Study designs for time aspects

CTU Lecture

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Questions of time

or counts, dose, …

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- Antibiotic treatment duration
- Duration of dual antiplatelet therapy in patients after percutaneous coronary intervention
- Start of anticoagulation in patients with stroke and atrial fibrillation

- Timing and number of COVID-19 vaccination boosters (jabs)
- Optimal dose of aspirin after myocardial infarction
- Number of chemotherapy cycles (e.g. $BEACOPP_{esc}$, ABVD) for patients with advanced stages Hodgkin lymphoma

Antibiotic treatment in cystic fibrosis

Duration – STOP2

– “To test **differing durations** of intravenous antimicrobials for CF [cystic fibrosis] exacerbations”

Goss CH et al. 2021

Dual antiplatelet therapy after PCI

Duration – MASTER DAPT

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– “The **appropriate duration** of dual antiplatelet therapy in patients at high risk for bleeding after the implantation of a drug-eluting coronary stent remains unclear.”

Valgimigli M et al. 2021

When to (re-)start anticoagulation

Timing – ELAN etc.

- Patients on anticoagulation
  - Re-start after ischemic stroke
  - Re-start after specific type of intracranial hemorrhage
  - …
- Standard of care based on observational evidence (at best) or (arbitrary) timepoints used in pivotal trial(s) (which were never tested …)

When to boost

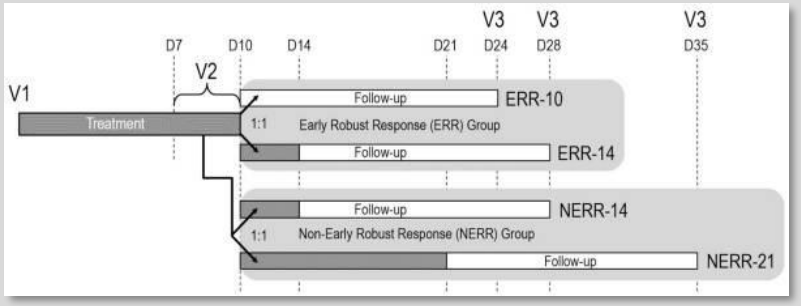
Timing - EU-COVAT-2 BOOSTAVAC

– “To determine the need for, **optimal timing** of, and immunogenicity of administering a 4th homologous vaccination dose against SARS-CoV-2 in the general population (18+ years) already vaccinated with the BNT162b2 vaccine.”

STOP2

Design

– "… to test in STOP2:
  1. abbreviated (10 ±1 day) IV treatment would not be inferior to 14 ±1 day treatment in ERR patients, and
  2. extended (21 ±3 day) IV treatment would be superior to 14 ±1 day treatment in NERR patients."



ERR ≈ early responders; NERR ≈ non-responders; iv, intravenous

Heltshe SL et al. 2018

MASTER DAPT

Design

– “The trial was designed to test hierarchically whether the abbreviated dual antiplatelet regimen, …, would be noninferior with regard to net adverse clinical events, …, and superior with regard to major or clinically relevant bleeding …”

