MRC Clinical Trials Unit

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A practical trial design for optimising treatment duration

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Acknowledgements

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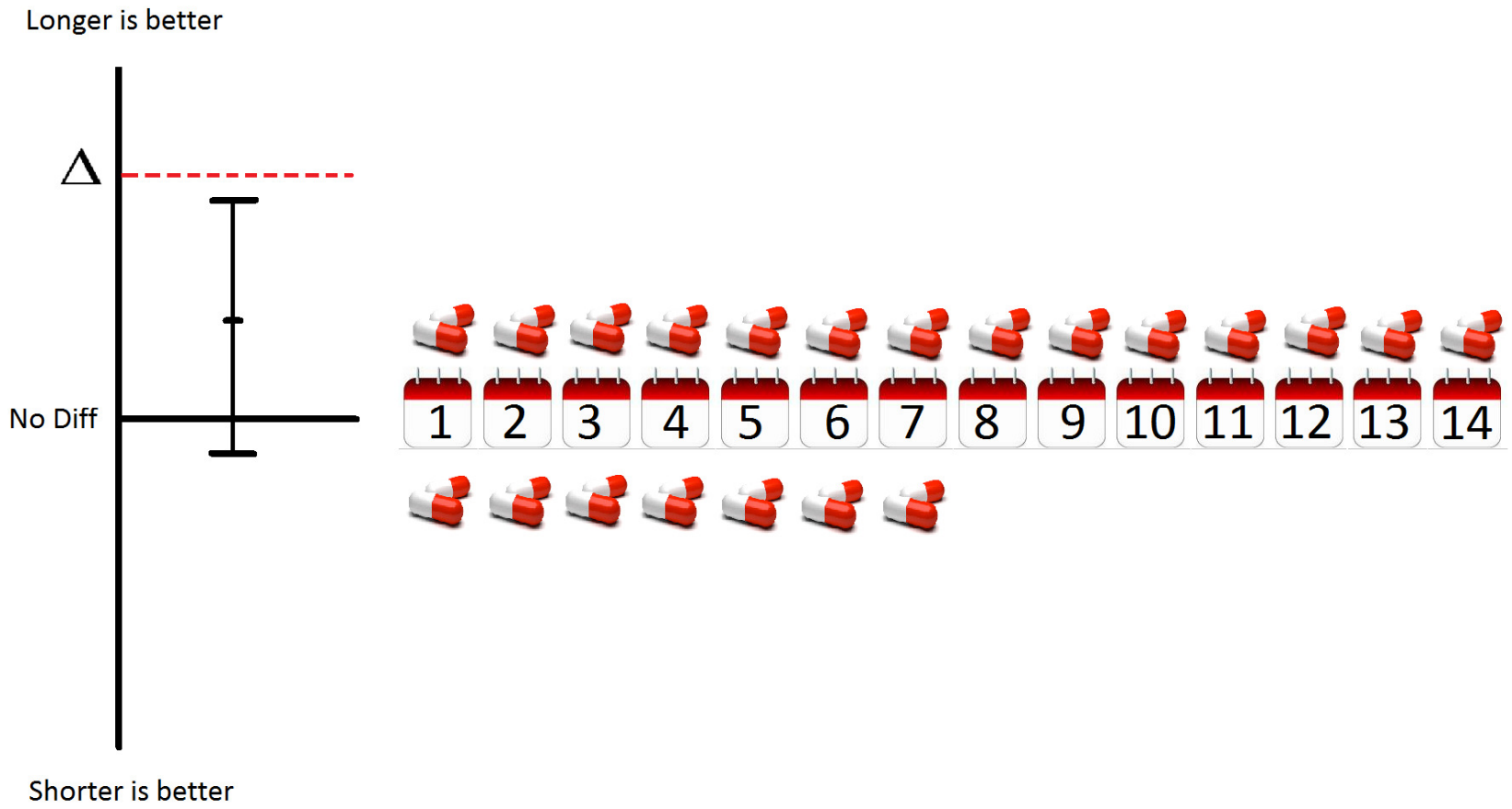
- MRC Clinical Trials Unit at UCL

Treatment duration: what evidence?

