **9.1%**)
- “There were, however, **some differences in the components of the composite outcome that merited further investigation...**
  - ...**bacteriologic unfavourable outcomes** were more common in the **Short regimen**,
  - ...whereas ...**loss to follow-up** was more common in the **Long regimen.**”

## Alternative efficacy outcomes by study arm

WHO end of treatment outcomes for RR-TB

A.



WHO outcomes for RR-TB with relapse added

B.



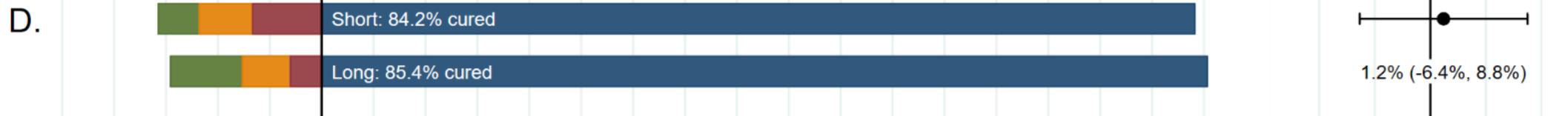
TB-NET MDR-TB outcomes (Lange, NEJM, 2016)

C.



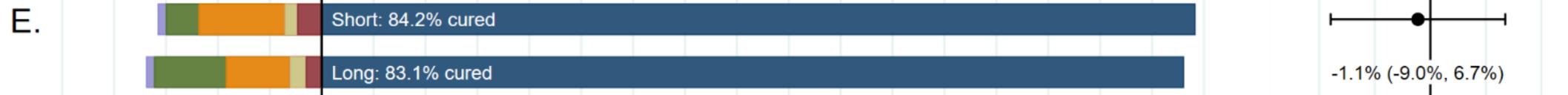
Modified MDR-TB outcomes for short regimens (Schwoebel, IJTLD, 2019)

D.



End of follow-up outcomes, ignoring treatment changes

E.