Valgimigli M et al. 2021

(Point) Null Hypothesis Significance Testing

CTU Lecture June 2018

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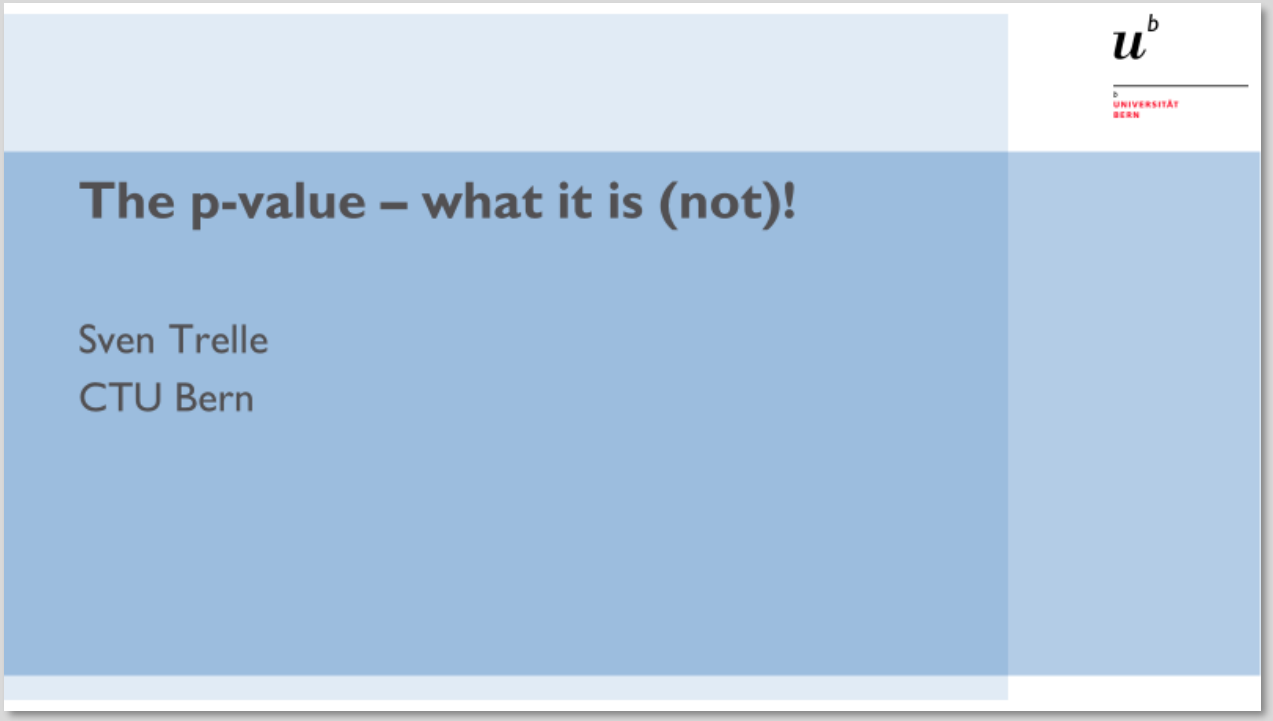
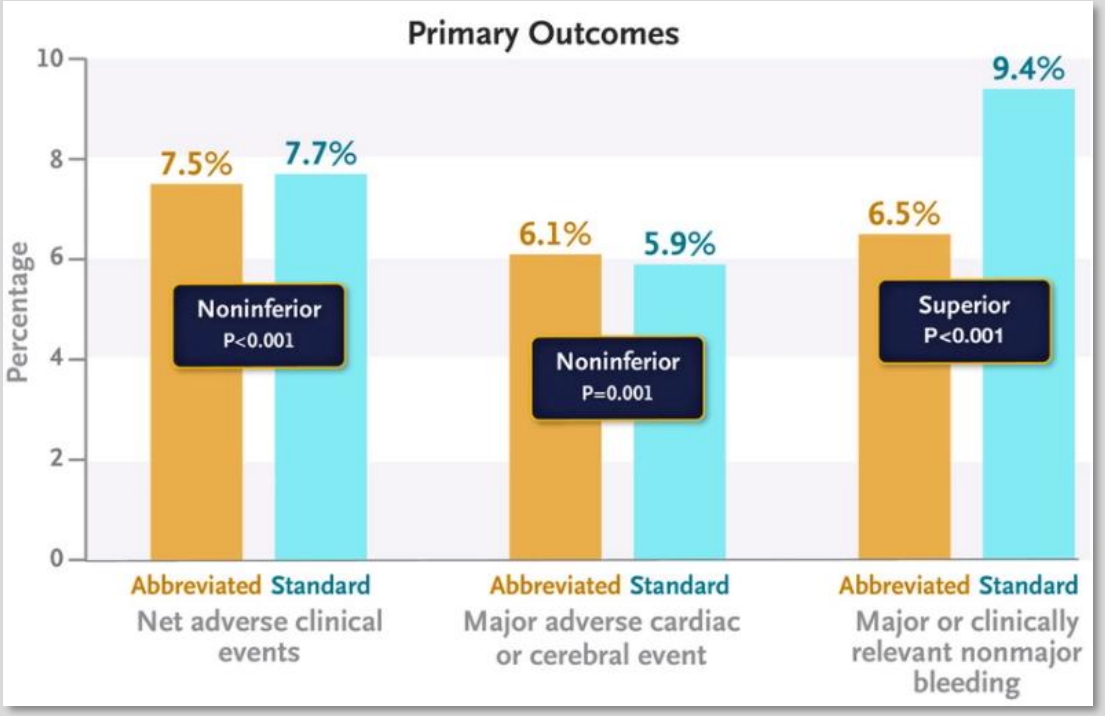


MASTER DAPT

Results



Valgimigli M et al. 2021

What do we (not) know?

MASTER DAPT

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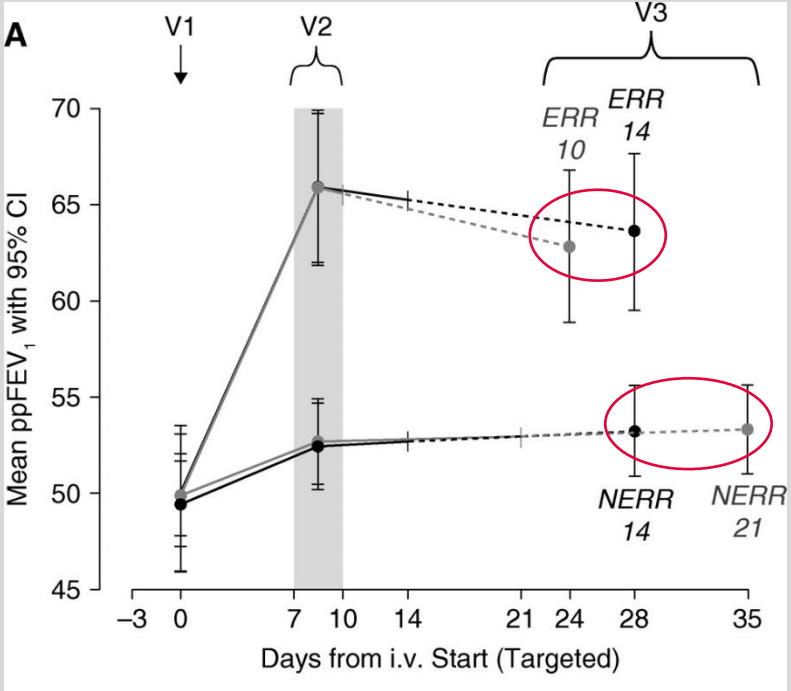
- Reminder: the original question → *appropriate duration*
- The trial tells us a lot but does not (fully) answer the original research question because it **tests a point null hypothesis**
- Whereas the word *appropriate* refers to a concept of optimum/best

STOP2

Results

– “Among adults with CF with early treatment improvement during exacerbation, ppFEV1 after 10 days of intravenous antimicrobials is **not inferior** to 14 days. For those with less improvement after one week, 21 days is **not superior** to 14 days.”