- There is little (if any!) evidence in favour of currently recommended treatment durations for many drugs;
  - Focus is often mainly on dose-finding.
- Minimizing treatment duration important in different therapeutic areas:
  - Antibiotics (AMR);
  - TB (promote adherence);
  - Hep C (costs).
- How to design a trial to 'optimise' treatment duration?
  - Non-inferiority? Superiority?
  - 2-arm? Multi-arm?

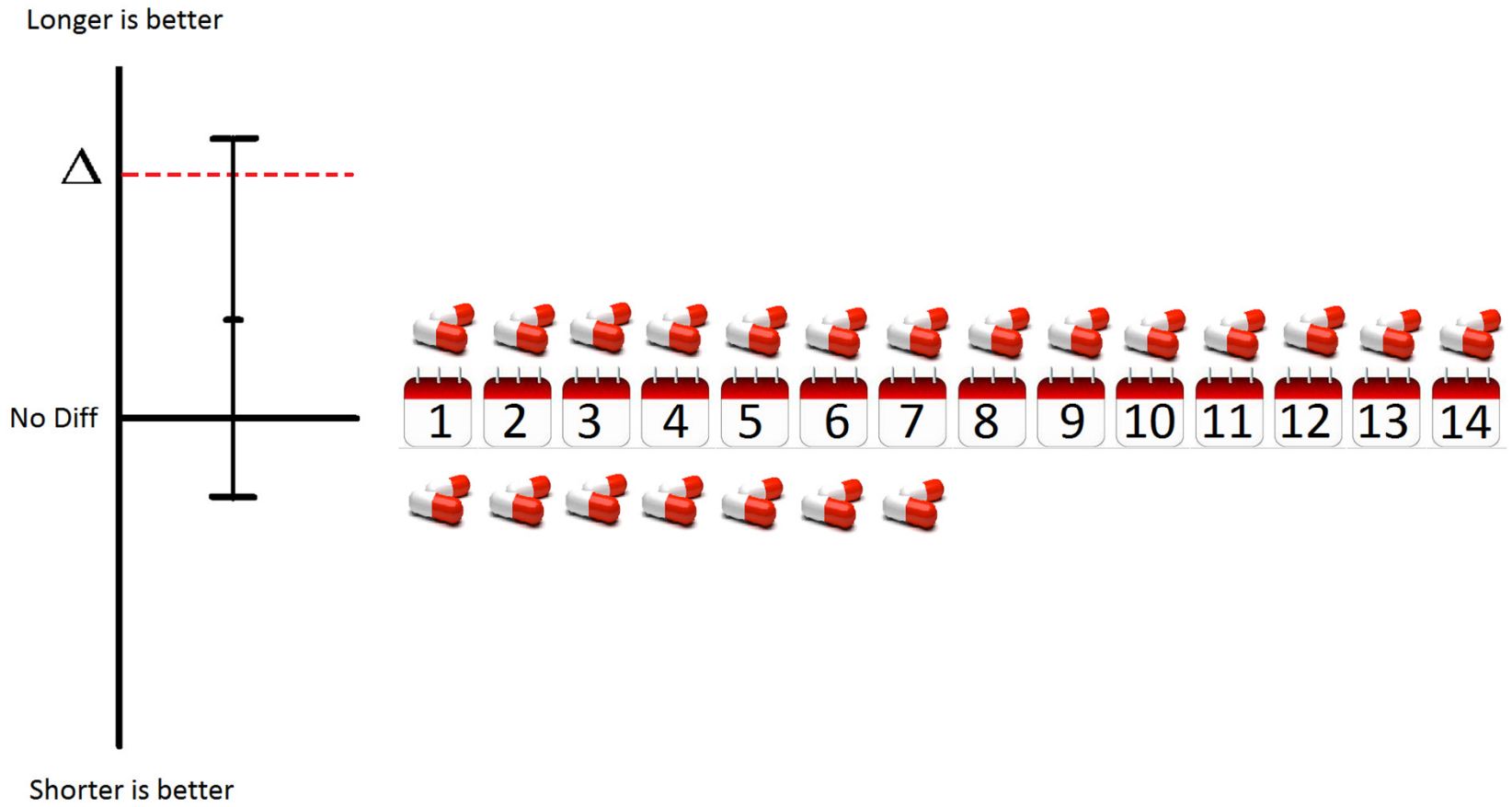
Standard design: two-arm non-inferiority

