MRC HTMR Network Project N97 Final Report

Title: Investigating the reasoning behind the use of non-randomised single-arm designs in phase II clinical trials

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Budget: £3071

Background, aims, and objectives

- Most phase II oncology trials were historically designed using non-randomised, single-arm, approaches. However, over the past 25 years or so, the number utilising randomised designs has steadily increased, with several reviews of completed phase II trials now available that together clearly exemplify this trend.
- What the reviews of completed phase II trials did not examine in detail, though, was *why* the number of randomised designs has steadily increased. That is, they did not explore the reasonings around the choice between randomised and non-randomised approaches in practice.
- This project therefore aimed to elucidate such reasonings, primarily via a survey and follow-up discussions conducted with UKCRC Registered CTUs. It then aimed to create an associated guidance document for inclusion in the Network Guidance Pack.

Achievements and outputs

- A literature review, which involved the screening of over 7500 articles, was conducted to identify historical and contemporary arguments on how phase II trials should be designed. The findings from this review were used to construct an article focusing on the use of randomisation in phase II oncology trials. This article has now been published in the *Journal of the National Cancer Institute*[1].
- Based on the findings of the aforementioned literature review, a survey on key considerations around phase II oncology trial design was constructed for circulation to lead statisticians at UKCRC Registered CTUs (ethical approval to proceed in this work provided by Newcastle University). It consisted of 24 questions and was carried out using Survey Monkey as intended. Unfortunately, only nine complete responses were accrued (for reference, the UKCRC CTU Network website suggests 28 CTUs have experience in phase II studies and cancer trials), and follow-up discussions were then carried out with five CTU representatives. However, this work still highlighted several interesting considerations:
    - By and large, statisticians agreed that randomised designs should often be viewed as preferable to single-arm designs. However, in practice, the use of randomised designs is often inhibited by (a) the number of available participants or (b) the level of available funding support.
    - The breadth of available phase II designs and associated difficulties in identifying a design for a given deadline may typically lead to a preference for more familiar methods. A related consideration is the value of easy-to-use design software, which may become more important as phase II trials are increasingly conducted using complex designs (e.g., adaptive and basket designs).

    - Increased use of more complex designs could perhaps be aided by the availability of more support materials (e.g., practical guidance/overview articles on available designs with particular features in common) and suitable training courses.

- An abstract was submitted to the Annual Meeting of the Society for Clinical Trials, as planned, and was subsequently accepted for oral presentation. MG gave the talk to an audience of approximately 50 delegates, describing both the literature review and the survey's findings.

- As planned, based on the above, a document for inclusion in the MRC HTMR Guidance Pack has been developed that provides a summary of the key considerations on when randomised and non-randomised designs may be most appropriate in phase II. In addition, because the literature review identified a wider variety of material relating to phase II oncology trials (i.e., not just that which focuses on randomisation), a website has also been created that curates a larger selection of information relating to phase II trials. The current draft version is available at https://mjgrayling.shinyapps.io/phaseII/. In particular, it incorporates a searchable tool for suitable design methodology determination.

Next steps

- The website will be developed further to include additional information on phase II oncology trials. In particular, details relating to recent published design methodology that can be incorporated in to the searchable tool will be added (see below). Following this, the website will be given a more permanent URL address and will be disseminated through a variety of means (including as part of a talk MG is giving at ICTMC 2019). Its content will then be revised and updated as appropriate, and its uptake will be monitored via Google Analytics.

- It is clear that a large volume of design methodology for phase II oncology trials has been published since the last comprehensive review of this type of literature. An up-to-date review is therefore now being planned in order to identify as much appropriate available methodology as possible.

- The work conducted as part of the project highlighted the fact that, in comparison to single-arm designs, there is relatively little software available for the now far more often utilised randomised phase II designs. Therefore, an R package is being developed to ease the determination of such trial designs[2]. It will be included in the website discussed above to allow design determination without the need for command line executions and will be used in a planned course on modern phase II design.

References

[1] Grayling MJ, Dimairo M, Mander AP, Jaki TF (2019) A review of perspectives on the use of randomization in phase II oncology trials. *JNCI: J Natl Cancer I* **111**(12)**:**djz126. DOI: 10.1093/jnci/djz126.

[2] Grayling MJ (2019) ph2rand: Design of randomized comparative phase II oncology trials. URL: https://github.com/mjg211/ph2rand.