Goss CH et al. 2021

What do we not know?

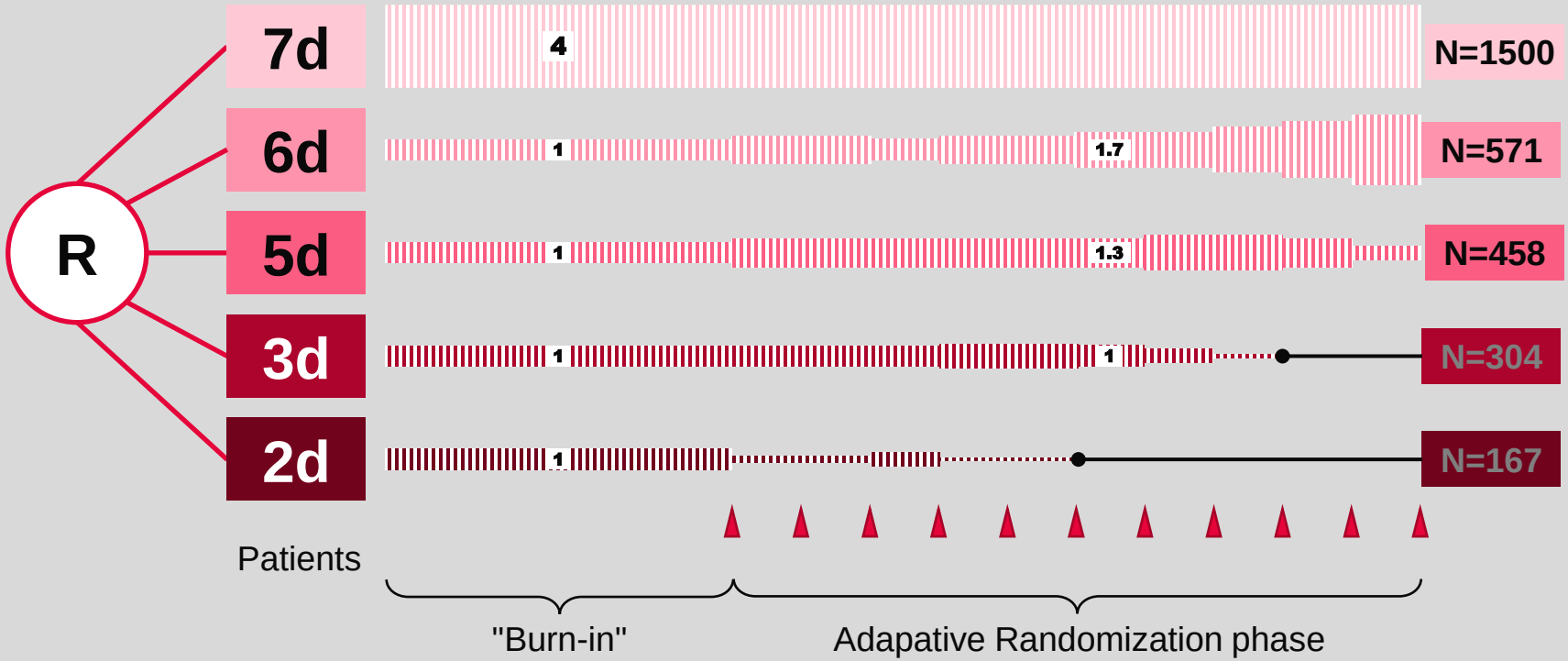
STOP2

- We still do not know the optimal treatment duration in responders, could an even shorter duration also be non-inferior?
- We still do not know the optimal treatment duration in non-responders
  - Could <14 days be sufficient (because early non-responders do not improve beyond a certain timepoint anymore)?
  - Why was 21 days chosen, maybe 18 days would be optimal?
    - In this case unlikely, but to make the point
  - Could a longer treatment be needed?
    - In this case unlikely, but to make the point

→Point null hypothesis significance testing will never tell us the optimum/best option