- 7-day non-inferior to 14-day



Standard design: two-arm non-inferiority

- Inconclusive trial



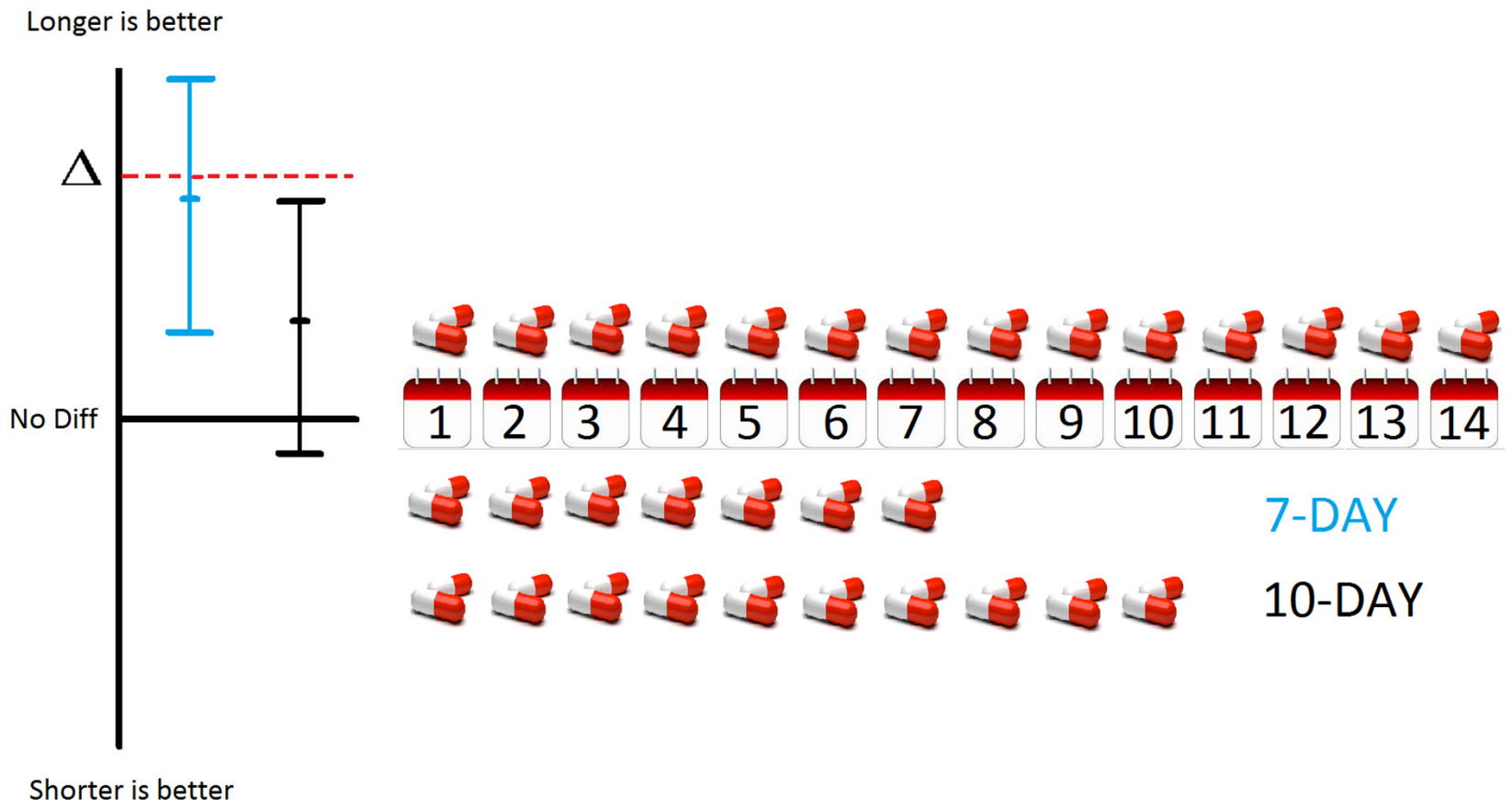
Standard design: two-arm non-inferiority

Issues:

- Arbitrariness of non-inferiority margin;
- Choice of research arms to test against control;
- Very large sample size required (since we expect increasing cure rate with increasing duration).
- Risk of bio-creep phenomenon;
- Often design not resilient: if a single expected parameter is wrong, lose power/interpretability
- Non-adherence: ITT anti-conservative, PP selection bias.

