Past and Future

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Early Phase Clinical Trials Meeting
28th February 2019

Papers

Wheeler et al. BMC Medical Research Methodology (2019) 19:18
https://doi.org/10.1186/s12874-018-0638-z

BMC Medical Research Methodology

TECHNICAL ADVANCE Open Access

How to design a dose-finding study using the continual reassessment method

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Abstract

Introduction: The continual reassessment method (CRM) is a model-based design for phase I trials, which aims to find the maximum tolerated dose (MTD) of a new therapy. The CRM has been shown to be more accurate in targeting the MTD than traditional rule-based approaches such as the 3 + 3 design, which is used in most phase I trials. Furthermore, the CRM has been shown to assign more trial participants at or close to the MTD than the 3 + 3 design. However, the CRM's uptake in clinical research has been incredibly slow, putting trial participants, drug development and patients at risk. Barriers to increasing the use of the CRM have been identified, most notably a lack of knowledge amongst clinicians and statisticians on how to apply new designs in practice. No recent tutorial, guidelines, or recommendations for clinicians on conducting dose-finding studies using the CRM are available. Furthermore, practical resources to support clinicians considering the CRM for their trials are scarce.

Methods: To help overcome these barriers, we present a structured framework for designing a dose-finding study using the CRM. We give recommendations for key design parameters and advise on conducting pre-trial simulation work to tailor the design to a specific trial. We provide practical tools to support clinicians and statisticians, including software recommendations, and template text and tables that can be edited and inserted into a trial protocol. We also give guidance on how to conduct and report dose-finding studies using the CRM.

Results: An initial set of design recommendations are provided to kick-start the design process. To complement these and the additional resources, we describe two published dose-finding trials that used the CRM. We discuss their designs, how they were conducted and analysed, and compare them to what would have happened under a 3 + 3 design.

Conclusions: The framework and resources we provide are aimed at clinicians and statisticians new to the CRM design. Provision of key resources in this contemporary guidance paper will hopefully improve the uptake of the CRM in phase I dose-finding trials.

Keywords: Adaptive designs, Continual reassessment method, Dose escalation, Dose-finding, Maximum tolerated dose, Phase I trials

BJC British Journal of Cancer (2017) 117, 332–339 | doi: 10.1038/bjc.2017.186 BJC OPEN

Keywords: model-based design; dose-finding trials; phase I; CRM; 3 + 3

Embracing model-based designs for dose-finding trials

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Background: Dose-finding trials are essential to drug development as they establish recommended doses for later-phase testing. We aim to motivate wider use of model-based designs for dose finding, such as the continual reassessment method (CRM).

Methods: We carried out a literature review of dose-finding designs and conducted a survey to identify perceived barriers to their implementation.

Results: We describe the benefits of model-based designs (flexibility, superior operating characteristics, extended scope), their current uptake, and existing resources. The most prominent barriers to implementation of a model-based design were lack of suitable training, chief investigators' preference for algorithm-based designs (e.g., 3+3), and limited resources for study design before funding. We use a real-world example to illustrate how these barriers can be overcome.

Conclusions: There is overwhelming evidence for the benefits of CRM. Many leading pharmaceutical companies routinely implement model-based designs. Our analysis identified barriers for academic statisticians and clinical academics in mirroring the progress industry has made in trial design. Unified support from funders, regulators, and journal editors could result in more accurate doses for later-phase testing, and increase the efficiency and success of clinical drug development. We give recommendations for increasing the uptake of model-based designs for dose-finding trials in academia.

Links – Open Access

- https://statistics-group.nihr.ac.uk/research/early-phase-clinical-trials/
- https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/s12874-018-0638-z
- https://www.nature.com/articles/bjc2017186

Public Engagement

In early-phase clinical trials we want to find the largest dose of a new drug that limits the risk of side-effects to an acceptable level, to use as an upper limit on dosing in subsequent trials. This paper explains a type of modern trial design that finds this dose: Continual Reassessment Method (CRM). CRM re-analyses all the data after each patient and chooses the dose for the next patient that is expected to provide some benefit whilst controlling the risk of side-effects. Old-fashioned designs often had a fixed sequence of doses and only analysed at the end of the study. The dose chosen to take forwards for future research is more often correct and more patients are treated at, or close to, the chosen dose if the CRM design is used. This prevents the failure of promising new drugs due to the incorrect dose being used, means more is known about the side effects before more patients take the drug and leads to new drugs becoming available quicker for clinical use.

The paper is a practical “how to” guide for trialists and statisticians using the CRM design for the first time. It presents the planning decisions that need to be made in advance and gives guidance on operational aspects.

The paper was the result of a sequence of workshops organised by the NIHR Statistics Group that brought together several leading statisticians from academia and industry. We were aware of the inefficiencies of traditional dose-finding study designs and the lack of usage of modern methods, including CRM. Another paper from an overlapping group of authors investigates from a survey the barriers to adopting modern trial designs. This paper gives guidance on how to use the CRM design.

Courses

- **Practicalities in designing, grant funding, setting up and running a Continual Reassessment Method (CRM) dose finding phase I trial –** Sharon Love (MRC HTMR) – September 2019
- **Phase I dose-finding trials: practical application of new designs for statisticians** – Graham Wheeler (UCL) – October 19

Dissemination Ideas?

- Webinar
- You Tube
- Local Talks
- Conferences
  - NIHR Annual Conference 20th June
  - ICTMC October 6-9th October
- Twitter - please do tweet about today
  - #NIHR #earlyphasetrials
  - Highlights for you
  - What have you learnt?
- Feedback form, slides, overall summary on the webpage

Action Points From Today?

- CRM
- Basket/Umbrella/Platform
- Lessons from real examples
- Regulatory aspects

Thanks

- NOCRI
- Birmingham BRC
- Christina Yap and Aimee Jackson
- NIHR Statistics Group