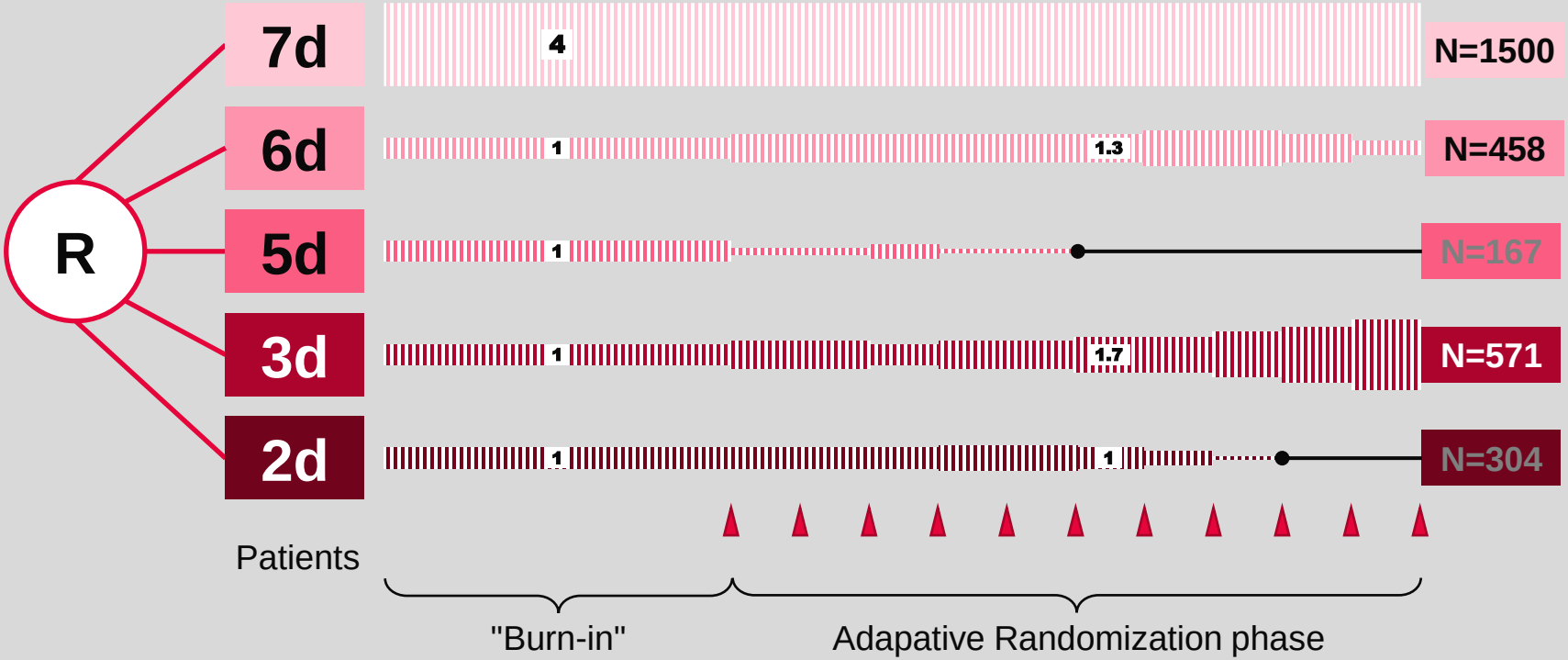
ELAN trial – possible concept (adapted)

Response Adaptive Randomization (one scenario in moderate stroke shown)



ELAN trial – possible concept (adapted)

Response Adaptive Randomization (another scenario in moderate stroke shown)



Multi-arm response adaptive randomization

Possible issues

- Only feasible with relatively short term endpoints
- How to prevent selection bias if blinding is not possible/feasible: investigators get access to accumulating endpoint data via the adapted allocation ratio
- Complete flexibility in the adaption algorithm might be too flexible: How to interpret data if it is at odds of what we expect from the mechanism of action (see previous slide)?
  - Build some model into the algorithm?

→ Implement a trial design that allows explicitly to model this mechanism (duration/time-response relationship) (Pouwels KB et al. 2019)

DURATIONS

Trial design

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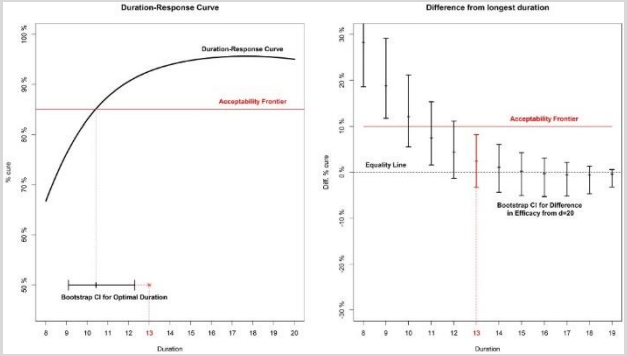
- To find the shortest duration of antibiotic treatment that is non-inferior to the control (maximum) duration within a specific risk difference margin
- Multi-arm trial with multiple ‘duration-arms’
- Modelling rather than individual arm comparisons