Multi-arm non-inferiority

- Only 10-day proven non-inferior to 14-day;



Multi-arm non-inferiority

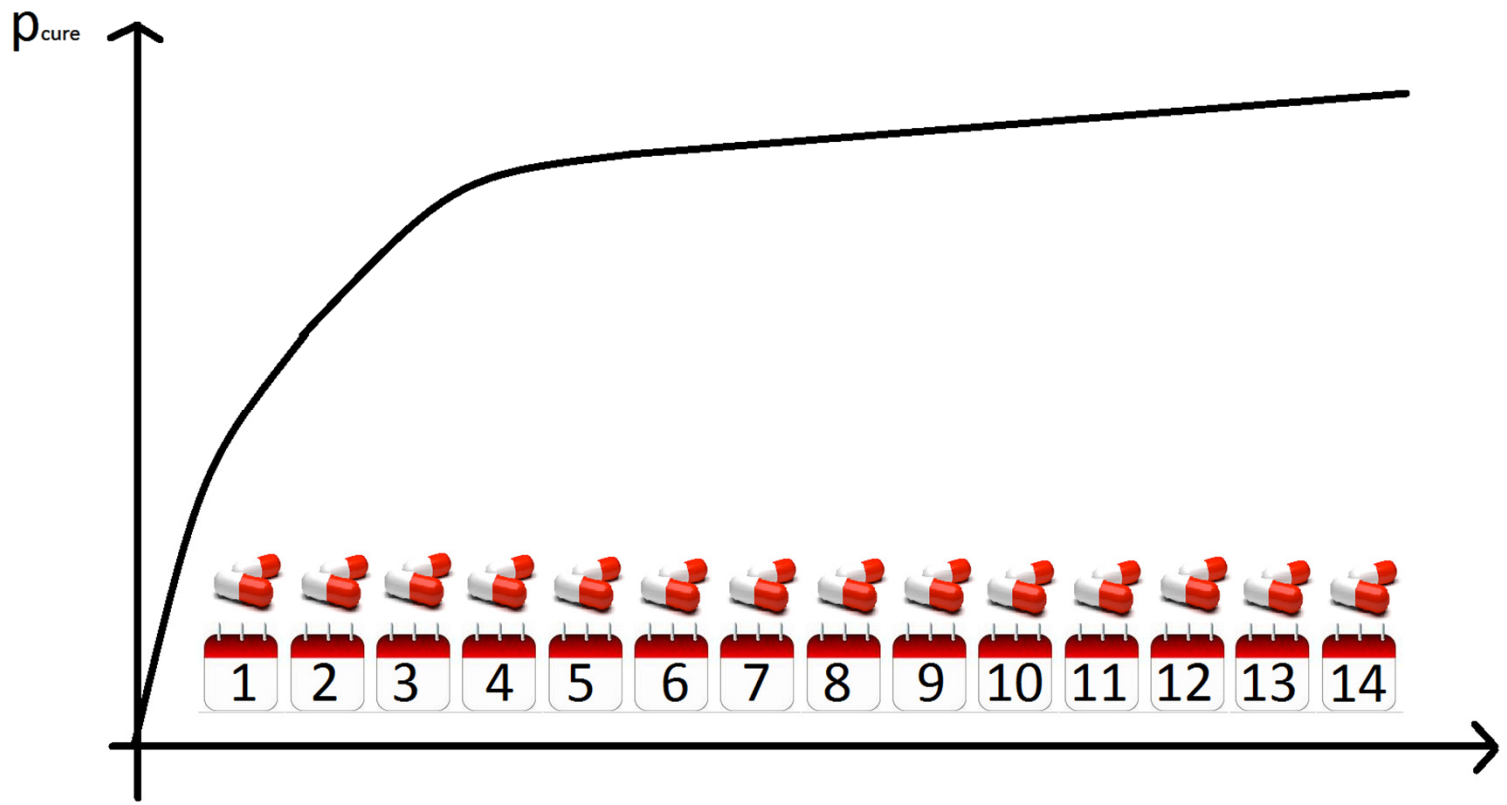
- Issues:
  - Increase chances to pick *right* research arms;
  - All other issues remain;
  - Increase sample size even further, often to a non-feasible level.

