Methodological and practical challenges in sequential designs

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WReN inaugural meeting: 21st April 2016

Content

- Definition of a group sequential trial
- PRESSURE2 trial
  - Motivation for the design
- Methodological challenges
  - Criteria for early stopping
  - Number and spacing of planned interim analyses
  - Choice of stopping boundaries
- Decision making process at interim analyses
- Practical considerations
  - Monitoring the overall event rate
  - Planning of activities and timelines for an interim analysis
  - Resource planning
  - Communication with centres / contracts

Group Sequential Design

- A clinical trial in which the results are analysed at various intervals with the intention of stopping the trial early

- **Double Triangular Group Sequential Trial** (2)**:**
  - Allows early stopping:
    - Overwhelming evidence of efficacy/effectiveness
    - Sufficient evidence study is unlikely to succeed →futility

- Timing of interims can be fixed by date or by number of events/patients

- **Efficient design**
  - **Potential for reaching conclusions earlier compared to a conventional RCT**

PRESSURE2 – Motivation for the trial

HSF

APM

- Alternating Pressure Mattresses (APM) and High Specification Foam (HSF) mattresses routinely used in clinical practice
- APMs considered to be superior mattress
  - lack of evidence in prevention of Category 2 or above pressure ulcers (PUs) in high risk patient populations

- PRESSURE 2 trial
  - designed to determine which is most effective mattress in preventing Category 2 or above PUs

Pressure Relieving Support Surfaces: a Randomised Evaluation 2 (PRESSURE 2)

Research Design

- The trial is a multicentre, open, adaptive, parallel group, randomised controlled trial
- Comparison of APM and HSF in high risk acutely ill patients for prevention of new Category 2 or above PUs
- **Setting:** acute secondary and community NHS Trust in-patients
- **Treatment phase** is from randomisation to earliest of:
  - no longer at high risk, discharge, 60 days post randomisation
- **Primary Endpoint:** Time to developing a new Category 2 or above PU from randomisation to 30 days post end of treatment phase or withdrawal / deaths (maximum of 90 days).

PRESSURE 2 trial

- Large trial with maximum of 2954 patients
- Trial powered to detect 5% absolute difference in event rate of developing a Category 2 or above PU [a]
- Assumed event rates
  - 18% on APM (PRESSURE1(1))
  - 23% on HSF
- Fixed design required 2786 patients
- Uncertainty around estimate of event rate for HSF
- Need to reach a conclusion quickly

⇨ Adaptive Design using a **Group Sequential Design**

[a] Powered at 90%, overall 2-sided 5% significance level

Group Sequential Design

- Data are analysed at intervals with the opportunity of stopping the trial early

