NIHR | Manchester Biomedical Research Centre

Rapid Translational Incubator Networking and Webinar

Generic aspects of Study Design for Experimental Medicine Studies and Trials

Thursday 17 October 2019, 12 – 12:30

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Today's webinar

- Generic aspects of Study Design for Experimental Medicine Studies and Trials
- Q&A

Speaker:
Chris Sutton, Senior Lecturer in Clinical Trial Statistics, Centre for Biostatistics, The University of Manchester (and Director of Methodology, Manchester Clinical Trials Unit)

Host:
Matt Krebs, Senior Lecturer in Medical Oncology, The Christie NHS Foundation Trust. BRC Cancer Precision Medicine theme

Outline

- Linking design to aims/objectives
- Principles of trial (or study) design
  - minimise bias
  - maximise efficiency
  - maintain quality

  and examples of how to address these
- Sample size
- Manchester Clinical Trials Unit (MCTU)
  - purpose and role
- Biostatistics Collaboration Unit

Study objectives

- Whatever the phase of trial or purpose of study, the key is to establish *specific* objectives (or research questions) which can be *assessed* using *valid* (and *reliable*) outcome measures
- Study objectives lead to the choices for:
  - Design
  - Outcome measures
  - Sample size
  - Statistical analysis

Principles of trial design - I

- All trials/studies should be designed to:
  - Minimise *bias*
    - *systematic* deviation from the true parameter of interest (e.g. 'effect')
    - caused by a structural defect in the trial
- When assessing *efficacy* we should ideally use …
  - Randomisation with allocation concealment
    - avoids selection bias
  - Blinding (although may be limited in applicability)
    - limits performance and (differential) ascertainment bias

Principles of trial design - II

- All trials (or studies) should also be designed to:
  - ➢Be efficient
    - use the optimal design to address the key objective(s)
    - aim to collect sufficient and appropriate data to address the trial objectives and use them well!
  - ➢Maintain ethical (and practical) acceptability
  - ➢Maintain quality

Phase I studies

Key objective is to determine maximum tolerable dose (MTD)

- Often to investigate pharmacokinetics and relationship with dosing
  - ➢ but traditionally separately from MTD assessment
- Traditionally uses 3+3 design
  - ➢ 0/3 have toxicity – escalate dose
  - ➢ Otherwise recruit 3 more
    - ○ 1/6 have toxicity – escalate dose
    - ○ 2/6 have toxicity – declare dose MTD
    - ○ ≥2/6 have toxicity – declare previous lower dose MTD
- OK, but **inefficient** …
- Alternatives, such as the continuous reassessment method (CRM) are more *complex* but more *efficient*

Phase II studies

Primary aim to assess whether efficacy is likely at the MTD

- Traditionally uses single-arm designs
  - Simon two-stage design (Simon, 1989)
  - Allows stopping if futility (i.e. effect likely to be insufficiently large) is established at end of Stage 1
  - If *not* futile at end of Stage 1, continue to recruit to (maximum) sample (Stage 2) to decide whether to progress to Phase III trial
- No **control** so reliant on appropriate historical controls
  - Substantial risk of misspecification of control outcome data

Phase II studies

- Sometimes uses two-arm or multi-arm designs
  - control arm?
  - multiple dose arms?
  - extensions to Simon's design (Thall et al., 1988)
- Have far larger sample sizes than non-randomised Phase II trials
- Again, these are **inefficient**
  - data from substantial number of patients traditionally not used in the overall assessment of efficacy at Phase II
- Increasing interest in more efficient *adaptive*, *seamless* Phase II/III designs

Sample size

- This depends on
  - Key trial/study objective(s)
  - Chosen design
  - Measure(s) to address key objective(s)
  - Strength of evidence required to ‘move forward’

Manchester Clinical Trials Unit (MCTU)

- Aim to collaborate and conduct high-quality clinical research that leads to individual and societal benefit.
- MCTU works with you to develop your application and trial design, and can provide information on:
  - study design;
  - statistics;
  - protocol development;
  - trial management;
  - data management with our Electronic Data Capture Database (REDCap Cloud);
  - quality assurance.

See https://www.bmh.manchester.ac.uk/research/manchester-ctu/

Biostatistics Collaboration Unit (BCU)

- Based in Centre for Biostatistics, School of Health Sciences
- BCU provided general statistical expertise for grant-funded research
- Statistics support for MCTU is provided through trial-specialist statisticians in Centre for Biostatistics / BCU
  - ➢ Co-Investigator (Lead Statistician)
    - ○ Academic in Centre for Biostatistics
  - ➢ Trial/Study Statistician based in BCU
    - ○ Research Associate or Research Assistant
- More on BCU in next webinar!

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Thursday 21 November, 12-12:30

Making best use of statistical advice and support in research

Jamie Sergeant, Lecturer in Biostatistics, Centre for Biostatistics, The University of Manchester

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