Our idea: modelling duration-response curve

- Instead of testing fixed number (usually 2) of research arms against control, we design trial to estimate the whole duration-response curve;
- Share information across durations, decreasing sample size needed;
- Only choice is minimum duration;
- Extension of work from Horsburgh et al.

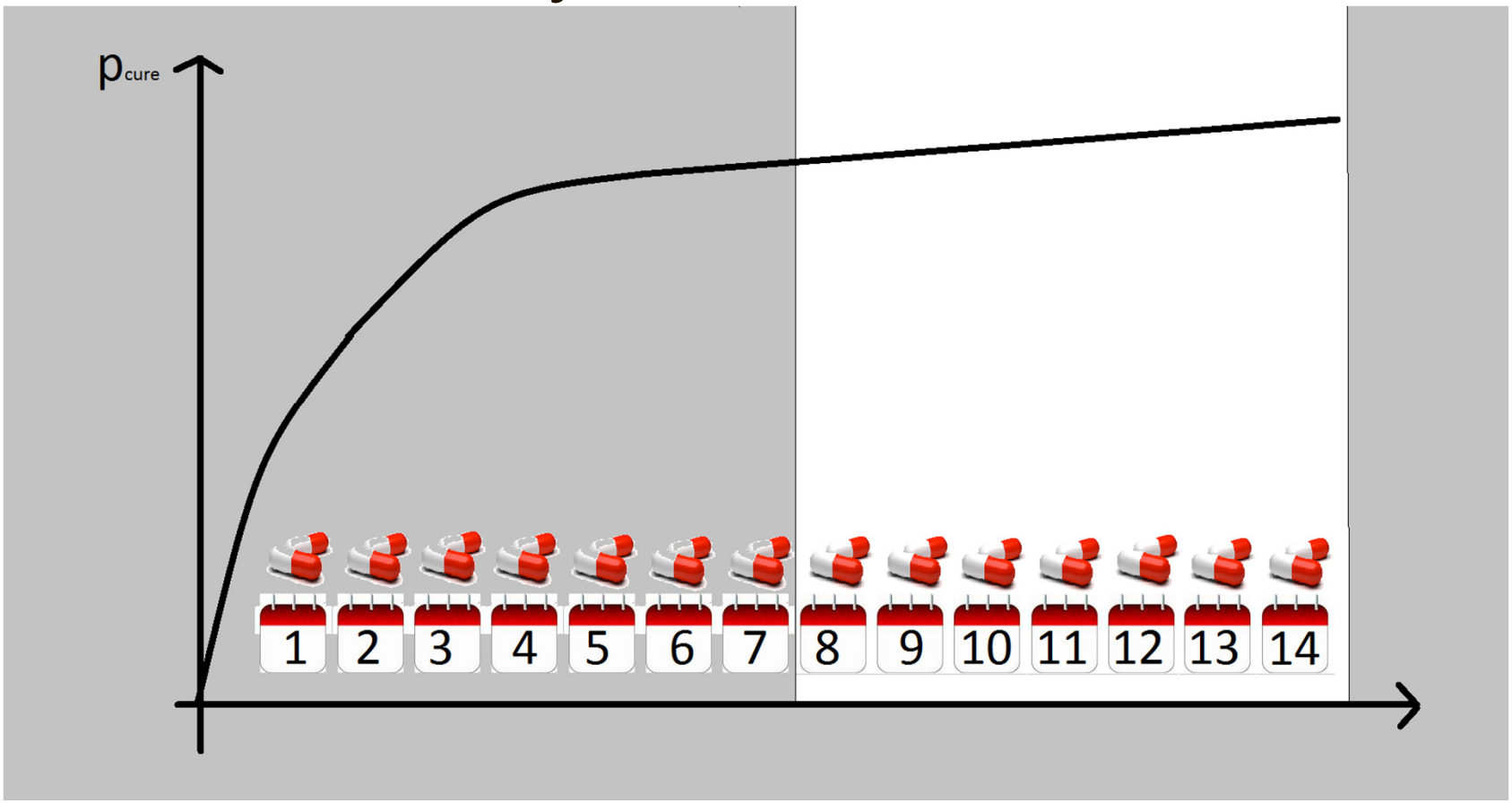
Modelling duration-response curve

- Example: currently recommended duration is 14 days.



Modelling duration-response curve

- Example: cannot randomise patients to no treatment. Only choice: minimum duration.



Modelling duration-response curve

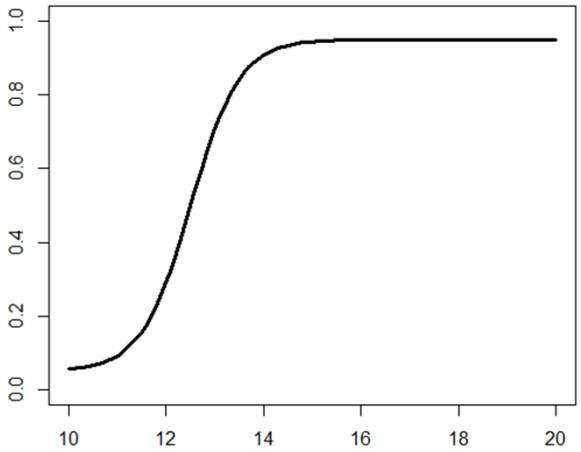
Questions:

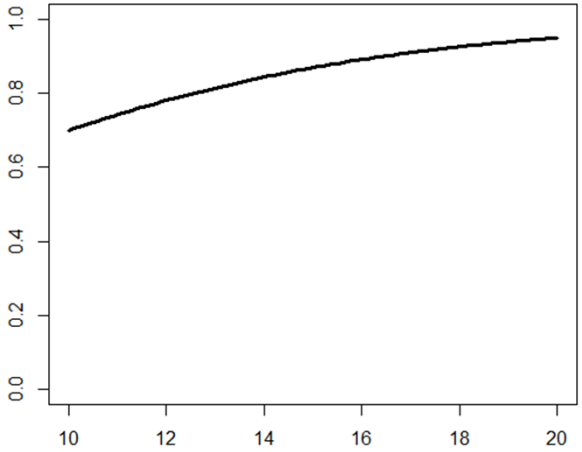
- How do we design a trial to better estimate this curve?
  - How many research arms?
  - How do we space research arm?
  - What about sample size?
- How do we model duration-response curve?
  - No prior knowledge about the shape of the curve;
  - Flexible regression models (FP, splines, etc).