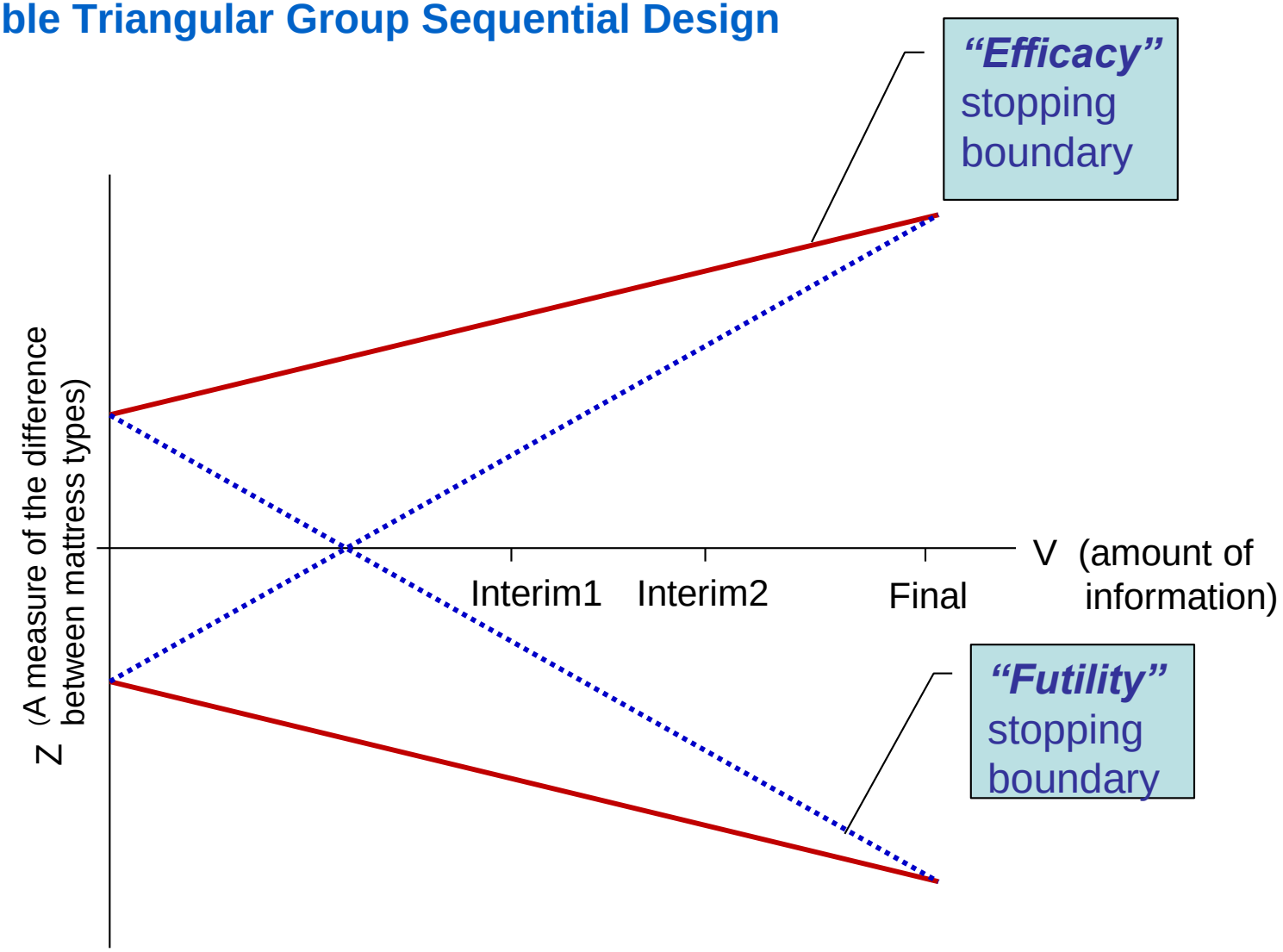
- **Double Triangular Group Sequential Trial** (2)**:**
  - Allows early stopping:
    - demonstrating effectiveness of either mattress
    - futility of the trial

- Early primary endpoint
  - Time to developing a Cat 2+ PU

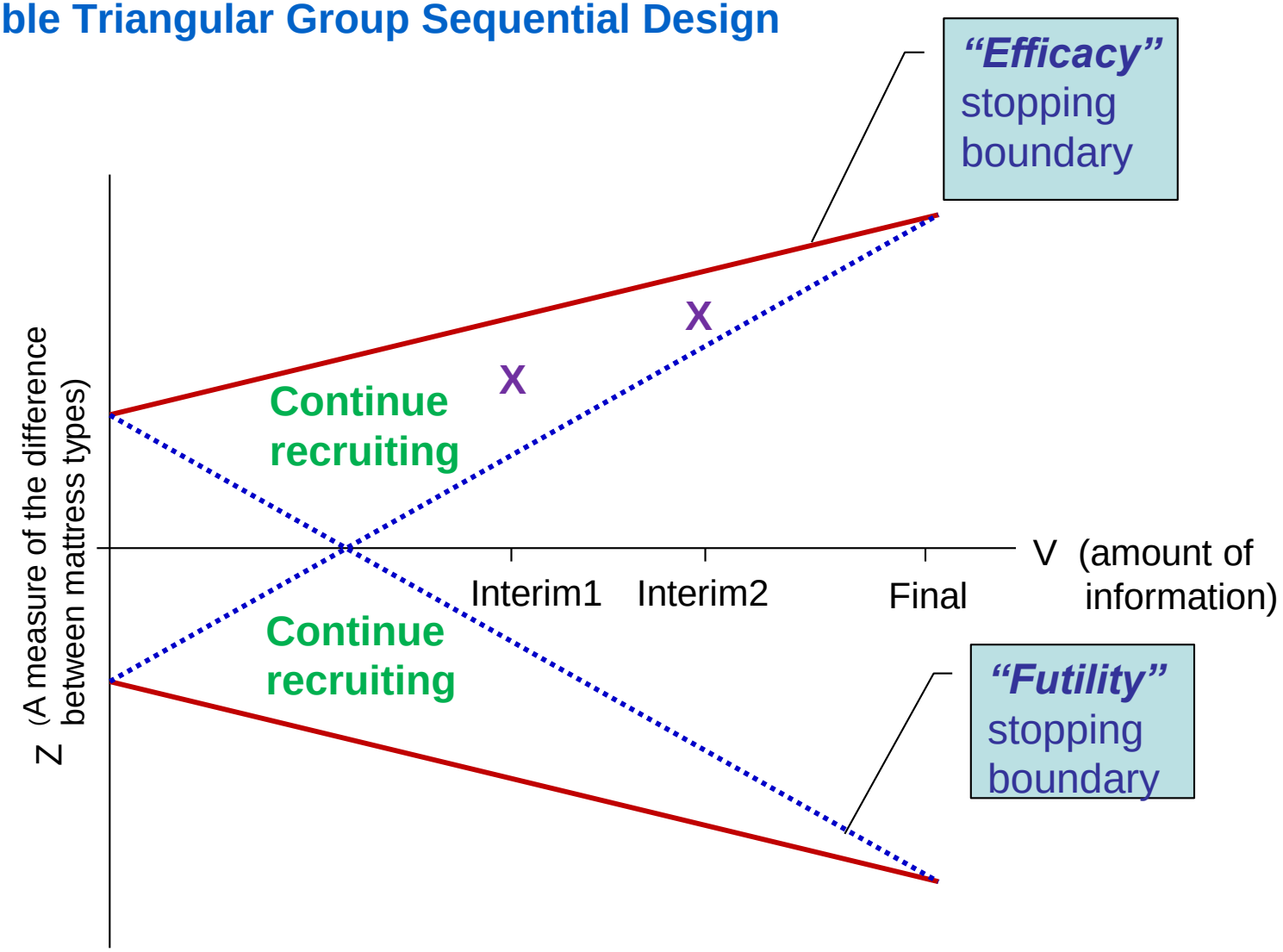
  $\Rightarrow$ assess early stopping in a timely manner

