

TAILoR: Lessons from a multi-arm multi-stage clinical trial

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Hubs for Trials
Methodology Research

North West Hub



Medical and Pharmaceutical
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The TAILoR study

TAILoR: Telmisartan And Insulin Resistance in HIV.

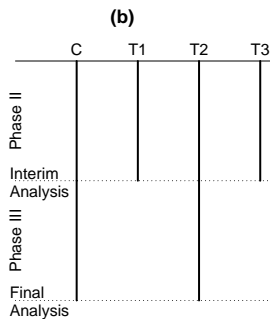
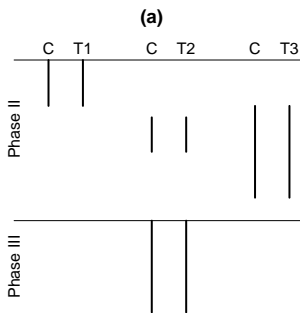
Ambition: Reduce insulin resistance in HIV patients receiving antiretroviral therapy.

Treatment: Different doses of a licensed drug (in a different therapeutic area). Inappropriate to assume a monotone dose-response relationship.

Endpoint: Change in insulin resistance as measured using HOMA-IR index (baseline - week 12).

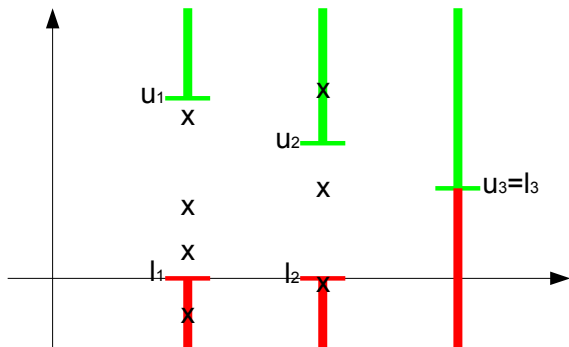
Multi-arm multi-stage trials

- Compare several active treatments against common control
- Select one of more treatment at interim



At interim analysis j

- if $Z_{k,j} < l_j$: treatment k is dropped from trial.
- if $Z_{k,j} > u_j$: can reject H_k and stop trial.





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- 2 interim analysis with O'Brien and Fleming type boundaries
- Method developed for this purpose - see Magirr et al. (2012)

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Lesson: Do not be afraid to propose an adaptive design to a funding agency

Interim analysis

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Lesson: Make sure TMG understands decision process and buys into the stopping rules.

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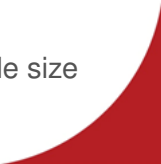
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Lesson: An adaptive design does not always reduce sample size but here improved decision making.



A buddy system

- First multi-arm multi-stage design done by this CTU
- Worked closely with CTU statistician and provided oversight
 - e.g. CTU statistician drafted stat section for application, protocol, SAP... I commented/refined.
 - Strongly involved in communications around interim analysis
- In the meantime CTU has submitted at least 3 more multi-arm proposals for funding with limited involvement from us.

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Lesson: Buddy system can be very effective in training staff in novel methods.

Magirr D, Jaki T, Whitehead J. (2012) A generalized Dunnett test for multi-arm multi-stage clinical studies with treatment selection. *Biometrika*. 99(2):494-501.

Pushpakom S, Taylor C, Kolamunnage-Dona R, Spowart C, Vora J, Garca-Fiana M, Kemp G, Whitehead J, Jaki T, Khoo S, Williamson P, Pirmohamed M (accepted) Telmisartan and Insulin Resistance in HIV(TAILoR): Protocol for a dose-ranging phase II randomised open-labelled trial of Telmisartan as a strategy for the reduction of insulin resistance in HIV-positive individuals on combination antiretroviral therapy. *BMJ open*. 5(10), e009566.