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Considerations and recommendations on using randomised designs in phase II oncology trials

Prior to approximately the year 2000, almost all phase II oncology trials were conducted using single-arm (i.e., non-randomised) designs, with tumour response[1,2] as their primary outcome variable[3,4]. Since then, the number of phase II oncology trials that have utilised randomised designs has grown substantially, with recent review work suggesting approximately one third of phase II oncology trials now use randomised designs[5].

This document summarises the main arguments that have been appeared in the literature for and against the use of randomised designs in phase II oncology trials. In addition, consensus recommendations on phase II oncology trial design, randomised vs. non-randomised, are given.

For further details see Grayling *et al* (2019)[6]. Additional extended guidance is also available in Brown *et al* (2012)[7], which describes a framework for determining a suitable phase II oncology trial design, and at a companion website to this document, which provides a wider range of information on phase II trials.

Introduction

In many disease areas, randomised designs are the norm in phase II. However, this is not the case in oncology. The use of single-arm designs was historically accepted in oncology because of the cytotoxic nature of the treatments under investigation. That is, the treatments aimed to shrink tumours, and therefore given that tumours do not typically spontaneously shrink, it was viewed as appropriate to forego a randomised comparison to a concurrent control arm.

Following the development of several cytostatic targeted therapies though[8,9], concerns arose around the use of tumour response as the primary outcome[10-13]. Numerous alternative outcome variables were suggested[14,15], and with this many authors argued that randomised designs were essential to either (a) account for a tumour's history when utilising time-to-event outcomes such as progression-free survival, or (b) to assist in hypothesis specification when utilising a novel outcome for which little historical data is available to help specify a null hypothesis[12,16-19].

In addition, low success rates in phase III led to arguments that randomised designs are needed in phase II to improve decision making. Specifically, it was contended that single-arm trials do not provide high enough quality evidence to reliably differentiate between the activity of established efficacious therapies and novel treatment regimens.

Consequently, a large body of literature has grown around when randomised designs may be more appropriate in modern phase II trials than single-arm designs. Such considerations are described briefly below.

Randomised vs non-randomised designs: Considerations

- It has been argued that single-arm designs have performed poorly in predicting long-term clinical benefit, and that randomised designs would improve decision making at the end of phase II[14,16,20-23]. However, it is important to recognise that to date there remains no evidence to suggest that this has been the case[24,25]. It has been argued, though, that such retrospective evaluations of trial success rates are likely to be influenced by publication bias[26].
- It is well known that randomisation will, given a sufficiently large sample size, balance (unknown) prognostic factors between treatment arms. Several articles have contended that randomisation will therefore allow treatments activity levels to be more reliably compared than non-randomised designs. However, other authors have noted that with the sample sizes often used in phase II, randomisation cannot guarantee such balance[26-30], and that modelling could be used instead to account for prognostic factors in single-arm trials[31]. In addition, much caution has been expressed against the pitfalls of small randomised trials[30]. As a counterpoint to assertions on the utility of modelling techniques for single-arm trials, though, it has been argued that such approaches cannot be viewed as reliable, even if they will likely improve decision making over a simple unadjusted analysis of non-randomised data[20,32].
- Whilst several articles have argued for use of more novel endpoints when assessing the activity of cytostatic agents[28,33,34], which may necessitate the use of randomised designs, others maintain that use of tumour response

is still often appropriate. This may be particularly true for biomarker-guided trials in which high levels of response are anticipated[35]. With this, the appropriateness of single-arm designs may be increased.