- **Efficient design**
  - **Potential for reaching conclusions earlier compared to a conventional RCT**

Double Triangular Group Sequential Design



Double Triangular Group Sequential Design



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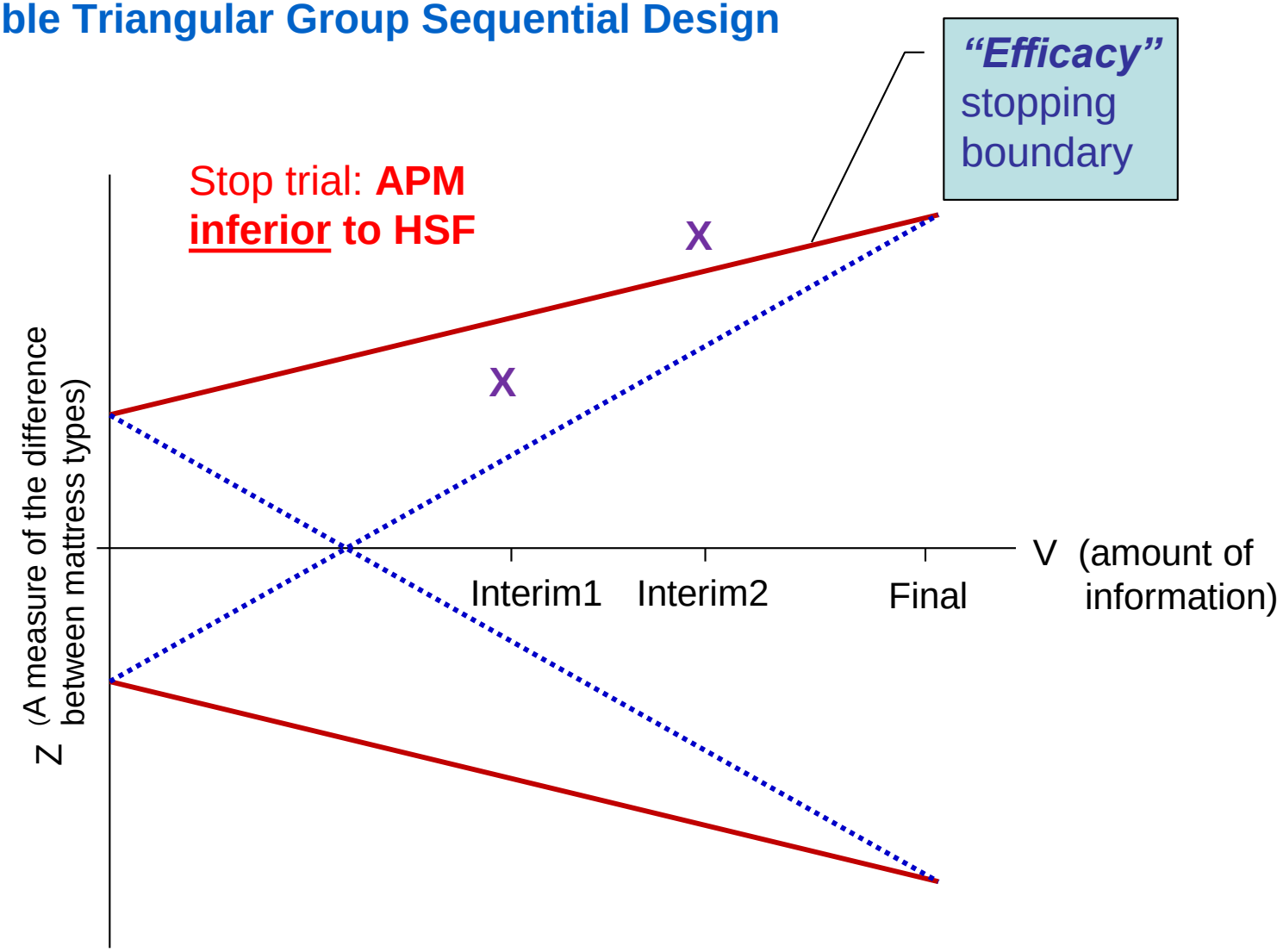

