

Adaptive clinical trials: an introduction

What are the advantages and disadvantages of adaptive clinical trial designs?



Introduction

Adaptive clinical trial design is becoming a hot topic in healthcare research, with some researchers arguing that adaptive trials have the potential to get new drugs to market quicker. In this article, we explain what adaptive trials are and why they were developed, and we explore both the advantages of adaptive designs and the concerns being raised by some in the healthcare community.

What are adaptive clinical trials?

Adaptive clinical trials enable researchers to change an aspect of a trial design at an interim assessment, while controlling the rate of type 1 errors.¹ Interim assessments can help to determine whether a trial design is the most effective one for answering a specific research question, or if the accumulating data suggests that a trial should be stopped early for safety reasons.¹

How and why were adaptive clinical trials developed?

In 2004, the FDA published a report on the problems faced by the scientific community in developing new medical treatments.² The report highlighted that the pace of innovation in biomedical science is outstripping the rate of advances in the available technologies and tools for evaluating new treatments. Outdated tools are being used to assess new treatments and there is a critical need to improve the effectiveness and efficiency of clinical trials.²

The current process for developing new treatments is expensive, takes a long time and in some cases, the development process has to be stopped after significant amounts of time and resources have been invested.² In 2006, the FDA published a "Critical Path Opportunities List"³ that listed potential ways of reducing the time it takes to develop and approve new medical treatments.³ The use of novel designs for clinical trials (including adaptive trial designs) was one of the methods identified for achieving this aim, and the European Medicines Agency (EMA) and the FDA have published guidance on the use of adaptive clinical trials.^{1, 4} Recently, the move towards the use of personalised (or precision) medicine has led to an increasing interest in adaptive trial designs with subgroup selection.⁵

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What are the benefits of adaptive clinical trials?

As discussed previously, adaptive trial designs allow for changes to be made to a clinical trial after an interim analysis of data from the trial itself¹ or from knowledge obtained from other clinical trials.^{1, 6} The benefits of being able to do this include:⁶

- Reducing the time it takes to develop a new medical product
- Correcting assumptions that were made at the start of the trial if they are subsequently found to be incorrect
- Helping to identify the treatments that show the most promise at an early stage in the development process
- Increasing the likelihood that the trial will be successful

Examples of adaptive trial designs include group sequential designs, response-adaptive designs and adaptive dose escalation designs. The specific benefits of these types of designs are listed below:

Group sequential designs

Researchers can stop a trial early⁶ (for example, if an interim analysis shows that an experimental treatment is effective⁷ or that the results are unlikely to be statistically significant.⁸)

Response-adaptive designs (also known as outcome adaptive designs)

In these trials, patients are allocated dynamically to treatments depending on what the accumulating outcome data from the trial show.^{9, 10} This means that more patients can be assigned to treatments that are more effective.¹⁰



Adaptive dose escalation designs

These trials use a continual re-assessment method (CRM) that's based on dose toxicity models to establish what the maximum tolerated dose (MTD) of new drug is. This increases the likelihood of identifying the correct MTD and it's also possible to add groups of participants to the trial after it has started.⁶

What are the arguments against the use of adaptive clinical trials?

Adaptive clinical trials are appealing because of their flexibility, the potential to increase efficiency and the ability to identify which treatments are the most effective with limited resources.⁶ However, there are concerns that making changes to the design can introduce bias and may affect the integrity and validity of the trial.^{6, 11}

Any major changes to a trial design may result in changing the target population, which means that the results from the trial may not be able to answer the question that the original trial was designed to investigate.⁶

In response-adaptive trials the randomisation process is changed so that more patients are assigned to the treatment that is more effective. However, for ethical reasons, researchers should tell patients that they have more chance of being allocated to the treatment that's more effective the later they enrol in the trial. Patients who are less unwell may choose to enrol later in the study (to increase their chances of being allocated to the treatment that's more effective) and patients who are more unwell may enrol earlier because they need early access to the treatment. Thus, disease severity is a potential confounding factor and could introduce bias into the trial.⁶

The use of accumulated clinical data in adaptive clinical trials may introduce operational bias, resulting in:⁶

- p values that are incorrect
- Unreliable confidence intervals
- An inability to maintain the rate of type I errors at the significance level that was pre-specified before the start of the trial

There are concerns that making changes to trial designs can introduce bias and may affect the integrity and validity of the trial.



Adaptive trials offer flexibility but should not be seen as a way to avoid thorough planning.

Summary

Despite their flexibility, adaptive clinical trials should not be seen as a way to avoid the need for thorough planning, which is a requirement for conducting conventional clinical trials.¹

Researchers must be able to show that there is a robust justification for making any modifications to a clinical trial¹ and there is a need for more regulatory guidance on how to conduct specific types of adaptive clinical trials.⁶ The safety of participants in an adaptive trial is of utmost importance, and regulatory bodies should monitor the safety of participants throughout the trial period.⁴

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