How to define a clinically relevant difference: the DELTA (Difference ELicitation in TriAls) project

Jonathan Cook

Centre for Statistics in Medicine &
NDORMS,
University of Oxford

Outline

Background

- Trial size and sample size calculation
- DELTA project

Findings from the DELTA project

- Systematic review
- Initial guidance

Summary and future work

Determining trial size

Fundamental aspect of RCT design

- How many participants are needed?

Scientifically and ethically important

- Add to knowledge
- Legitimate experimentation

Impact upon trial conduct (e.g. 100 versus 2000)

- Management of project
- Timeframe
- Cost

Sample size calculation

Sample size calculation sets the trial size

- Provides reassurance

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 (i.e. δ)

What about the *(target) difference*?

Example – CATHETER trial

"Based on the Cochrane review and other data, the anticipated UTI level in the control group was 7.0% and a reasonable estimate of the effect of the intervention catheters would reduce this to 4.2% [absolute risk reduction 2.8%]. We estimated that based on an alpha error rate of 0.025 (to correct for the two principal comparisons) and 90% power, 1750 participants were required for each arm..."

Example - FILMS trial

"….. to detect a 6-point ETDRS score difference (an effect size of 0.5) using a t-test at a 5% level of significance and 80% power, it was estimated that 64 participants would be necessary in each group. This calculation was based on data from published studies.[14,15]"

Which methods could be used?

DELTA project

DELTA (Difference ELicitation in TriAls)

- Assessing formal methods for specifying the target difference
- Medical Research Council/NIHR UK funded

Three components

- Systematic review of methods within and outside the health field
- Survey of trialists to determine current practice
- Guidance on specifying the target difference and using available methods

Systematic review

Aim

- To identify potential methods

Methods

- Comprehensive search (biomedical/non-biomedical databases plus clinical trials textbooks)
- Included if reported a method for determining an important and/or realistic difference

Results

- 11485 abstracts screened (15 textbooks plus ICH)
- 1434 papers full-text assessed
- 777/7 included studies/methods

Specifying the target difference

Seven methods available

- Diversity in conception and implementation (judgement based, data driven or a combination)

Seek to identify a difference which is

- *Important* e.g. minimum clinically important difference (MCID)
- *Realistic* e.g. based upon prior evidence, or
- Both *important* and *realistic*

Methods for specifying the target difference

1. Anchor: The outcome is “anchored” by using a judgement (patient’s or health professional’s) to define an “important” difference.
2. Distribution: Methods based upon distributional variation/assumption e.g. a value that is larger than the inherent imprecision in the measurement.
3. Health economic: Assessment incorporating cost and benefit e.g. determine threshold recurrence rate based upon cost-effectiveness.
4. Opinion-seeking: Elicitation of expert opinion e.g. survey of clinicians.

Methods for specifying the target difference

5. Pilot study: A pilot study might be carried out to guide expectations.
6. Review of evidence base: Summarising current empirical evidence e.g. systematic review and meta-analysis.
7. Standardised effect size: The magnitude of the effect upon a standardised scale is used to define the value of the difference e.g. Cohen's (d) effect sizes.

How should methods be used and reported?

Guidance - use of methods

General guidance

- Perspective adopted is influential (e.g. patient, clinician)
- Justification more difficult for some outcomes (e.g. quality of life)
- More than one method might be appropriate

Guidance - use of methods (2)

Method specific guidance

- Anchor: particularly suited to quality of life measures
- Distribution: not recommended
- Health economic: varies in complexity; unlikely to be accepted as the sole basis
- Opinion-seeking: framing in trial context

Guidance - use of methods (3)

Method specific guidance (continued)

- Pilot study: useful in combination with other methods
- Review of the evidence base: consideration of reliability/relevance of evidence
- Standardised effect size: “fall back”

Guidance – reporting

State:

1. Any divergence from conventional approach
   - 2 parallel groups superiority trial
   - Neyman-Pearson framework
   - Standalone definitive study
2. Statistical parameters (e.g. significance level & power)
3. Primary outcome(s)

Guidance - reporting (2)

4. Basis for determining the target difference
   - *realistic* difference
   - *important* difference
   - both
5. Fully express the target difference
   - absolute and/or relative effect (e.g. A% vs. B%; odds ratio of C)
6. Justification for the target difference (e.g. use of any formal methods)

Example text – Reworked

FILMS trial: The primary outcome is ETDRS distance visual acuity. A target difference of a mean difference of 5 letters with a common standard deviation (SD) of 12 was assumed. Five letters is equivalent to one line on a visual acuity chart and is viewed as an important difference by patients and clinicians. The SD value was based upon two previous studies – one RCT and one observational comparative study. This target difference is equivalent to a standardised effect size of 0.42. Setting the statistical significance to the 2 sided 5% level and seeking 90% power, 123 participants per group are required; 246 in total.

Summary

- Target difference has a key role in RCT design

- Variety of methods available to inform what is an important and realistic difference in this context

Where next?

DELTA^2

- To build upon existing DELTA guidance
- Undertake update review of literature & engage with stakeholders to produce
- Working with funders to tailor the guidance

Where have we got to

- Stakeholder workshop held Sept 2016
- New guidance drafted and revised based upon stakeholder feedback
- Finalise guidance in (very) late 2017
- Dissemination to follow

Cook et al Trials, 2015

References

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