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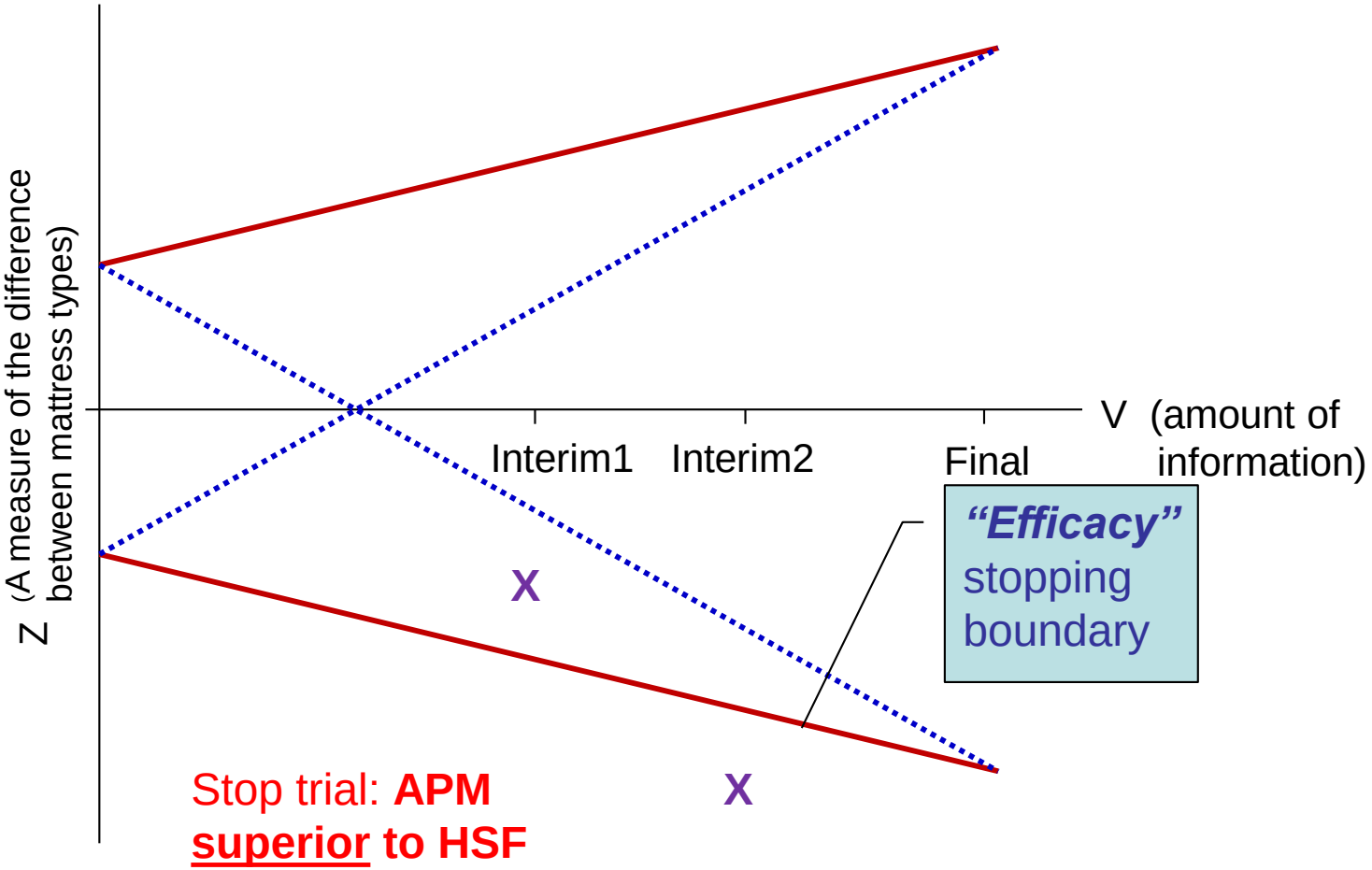

