DELTA 2

Difference ELicitation in TriAls

Guidance on specifying the target difference ("effect size") for a RCT

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Acknowledgements

- DELTA^2 group
  - JA Cook, W Sones, DG Altman, CR Ramsay, DA Fergusson, R Emsley, C Hewitt, J Rothwell, LV Hampson, LD Vale, Bland M, J Berlin, SJ Walters, S Julious
- Funders
  - National Institute for Health Research, UK
  - Medical Research Council, UK
- Survey respondent (SCT & its membership)
- Session speakers
  - S Julious, J Rothwell, M Bell, DA Fergusson

RCTs & sample size

- No one size fits all
  - All trials are different
  - Need to deal with variability and play of chance
- Central to RCT design is a sample size calculation
  - Provides reassurance
- Sample size matters
  - Scientifically
  - Ethically
  - Trial conduct (e.g. 100 versus 2000)

How is the sample size calculated?

- Required size is dependent upon:
  - Trial design (e.g. cluster trial)
  - Statistical analysis (e.g. t-test)
  - Statistical parameters (e.g. sig. level and power)
  - Difference we desire to detect
    - Target difference or "effect size"

DELTA^2

- DELTA (Difference ELicitation in TriAls)^2
  - Producing guidance on specifying the target difference for randomised trial
  - Follows on DELTA project
- DELTA had three components
  - Comprehensive systematic review of methods within and outside the health field
  - Two surveys of trialists to determine current practice
  - Structured initial guidance

Systematic review

- Aim
  - To identify potential methods
- Methods
  - Comprehensive search (biomedical/non-biomedical databases plus clinical trials textbooks)
- Results
  - Review 11485 abstracts +15 textbooks +ICH/1434 papers
  - 7 methods
    - Diversity in concept and implementation
    - Identify a difference which is important and/or realistic

Hislop et al PLOS Med, 2014

Surveys

- Two surveys (SCT membership/UK & Ireland trials related groups)
- Awareness and use, and willingness to recommend methods generally high
- Sample size process is complex
  - Use of methods often not reported
  - "hidden" influence of practicalities, regulators and funders
- Role for guidance

Cook et al Clin Trials, 2014

Initial guidance produced

- Generic guidance on use
  - Perspective important (e.g. patient, clinician)
  - Need to consider basis (important, realistic or both)
- Method specific guidance
- Recommended level of reporting trial protocols and reports
- Limited in scope
  - Two-arm parallel groups superiority phase 3 trial

Cook et al Trials, 2015

Session outline

- Series of short presentations
  - Steven Julious – Sample sizes and target differences for trials
  - Melanie Bell – Patient reported outcomes & important differences
  - Joanne Rothwell – Review of target difference in trials
  - Dean Fergusson – A trialist's perspective
- Interactive section
  - Opportunity to inform guidance development

Presentations

Interactive part of the session

Topic 1 – Type of trial

- Most trials are designed as a late phase (3 or4) study
  - Also referred to as definitive, confirmatory, or pivot trials
  - Evaluating clinical efficacy or effectiveness
- Other types of trials exist though the sample size is may not be justified by statistical considerations

Question 1 – Type of trial

Should the scope of the guidance be restricted to late phase (often called "definitive" or "confirmatory") trials?

- **Yes**
- **No**
- **Don't know**

Topic 2 – Alternative research questions

- Most trials are designed to answer a superiority question (is there a difference?)
- Equivalence (is it the same?) and non-inferiority (is it no worse?) questions are sometime used
- How the sample size is calculated varies according to the research question

Question 2 – Alternative research questions

Should the guidance cover in-depth trials with alternative research questions (e.g. equivalence and non-inferiority)?

- **Yes, it needs to be covered in-depth**
- **No, a brief discussion is enough**
- **Don't know**

Topic 3 – Complex designs

- Most trials are designed use a parallel-group design
- More complex designs (e.g. cluster randomised and adaptive trials) are also used
- How the sample size is calculated varies accordingly to the design

Question 3 – Complex designs

Should the guidance cover in-depth trials with more complex trial design?

- **Yes, need to cover in-depth**
- **No, a brief reference is enough**
- **Don’t know**

Topic 4 – Standardised effect size

- The magnitude of the effect on a standardised scale defines the value of the difference
  - E.g. for a continuous outcome, Cohen's d ''effect size'' cutoffs of 0.2, 0.5, and 0.8 for small, medium, and large effects are often used.
- Binary or survival outcome metrics (e.g., an odds ratio) can be utilised in a similar manner, though no widely recognised cutoffs exist.

Question 4 – Standardised effect size

Should the "standardised effect size" approach be considered a method?

- **Yes**
- **No**
- **Don't know**

Topic 5 – Value of information

- Value of information approach can be used to determine from a health economic perspective the optimal sample size
- Implicitly specifies a target difference but the conception is very different from conventional sample size approach

Question 5 – Value of information

Should the guidance cover the "value of information" approach?

- **Yes**
- **No**
- **Don't know**

Where next?

DELTA^2

- Conducting an update review of literature on methods
- Delphi process
  - You can be involved!
- CONSENSUS workshop in the autumn
- Working with funders to produce programme specific guidance
- Publications to follow

DELTA^2 – Get involved!

- **Contact Will Sones**
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We like to hear from:

- Researchers involved in trial sample size determination process
- Researchers involved in commissioning research
- Individuals working for funders/regulatory bodies

References

- Cook J, et al. Specifying the target difference in the primary outcome for a randomised controlled trial - guidance for researchers. *Trials* 2015; 16:12.
- Cook J, et al. Assessing methods to specify the target difference for a randomised controlled trial – DELTA (Difference ELicitation in TriAls) review. *Health Technol Assess* 18:28 2014.
- Hislop J, et al. Methods for Specifying the Target Difference in a Randomised Controlled Trial: The Difference ELicitation in TriAls (DELTA) Systematic Review. PLOS Med 11(5): e1001645. 2014.
- Cook J. Use of methods for specifying the target difference in randomised controlled trial sample size calculations. Clin Trials 2014;11:300-308.