Quartagno M et al. 2020

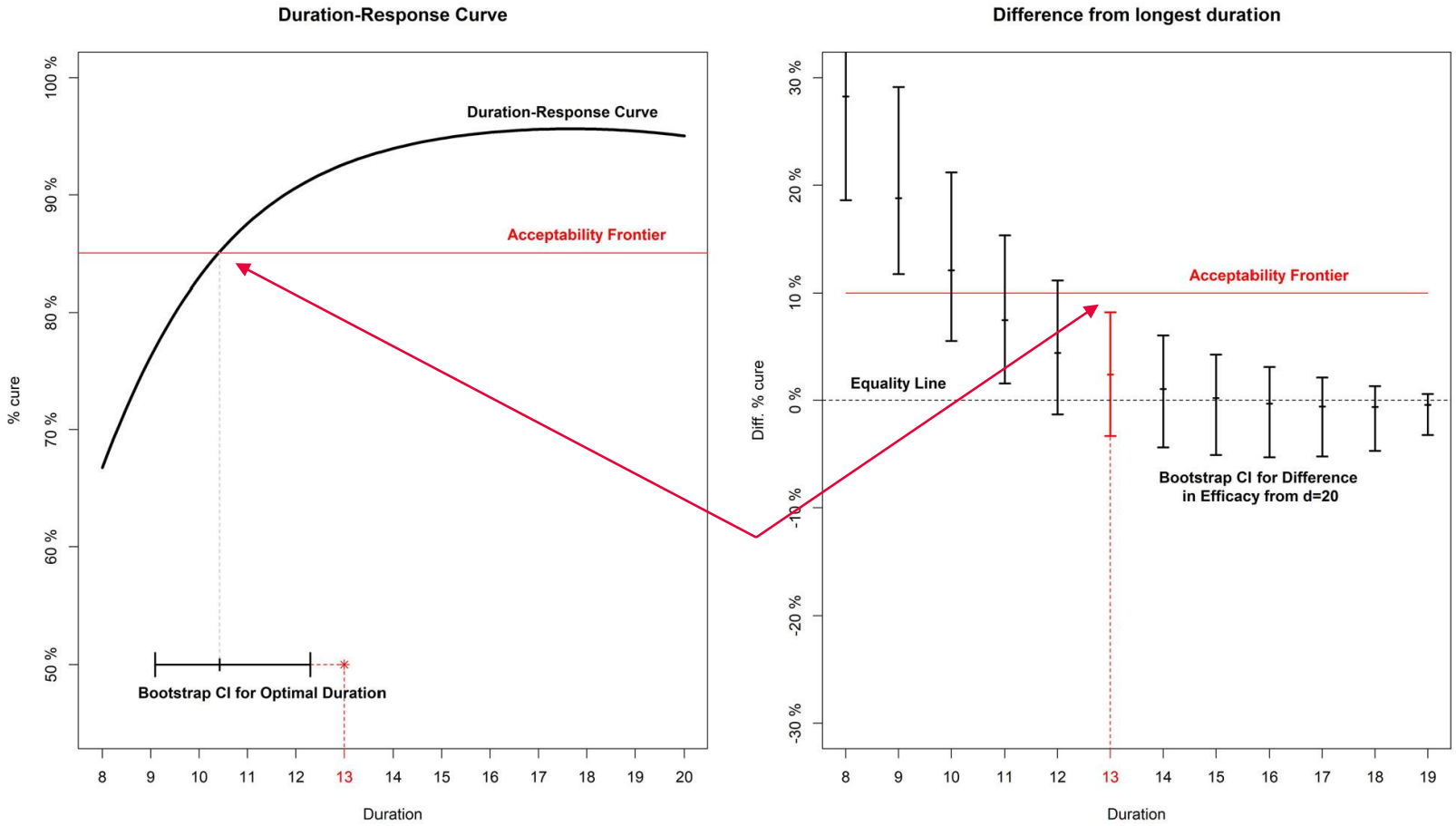
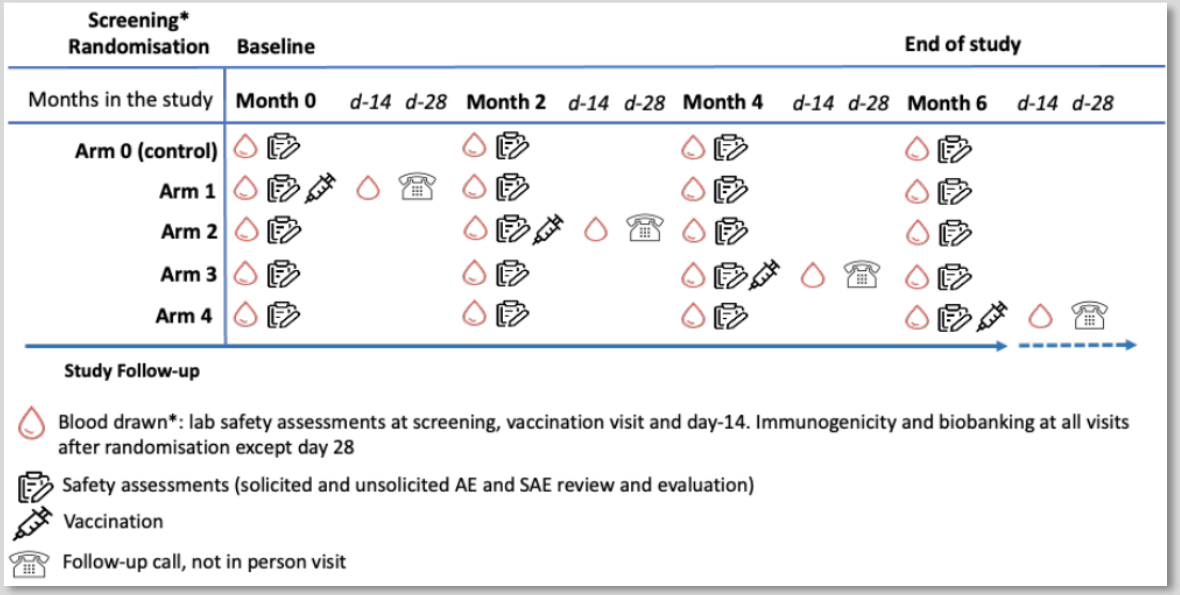


Figure 4. Analysis example for a hypothetical trial. On the left panel, the duration-response curve is estimated and then a bootstrap CI is built around the point where it crosses the acceptability frontier. On the right panel, bootstrap CIs are built around the difference in efficacy (cure rate) between each arm and the longest (d = 20).