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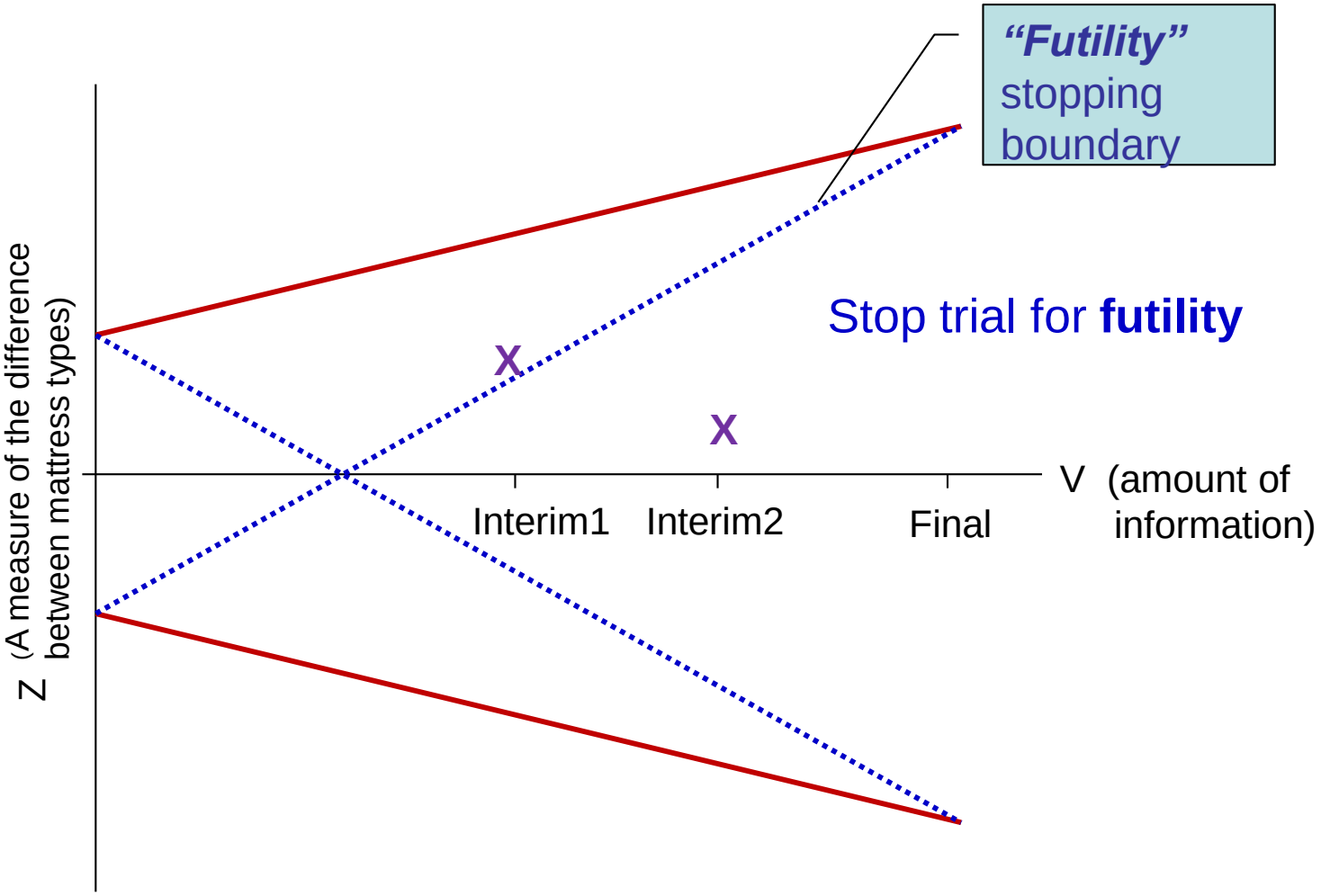