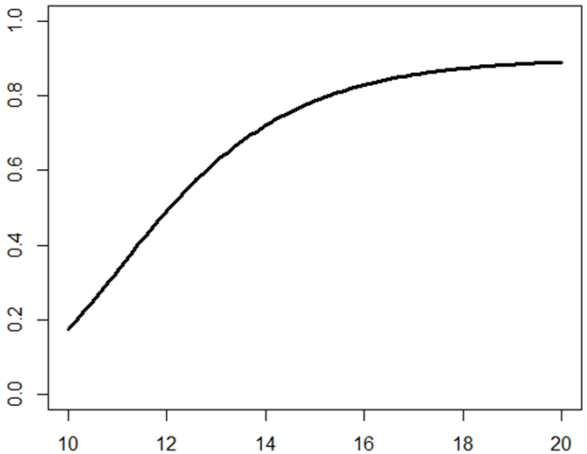
Setting up simulation study

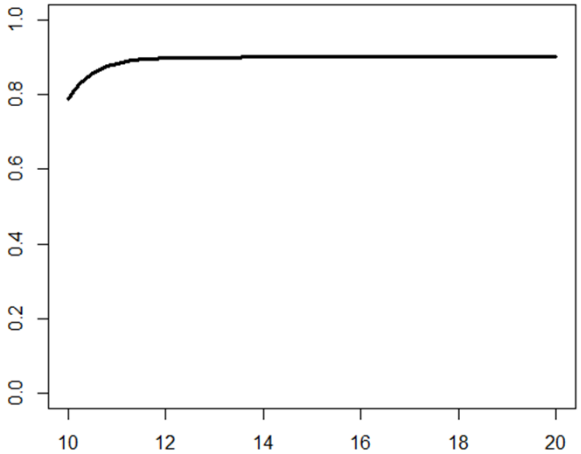
- We do not know shape of duration-response curve:
  - Simulate from a set of plausible scenarios;
  - Evaluate method across different scenarios;
- Start from base-case design and explore sensitivity of results to choice of design parameters
- Evaluate goodness of estimate through area between true and estimated curve;