## Risk difference

Favors Long regimen →

25% 15% 5% 5% 15% 25% 35% 45% 55% 65% 75% 85% -10% -5% 0% 5% 10%

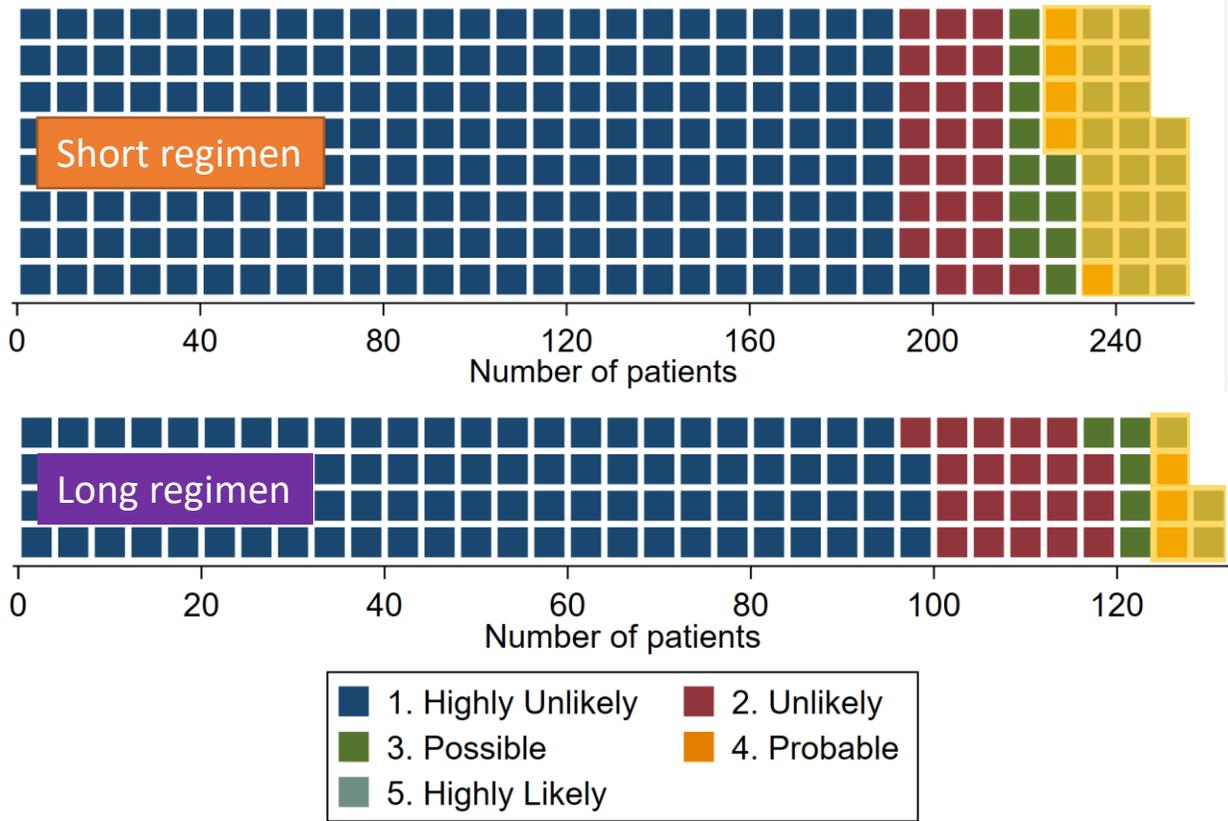


Approach 1.

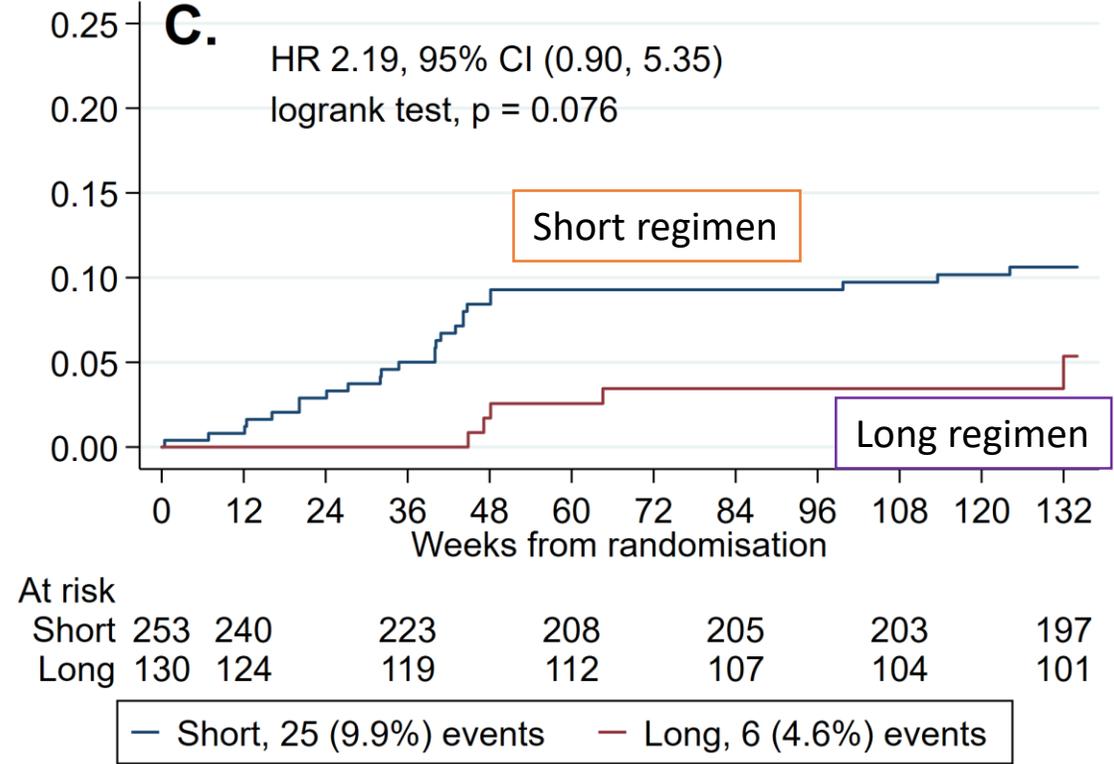
# Time to a Failure or Relapse (FoR) event

Re-classification of all 'unfavourable' and 'not assessable' events:  
 What was the likelihood that it was a pre-cursor of a FoR event?