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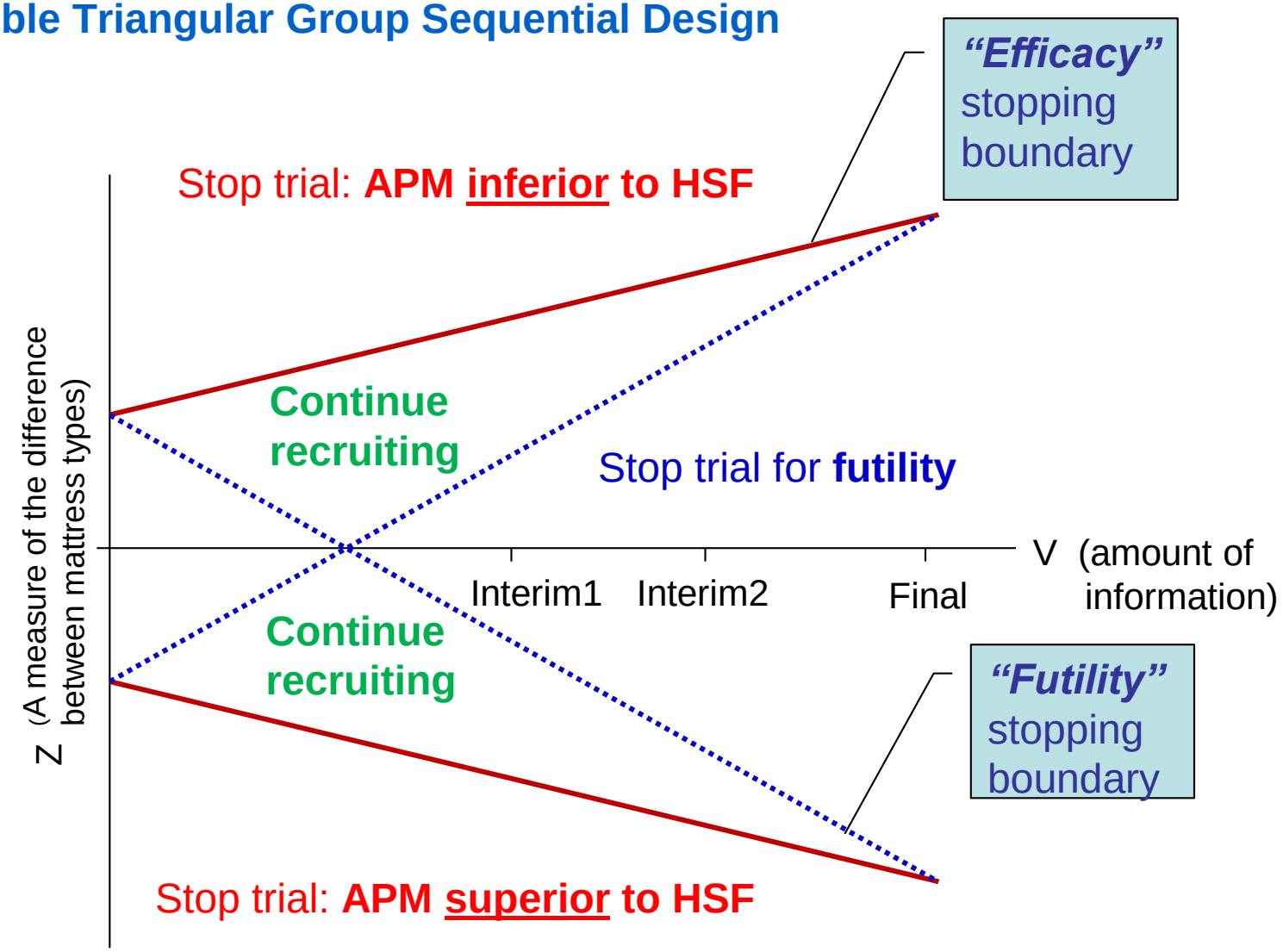


Number & spacing of planned interim analyses

- Two interim analyses and a final analysis

- Unequally spaced interim analyses at event driven coherent time points:
  - First analysis after **300 events**
    - minimum number of events required for economic evaluation
  - Second analysis after **445 events**
    - number of expected events required to stop early for futility
  - Final analysis after **588 events**