EU-COVAT-2 BOOSTAVAC

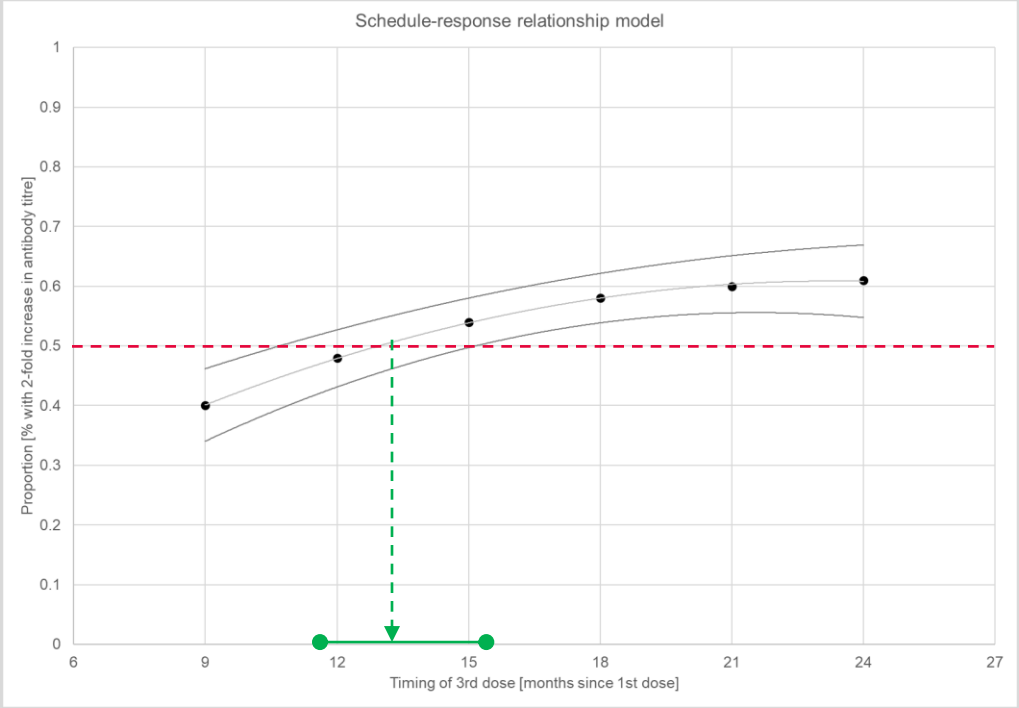
Study design

– Primary endpoint: increase in anti-Receptor-Binding-Domain antibody titre to at least a defined threshold (== ‘response’)



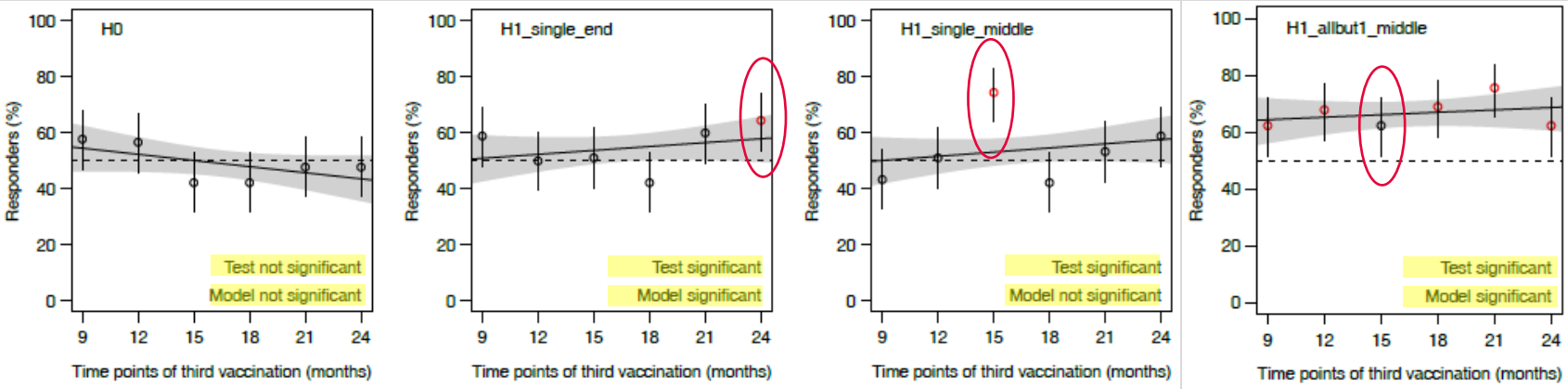
Identifying the optimal timepoint

Possible scenario (here with 3rd dose!)