Each box represents the outcome for a single study participant



Consider Highly Likely and Probable as events;  
Possible, Unlikely, Highly Unlikely censored.



# Sensitivity analyses to account for non-independent censoring

## 1. Inverse probability of censoring weighting (IPCW)

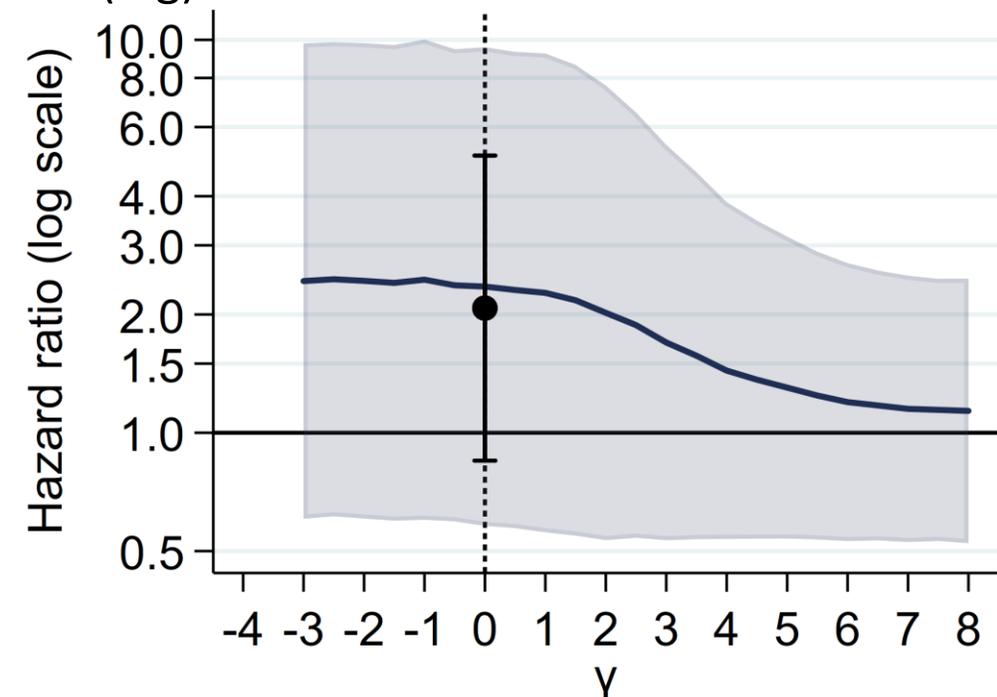
- Up-weighting of comparable non-censored patients in the analysis
- **Probability of censoring model** includes:
  - Baseline factors:
  - Cumulative number of grade 3-5 AEs experienced

Unadjusted, assuming independent censoring	2.19 (0.90, 5.35)
Adjusted, assuming independent censoring	2.08 (0.85, 5.07)
Adjusted, using IPCW for non-independent censoring	2.08 (0.83, 5.20)

Hazard ratio  
(95% CI)

## 2. Multiple imputation with imposed departures from independent censoring

- **Imputation model** includes:
  - Baseline factors,
  - Likelihood of Failure or Relapse (FoR),
  - and user-specified (log) ratio of hazard of FoR event between censored and non-censored individuals ( $\gamma$ )



# Conclusions

1. Alternative efficacy outcomes are for programmatic reporting and are not well suited to clinical trials,
  - But nonetheless gave between-regimen results that were consistent with the primary analysis of the composite outcome.
2. From post hoc analyses, the hazard of failure or relapse is likely to be higher in the Short 9-11 month regimen than in the Long regimen,
  - Results depend how *Possible* and *Unlikely* events are considered in the analysis.
3. We believe ***time to failure or relapse event*** is an improvement on a composite outcome and should be considered as a primary outcome for future treatment trials in DS- and DR-TB.

# Acknowledgements

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