Stopping boundaries

- Efficacy and futility boundaries defined using Lan-DeMets *"spending functions" (3)*
- Provide conservative stop/continue criteria at the interim analyses
  - Resemble O'Brien & Fleming stopping boundaries (4)
- Important to maintain overall Type I error rate of α
- Two planned interim analyses and a final analysis:

Cumulative α spent at each analysis

Interim 1	Interim 2	Final
0.003	0.02	0.05

Decision making process

- Data Monitoring Committee (DMC)
  - Independent group of experts (Clinicians, Statistician, Health Economist)
  - Review patient interim analysis results on effectiveness and safety
  - Make a recommendation on whether trial stops or continues

- Statistical stopping boundaries provide guidance to DMC on stopping trial early

- Further considerations:
  - safety profile
  - economic evaluation
  - Information external to the trial

Decision making process

- No stopping boundaries are crossed
  - Continue recruitment

- Efficacy boundary is crossed
  - One mattress is more effective than the other

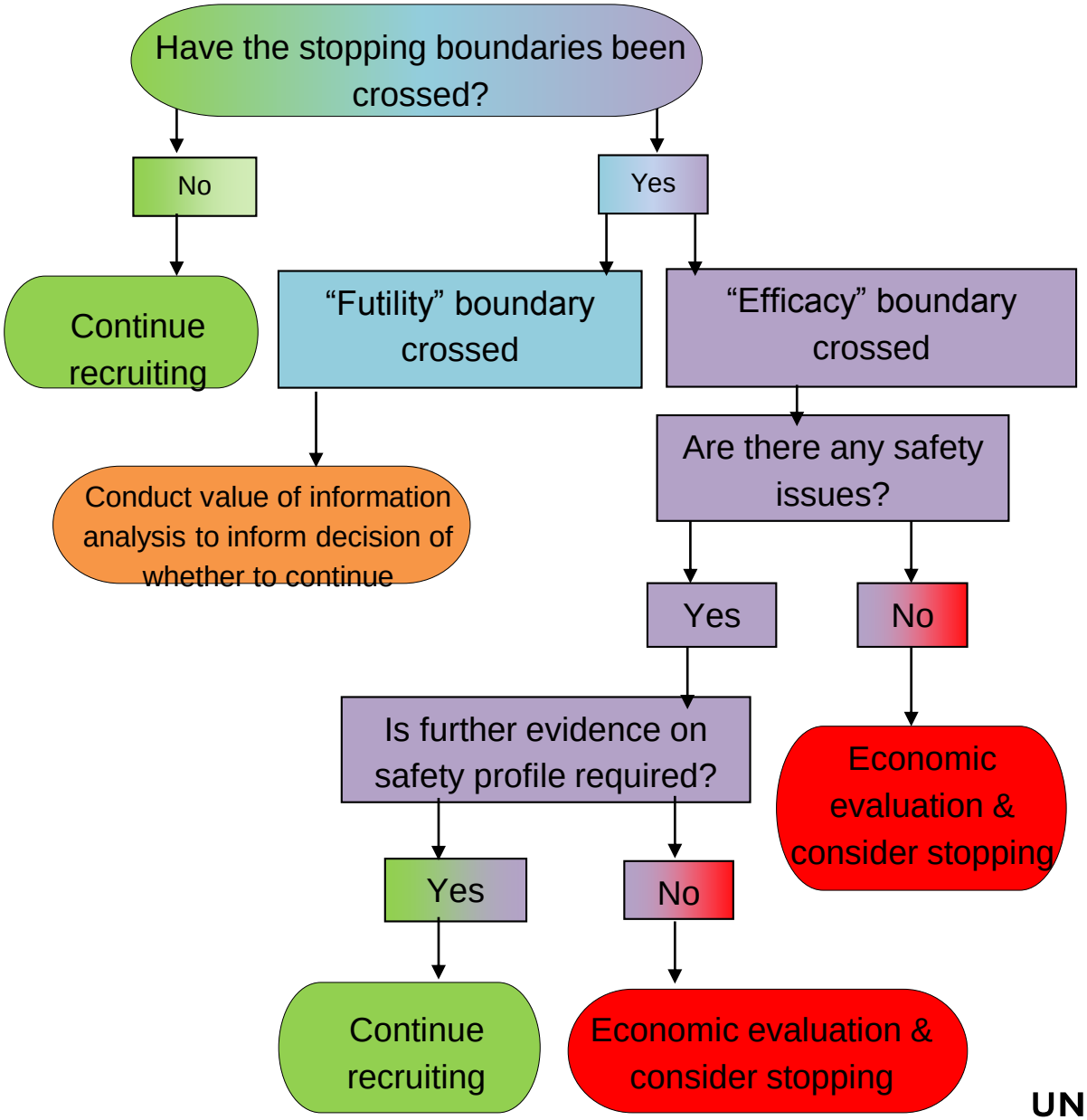
  → Stop the trial early??
  - Safety issues on “superior” mattress
  - Conduct a “*Value of Sample Information*” analysis