Simulation study: some scenarios





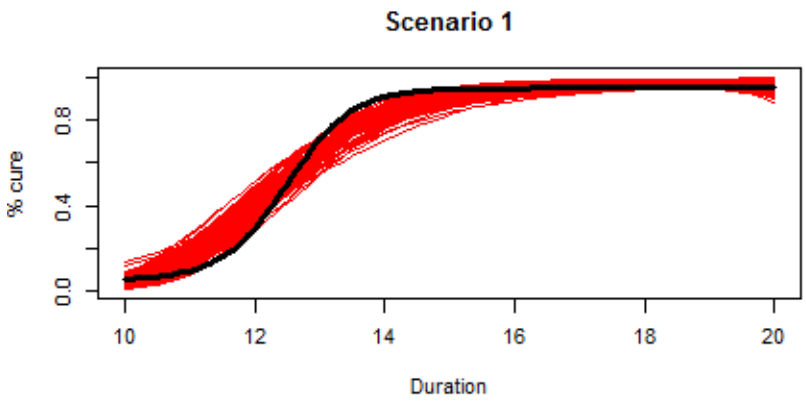


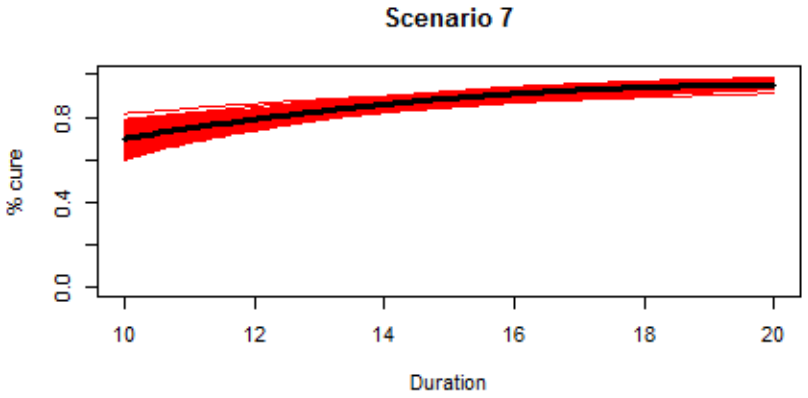


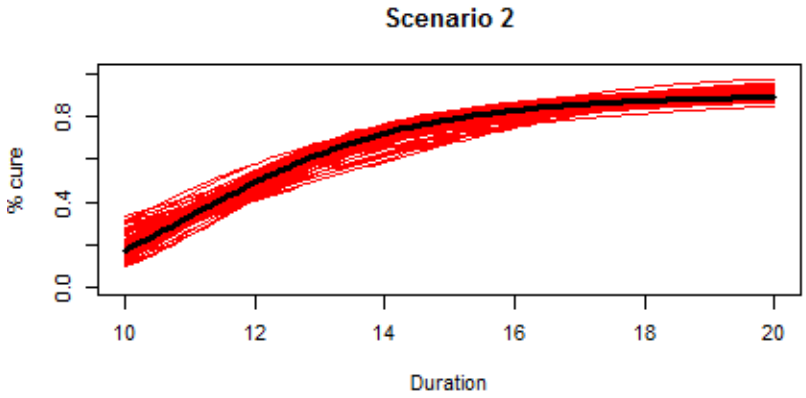
Simulation study: base-case design

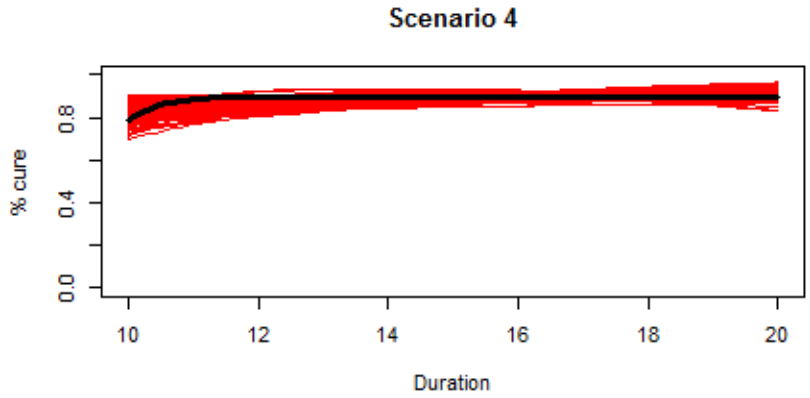
- 1000 simulated trials for each of 8 scenarios;
- Base-case design parameters:
  - Sample size: 504 patients
  - Number of Arms: 7
  - Position of Arms: Equidistant
  - Flexible model: fractional polynomials (FP2)
- We then re-run simulations varying, one at a time, sample size (200-1000), arms (3-10, equidistant or not), model (FP, splines).

Simulation study: base-case design









Simulation study: summary

- Sample size: ~500 enough to estimate duration-response curve within 5% error in 95% simulations;
- Number of arms: Using FP2, need at least 5, we gain nearly nothing for N>7 arms;
- Position of arms: Equidistant or more condensed in part of curve we expect to be less linear: similar results;
- Flexible model: FP more stable, standard implementation, no additional choices.

Issues of NI trials

- Does our proposal solve issues of NI trials?
  1. NI Margin Arbitrariness: ✓
  2. Choice of arms: ✓
  3. Sample size: ✓
  4. Bio-creep: ✓*
  5. Resilience: ✓
  6. Non-adherence: ✗

Summary

- Designing trials to optimise treatment duration important in different areas;
- Standard non-inferiority has several issues, moving to superiority is problematic as well;
- We propose modelling whole duration-response curve with flexible methods;
