Assessing the efficacy of tuberculosis regimens in the presence of treatment non-adherence

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Background

What is treatment non-adherence?

- When participants do not receive their allocated regimen as planned (missed doses)
- Common in trials ⇨ potential to bias estimates of efficacy

How can treatment non-adherence be handled?

- In NI trials, intention-to-treat (ITT) and per-protocol (PP) analyses advocated
- If treatment non-adherence occurs ⇨ possible for these analyses to be biased in same direction

More sophisticated statistical methods are available[1], but it is unclear how well they perform in NI trials comparing two active drugs

[1] Dodd M, Fielding K, Carpenter JR, Thompson JA, Elbourne D. Statistical methods for non-adherence in non-inferiority trials: useful and used? A systematic review. *BMJ Open*. 2022;12(1):e052656

Study design

- Simulation study based on REMoxTB trial for drug-sensitive TB[1]

Randomisation	6-month control regimen (CON) 4-month experimental regimen (EXP)
Primary outcome	Composite unfavourable outcome within 18 months (treatment failure or recurrence)
Effect measure	Risk difference
Non-inferiority margin	6%
Sample size	1,280 participants required (assuming 15% event rate, 85% power, 2.5% one-sided type I error)
Number of simulated datasets	2,000

[1] Gillespie SH, Crook AM, McHugh TD, et al. Four-Month Moxifloxacin-Based Regimens for Drug-Sensitive Tuberculosis. New England Journal of Medicine. 2014;371(17):1577-1587

Data generation

The following variables were simulated based on the REMoxTB dataset:

1) Age, smoking status, and HIV status

2) Random allocation 1:1 to CON or EXP

3) The overall percentage of doses received (adherence)

4) Unfavourable outcomes simulated so that those who were older (≥30 years), ever smokers, HIV positive, and received <100% of doses had a higher risk

Statistical methods

1) ITT analysis

2) PP analysis
   - Excluding non-adherent participants.
   - Three different definitions applied based on less than 100%, 90% and 80% of doses being received (denoted PP100, PP90 and PP80)

3) Adjusted ITT analysis
   - Observed levels of treatment adherence included as a covariate

4) Multiple imputation (MI) of outcomes
   - Imputing the outcomes of non-adherent participants as if they had been fully adherent

5) Inverse-probability-of-treatment weighting (IPTW)
   - Upweighting the outcomes of fully adherent participants to create a pseudo-population where all participants receive 100% of doses

6) Doubly-robust (DR) estimator
   - Combining properties of the MI and IPTW methods

Results

TE = 6%	Adherence = similar in CON/EXP	Confounding = No	Interaction = No

Analysis method	Mean risk CON (%)	Mean risk EXP (%)	Mean RD (%)	Mean bias (95% CI)	Type I error % (95% CI)
ITT	14.01	19.97	5.96	-0.04 (-0.13 to 0.05)	2.6 (1.9 to 3.3)
PP100	7.28	13.25	5.97	-0.03 (-0.12 to 0.05)	3.0 (2.3 to 3.8)
PP90	8.78	14.74	5.96	-0.04 (-0.13 to 0.04)	3.3 (2.5 to 4.1)
PP80	8.83	14.78	5.95	-0.05 (-0.13 to 0.03)	3.3 (2.6 to 4.1)
Adjusted ITT	14.01	19.97	5.96	-0.04 (-0.12 to 0.04)	3.2 (2.4 to 4.0)
MI of outcomes	7.66	13.64	5.98	-0.02 (-0.11 to 0.07)	3.1 (2.3 to 3.9)
IPTW	7.67	13.60	5.93	-0.07 (-0.16 to 0.02)	3.0 (2.3 to 3.7)
DR estimator	7.67	13.60	5.93	-0.07 (-0.16 to 0.02)	3.0 (2.3 to 3.7)

- Because quantities/mechanisms of non-adherence are same in two arms, all methods are unbiased and type I errors close to 2.5%

Results

TE = 6%	Adherence = better in EXP than Con	Confounding = No	Interaction = No

Analysis method	Mean risk CON (%)	Mean risk EXP (%)	Mean RD (%)	Mean bias (95% CI)	Type I error % (95% CI)
ITT	13.99	19.05	5.06	-0.94 (-1.04 to -0.84)	6.5 (5.4 to 7.6)
PP100	7.24	13.49	6.24	0.24 (0.16 to 0.33)	1.6 (1.1 to 2.2)
PP90	8.76	13.90	5.14	-0.86 (-0.95 to -0.77)	7.8 (6.6 to 9.0)
PP80	8.81	13.94	5.13	-0.87 (-0.96 to -0.78)	7.7 (6.5 to 8.9)
Adjusted ITT	13.48	19.81	6.33	0.33 (0.24 to 0.41)	1.6 (1.1 to 2.1)
MI of outcomes	7.63	13.74	6.11	0.11 (0.02 to 0.19)	2.0 (1.4 to 2.7)
IPTW	7.64	13.64	6.00	0.00 (-0.08 to 0.08)	2.5 (1.8 to 3.2)
DR estimator	7.64	13.64	6.00	0.00 (-0.08 to 0.08)	2.5 (1.8 to 3.2)

- ITT, PP90 and PP80 are biased in same direction by similar amounts; type I error rates inflated three-fold
- MI, IPTW and DR approaches are (approximately) unbiased; type I error rates close to 2.5%

Conclusions

- ITT and PP analyses can produce biased estimates of efficacy that can occur in the same direction, which could lead to the acceptance of inferior treatments or effective regimens being missed

- MI, IPTW and DR methods were able to correct bias under most non-adherence scenarios, but may perform less well in the presence of unobserved confounding (data not shown)

- Future NI trials should utilise more sophisticated statistical methods for handling treatment non-adherence in the primary analysis