- Futility boundary is crossed
  - Unlikely to demonstrate effectiveness of either mattress

  → Stop the trial early??
  - Conduct a “*Value of Sample Information*” analysis

- Information external to the trial

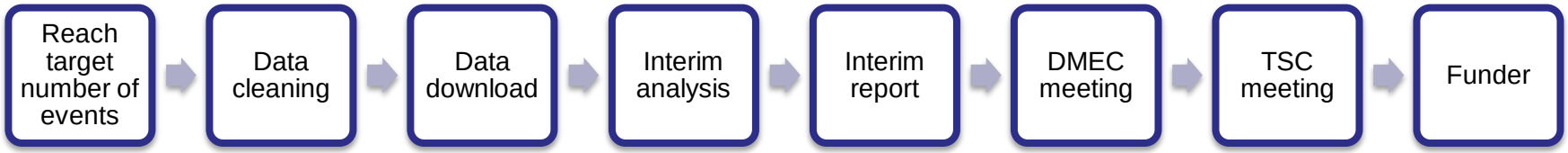
Summary of decision rules



Practical considerations

- Monitoring the event rate
  - Timing of interim analysis is event driven
  - Monitor event rate continuously
  - Data cleaned on an ongoing basis

- Planning timelines for an interim analysis
  - Careful planning required



Practical considerations

Resource planning

- Funding for the trial
  - Maximum research funding requested
  - Stated reduction in funding if stopped early
- Number of centres
  - Planned for maximum sample size
    - maximum of 40 research centres in England and Scotland
  - maximise potential for recruiting maximum recruitment target
- Contracts for Research Nurses
  - Arranged based on recruiting to maximum sample size
    - Potential problem if trial stops early

Practical considerations

- Communication with centres
  - Centres have knowledge of the:
    - trial design
    - overall recruitment rate

However….

- Centres do not have knowledge of the:
  - Overall event rate
  - Timing of an interim analysis
  - Results of an interim analysis unless decision made to stop early

  => avoids potential for bias at centres
    - Recruitment decisions based on knowledge that trial is continuing after an interim analysis
- Centres requested to continue recruiting to maximum planned sample size unless informed otherwise

Conclusion

- Group sequential designs are efficient
  - maximise the potential for producing robust clinical evidence earlier than in a conventional design
  - Allow for early stopping if unlikely to show a difference in mattress types

- Stopping boundaries provide guidance to the DMC on decision making
  - Other factors: patient safety, cost effectiveness and other information external to the trial needs to be considered

- Timelines, resources and contracts require careful consideration

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References

(1) Nixon, J., Cranny, G., Iglesias, C., Nelson, E. A., Hawkins, K., Phillips, A., Torgerson, D., Mason, S. & Cullum, N. 2006. Randomised, controlled trial of alternating pressure mattresses compared with alternating pressure overlays for the prevention of pressure ulcers: PRESSURE (pressure relieving support surfaces) trial. BMJ; 332:1413 -141

(2) WHITEHEAD, J. & TODD, S. 2004. The double triangular test in practice. *Pharmaceutical Statistics;* 3: 39-49.

(3) Lan, KKG & DeMets, DL. 1983. Discrete sequential boundaries for clinical trials. *Biometrika;* 70: 659-663

(4) O'Brien, PC, Fleming, TR. 1979. A multiple testing procedure for clinical trials. *Biometrics;* 35: 549-556

Acknowledgments

- **Co-applicants**
  - **NHS:** Elizabeth McGinnis, Nikki Stubbs, Val Henderson
  - **UoL:** Jane Nixon, Isabelle Smith, Sarah Brown, Julia Brown, Claire Hulme, Andrea Nelson, Susanne Coleman, Lyn Wilson, Delia Muir, Claudia Rutherford
  - **Service User:** Kay Walker
- **CTRU trial team**
- **NHS Centres**
- **Trial Steering Committee**
- **Data Monitoring Committee**

- **Research Funder**
- This presentation presents independent research funded by the National Institute for Health Research (NIHR) under its Health Technology Assessment Programme (11/36/33). The views expressed in this presentation are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health