- Using FP, and randomising ~500 patients to 7 equidistant arms lead to good results under a variety of duration-response curves.

What's next?

- The outcome of the trial is an estimate of the whole duration-response curve. What to do with this curve estimate?
  1. Simply calculate duration corresponding to specific cure rate (e.g. 5% less than with current control), bootstrapping CI.
  2. Assume there is "acceptability curve", defining minimum cure rate we would tolerate at each duration, and find point where estimated curve is farthest away from / crosses fitted curve.
  3. Decision based on trade-offs. Cost-effectiveness methods? Define acceptability curve as a function of costs?

What's next?

- Original motivation: Phase-IV trials, treatment already known to be effective.
  - Investigation of inferential properties in these settings under way;
- Possible to use this design for Phase-II trials as well.
- It could be used to select most promising duration(s) to use later at Phase-III.

What's next?

- Adaptive design?
  - Possibly change minimum duration tested
- Use of covariate data (age, sex…)
  - Move towards personalised medicine;
- Application in TB:
  - How shall we include control arm?
- Force monotonicity with FP;
- Any comments/suggestions welcome.

Bibliography

- Horsburgh CR, Shea KM, Phillips PPJ et al., *Randomized clinical trials to identify optimal antibiotic treatment duration*, Trials, 2013; 14:88.
- Quartagno M, Walker AS, Carpenter JR, Phillips PPJ, Parmar MKB, *Rethinking non-inferiority: a practical trial design for optimising treatment duration*, Clinical Trials, 2018; 15:5.