Archives of
Disease in Childhood

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Journal:	*Archives of Disease in Childhood*
Manuscript ID	edpract-2019-317826.R1
Article Type:	Research in practice
Date Submitted by the Author:	11-Oct-2019
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Keywords:	Evidence Based Medicine, Statistics

Title

Adaptive trial designs: what are multi-arm, multi-stage trials?

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Word Count excluding title page, abstract, references, figures and tables

986 words

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Abstract

Clinical trials can be separated into phases I, II, III or IV. New compounds usually have to go through each phase sequentially or in separate trials. This poses significant administrative and financial hurdles to the introduction of new medication into routine clinical use. The so-called multi-arm, multi-stage (MAMS) design is a novel form of adaptive trial design which allows several treatments to be assessed concurrently under a single trial framework. In this article we discuss the pros and cons of the MAMS design using examples from the literature to illustrate the point.

Introduction

Clinical trials can be separated into phase I (dose finding and safety), phase II (activity or early efficacy), phase III (efficacy compared to current standard of care) and occasionally phase IV (post-marketing studies). A new compound would usually have to go through phase I-III studies sequentially with all of the financial and regulatory hurdles this poses. A recent study has estimated that only 13.8% of compounds tested will be successful in achieving a marketing license.[1]

Adaptive designs are an extensive class of flexible tools which use accumulated data in the trial to make *pre-planned* adaptations to the trial's course. They can be used in all trial phases. The adaptations can include stopping an arm early for futility or safety, closing recruitment to an arm early if there is strong evidence of efficacy, changing of target sample size or allocation ratios. They are usually more efficient, informative and ethical than traditional fixed designs (where no interim adaptations are permitted). They can often offer savings in resources and even number of patients (figure 1).[2]

A novel paradigm for conducting adaptive trials, which allows several treatments to be assessed concurrently with pre-planned interim adaptations, is the so-called multi-arm, multi-stage (MAMS) design. We will review the pros and cons of MAMS trials in this article.

Multi-arm, multi-stage (MAMS) trials

Due to high failure rates, substantial cost and time required, novel trial methodologies are required to streamline the pipeline of drugs from pre-clinical work to proven treatments. One such adaptive design is the MAMS trial. MAMS trials were first reported over 20 years ago as a way to accelerate the process of drug development.[3]

MAMS has been more commonly implemented in Phase II/III settings, though it can be applied in any trial phase. Rather than a series of separate phase II/III studies, MAMS trials aim to answer multiple questions simultaneously under the same regulatory framework. Multiple different treatment options can be compared simultaneously, often against a control arm.[4] These can either be different drugs/combinations of drugs or different doses of the same drug. Through the use of interim analyses with pre-determined adaptation rules, different arms can be modified or even closed to further recruitment to focus the number of patients more on drugs which are showing good efficacy.[5]

One of the best-known examples of a MAMS trial is the STAMPEDE trial which looked at treatment of men with advanced or metastatic prostate cancer. The trial initially opened in 2005 with 6 arms (one standard of care arm and 5 experimental arms) with 2 planned interim analyses. Since opening, the initial 5 experimental arms have closed and new arms have subsequently been added. Clear evidence emerged that the addition of docetaxel to standard chemotherapy improved the survival of patients which resulted in the protocol being amended to allow the use of docetaxel as standard of care going forward from 2016 (figure 2)

Another example of a seamless Phase II/III MAMS trial is a paediatric rare cancer trial called rEECur (ISRCTN 36453794). This trial aims to identify the optimal treatment for relapsed/refractory Ewing's sarcoma, by comparing four commonly-used chemotherapy regimens, with a drop-a-loser approach.[7] There are two pre-planned interim analyses, where the least promising arm (based on objective response rate) will be dropped after each stage. In the final stage, the trial will proceed seamlessly to phase III comparing the two best remaining arms (based on progression free survival).

MAMS trials have also been proposed as potentially attractive designs for studies in multi-drug resistant TB and HIV.[8]

Benefits and risks of MAMS trials

The biggest advantage of a MAMS trial is the ability to answer multiple research questions simultaneously under a single trial protocol and regulatory framework rather than answer them sequentially or via a series of separate trials as in the traditional paradigm. The latter will require a longer period of time, substantial higher costs as well as potentially larger number of patients.

Furthermore, using amendments to trial protocols, MAMS can easily lend itself to a platform design where new arms can be added whilst the study is ongoing. This is much more efficient that designing a new trial.[6]

MAMS trials can also be considered more ethical and beneficial for patients as they reduce the number of patients treated at ineffective doses or with ineffective or harmful drugs as well as maximising the numbers treated on more efficacious arms (Figure 1).

There are some limitations of, or risks associated with MAMS trials. Due to the smaller number of patients at the interim analyses, there is a risk that potentially efficacious treatments may be rejected if they meet the pre-defined stopping rules.[5,9,10]

In addition, MAMS trials can be more resource intensive in the initial design phase and during trial conduct as there are multiple arms and multiple stages. The increased complexity may result in clinicians being less keen on using them due to lack of awareness or need for greater specialist input from statisticians.[10]

Though adaptive designs, such as MAMS, often provide notable efficiency benefits, there are situations where they may not be worthwhile. It is vital that careful consideration of key factors (including outcomes, recruitment, data quality and trial complexity) should be built into deciding and developing the most appropriate trial design to answer the trial's objectives.[10]

Conclusions

Historically, clinical trials have been designed using traditional phase I-III methodology with sequential or separate trials that can take many years and have a low overall success rate in delivering drugs to patients.

MAMS trials aim to overcome many of these difficulties by combining multiple experimental arms into the same study. Through the use of interim analyses, MAMS trials can be more efficient and ethical by removing non-performing arms earlier and channelling more patients into the most efficacious arms. Although not widely used in paediatrics yet, some trials are being designed and run in this fashion. It is likely to increase further in the future.

Footnotes

Contributors: GCM wrote and revised the initial manuscript. CY wrote, reviewed and revised the manuscript prior to submission. Both authors approved the final manuscript.

Competing interests: None declared

Funding: CY is funded by Cancer Research UK Grant No. C22436/A15958

Provenance and peer review: Commissioned; externally peer reviewed.

Legends

Figure 1: Benefits of adaptive trial designs. Adapted from: Adaptive designs in clinical trials: why use them, and how to run and report them.

Figure 2. Schematic diagram of STAMPEDE trial. Adapted from: This is a platform alteration: a trial management perspective on the operational aspects of adaptive and platform and umbrella protocols. [6]

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