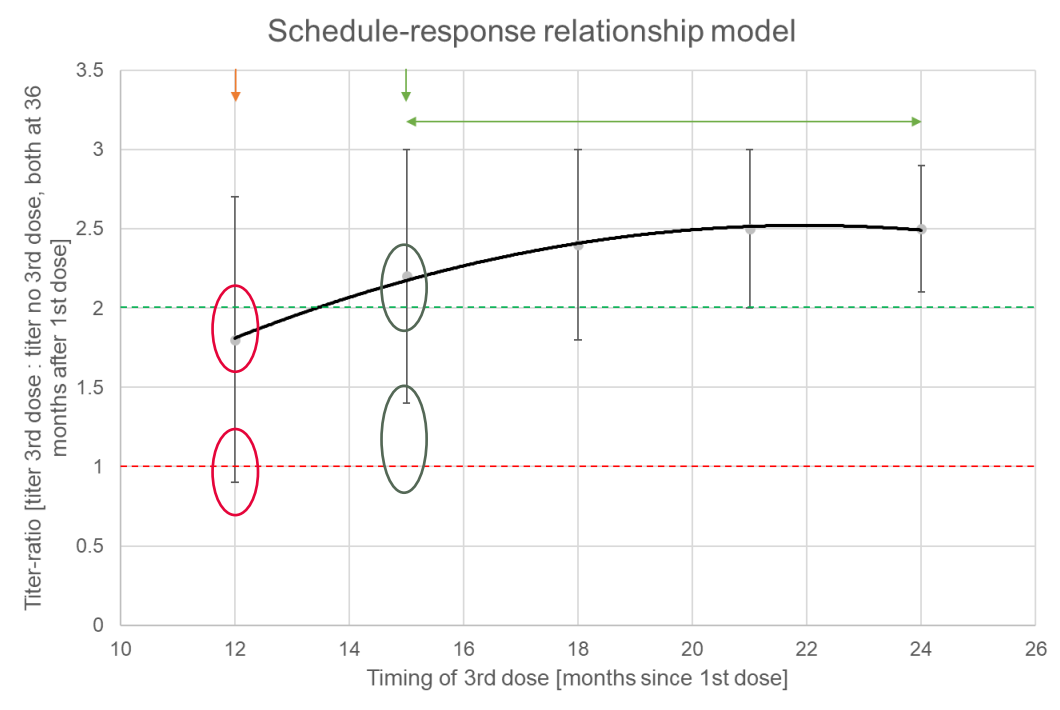
Schedule-response relationship model

Robustness



Identifying optimal timepoint

With two criteria (analogue to FDA*)



Time-Response relationship modelling

Design aspects

- Number of arms
- Number of participants
- Some theory/idea about the form of the relationship

How many arms?

When to re-start anticoagulation

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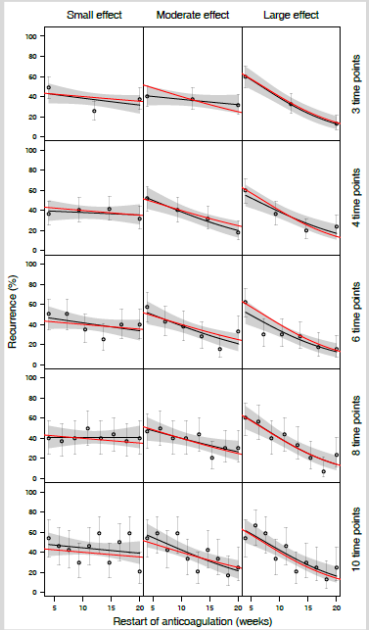
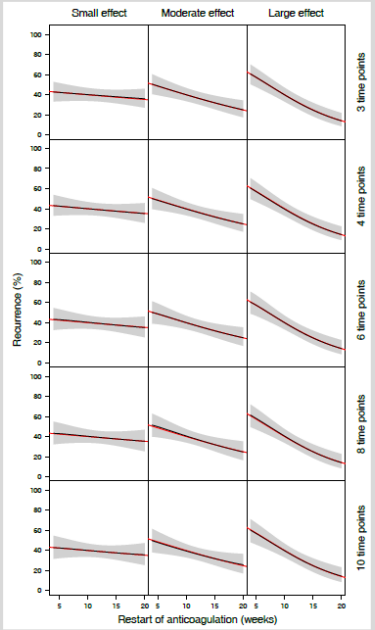
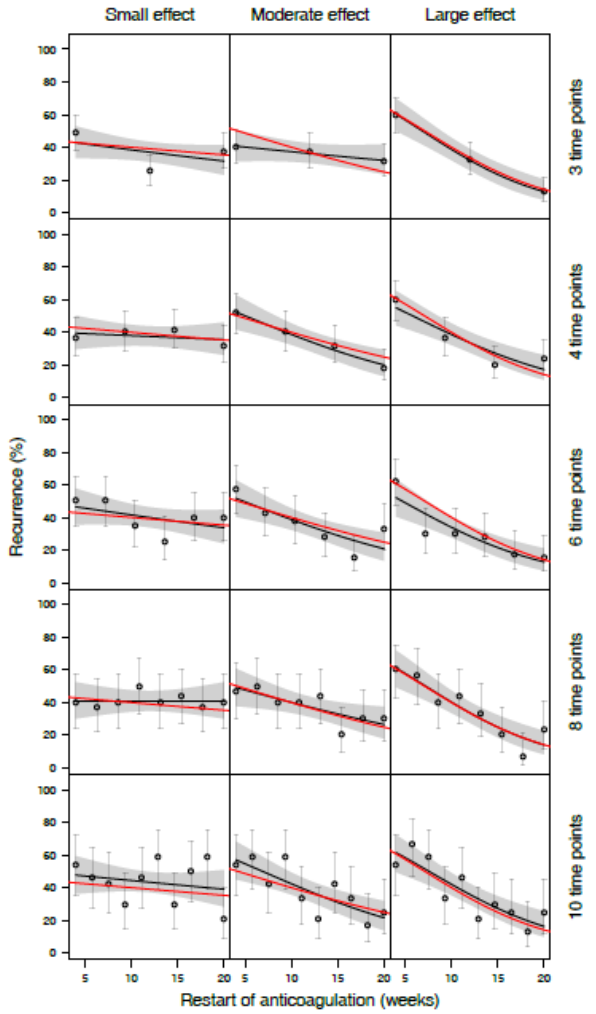
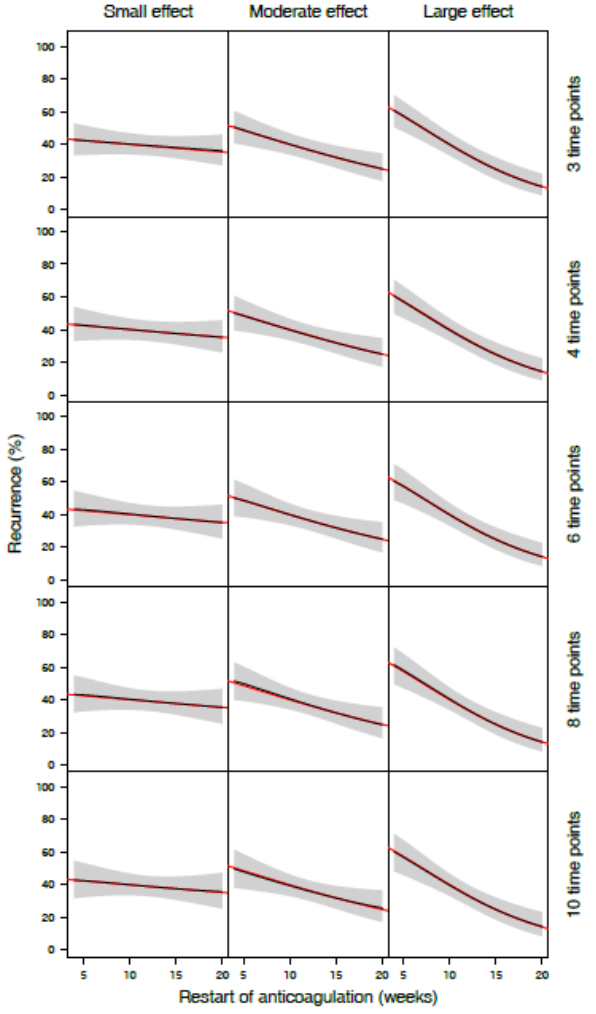
One scenario