- It has been suggested that randomised designs may afford a stronger case for seeking regulatory approval if a highly significant treatment effect is observed, which would be more challenging when only non-randomised data is available[26]. Yet, there are cases where results from single-arm trials have led to licensing, and subsequent analyses suggest that follow-up trials have validated the results from the non-randomised evaluations in most instances[36].
- Single-arm trials have long been favoured for the simplicity of their design, conduct, and analysis. However, articles have highlighted that simplicity should not in general be an over-riding reason for utilising a particular trial design, and that the improved quality of data provided by randomised designs makes them worth their increased complexity[13,14,23]. Subsequently, several simulation studies have been conducted to assess the decision making abilities of single-arm and randomised phase II designs under a variety of factors[37-43]. For the most part, they have recommended that randomised designs may often be worth their increased cost.
- Concerns have been expressed against single-arm trials because of the possibility that enthusiasm may result in either (a) the historical response rate being set too low[44,45], or (b) the enrolment only of patients that seem promising[21]. It has been noted, though, that randomised designs can also easily be influenced by selection bias, differential loss to follow-up, and patient drop-out[16].
- Randomised designs have most often been disfavoured because they require substantially larger sample sizes than their single-arm counterparts to attain the same type-I and type-II error-rates[26,46,47]. It has been highlighted, however, that only in randomised designs can error-rates ever be accurately known[26,32], and that required larger sample sizes can be mitigated by allowing one-sided testing and the use of increased error-rates[10,16,19,20,45,48]. As a counterpoint, it has been noted that increasing error-rates in phase II may simply lead to a larger number of negative phase III trials, negating a supposed advantage of randomising in phase II.
- It has been suggested that single-arm trials should be preferred on ethical grounds, as all patients will receive the experimental treatment[46]. This would be particularly true when large response rates have been observed previously. This though has been argued to be a rare scenario in practice, with equipoise generally holding at the commencement of phase II, making randomised designs entirely appropriate[23,32].
- Historically controlled trials have been criticised because their approach to specifying the target level of activity may be unreliable due to changes in supportive care, eligibility criteria, and many other factors[20,26,49-51]. But, numerous authors have pointed to the availability of well-established databases for particular cancer types through which single-arm trials could be more reliably designed[26,31,49]. It is reasonable to argue that the proliferation of trial data repositories may enhance arguments for single-arm trials on this ground in the future.

Randomised vs non-randomised designs: Recommendations

Two articles that provide group-based recommendations on appropriate phase II design are available[28,52]. In addition, Gan *et al* (2010)[26] contains an extensive point/counterpoint discussion on the use of randomisation and incorporates a table on several phase II design scenarios with indications on whether they would typically imply a preference for randomised or non-randomised designs. From these articles and many others, Grayling *et al* (2019)[6] outline the following contentions that have generally been agreed upon in the literature:

- Both single-arm and randomised designs are appropriate in certain settings. There is no assertion that all phase II trials should now use randomisation. However, it has been agreed that the number of randomised trials should increase.
- Single-arm designs are particularly appropriate for/when:
    - Novel, particularly single-, agents when tumour response is anticipated.
    - Rare cancers, when the number of potential patients is limited, and the sample size required by a randomised design would likely not be achievable.
    - It is anticipated that the tumour response rate may be substantially higher than that for the current standard of care, for example in certain biomarker-guided trials.
    - When no effective treatment is available, such as in certain late-stage disease settings.
    - If a reliable historical database exists.
- Randomised designs are particularly appropriate for/when:
    - Combination therapies that combine novel and established components, in order to evaluate the contribution of the novel component.
    - The primary outcome is a time-to-event variable.
    - There is a lack of suitable historical data upon which to design a single-arm trial.
    - The population is anticipated to be particularly heterogeneous.

With the above, a potential useful distinction to make is between phase IIA and phase IIB clinical trials. The former provides proof of concept and may more often resemble classical single-arm phase II trials, while the latter aims to provide a robust go/no-go decision on whether to proceed to phase III and thus may be expected to utilise randomisation.

Such a distinction could be useful not only to help explain the reason for the chosen design but may also more accurately reflect modern drug development where it could be felt inadvisable to proceed to a large confirmatory phase III trial without randomised evidence.

However, caution has been expressed against conducting separate consecutive phase II trials in this manner because of the possible increased length of development[52].

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