100 simulations




Small effect
Moderate effect
Large effect
3 time points
4 time points
6 time points
8 time points
10 time points
Recurrence (%)
Restart of anticoagulation (weeks)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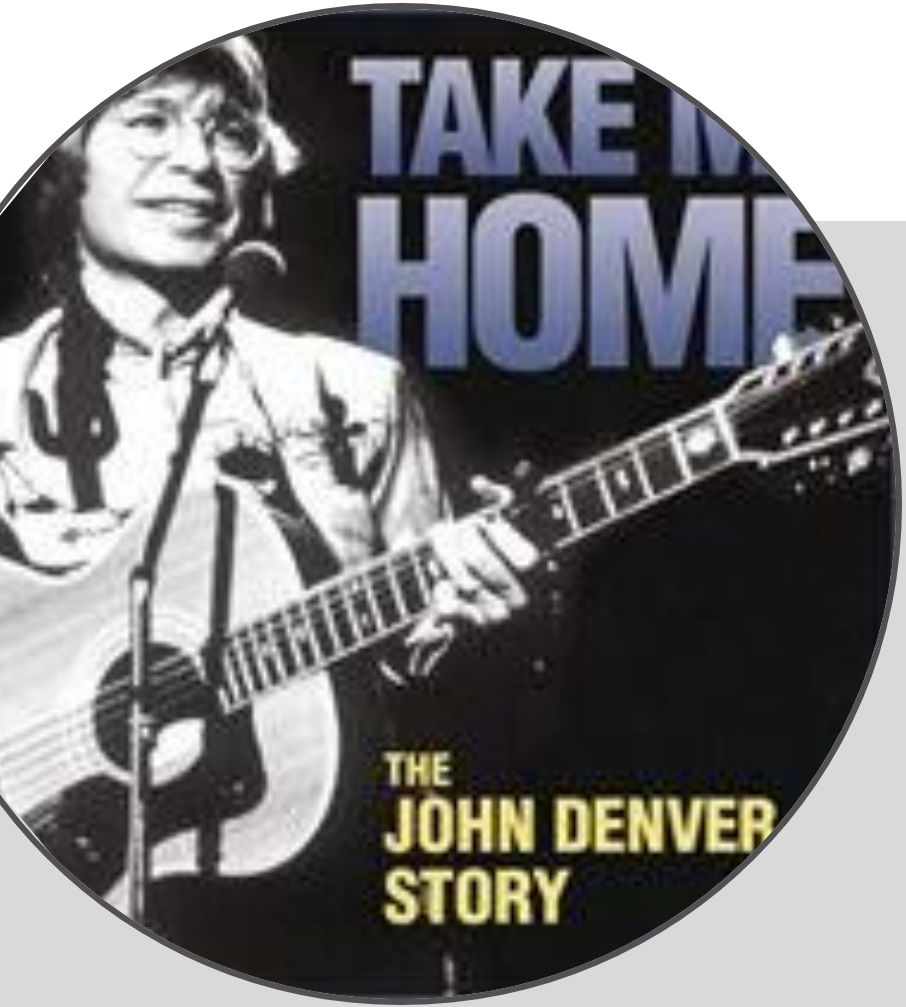

- Direct arm comparisons with null hypothesis significance testing might be okay to test a mechanistic hypothesis but might be of limited interest for time, schedule, etc. aspects
- Modelling probably more efficient (and informative → guides flexibility needed in clinical care)
- Consider the possibility of a non-significant standard two-arm comparison trial → how much evidence is produced (usually very little) as compared to a modelling approach with the same money and number of patients

Thank you

for your attention!

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References

- Goss CH et al. 2021. Am J Respir Crit Care Med. 204:1295.
- Heltshe SL et al. 2018. Contemp Clin Trials. 64:35.
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- Quartagno M et al. 2020. Clin Trials. 17:644.
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