

# Adaptive Designs

This document consists of a brief description of adaptive designs and gives an overview of some of the main points to consider for clinical trialists.

In its broadest sense an adaptive design is one that uses accumulating data from the trial to decide on how to modify aspects of the trial without undermining the validity or integrity of the trial.

There are clear differences between whether these adaptations are planned prospectively rather than retrospectively on inspection of some of the data.

The main reasons to plan an adaptive design are ethical, efficient use of resources, to avoid making strong assumptions in the planning stage of a study and to make more accurate decisions when it comes to determining safety and efficacy.

The FDA have provided a draft guidance on adaptive designs for drugs and biologics:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm201790.pdf>

and adaptive designs for medical device clinical studies:

<http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm446729.pdf>

while the EMA has an older document about adaptive designs, dated 2007, that is available at:

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003616.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003616.pdf)

## Adaptations

Some of the methods used to adapt a clinical trial include:

1. Stopping one or more arms of a trial early for futility or efficacy and/or toxicity/safety;
2. Altering the allocation ratio, this could be based on information from responses or covariates,
  - a. either by favouring better arms or
  - b. dropping some arms completely;
3. Altering eligibility criteria;
4. Altering the size of the study; and
5. Altering primary endpoints.

The context of when to do adaptive trials is equally important, and the types of acceptable designs may vary between early and late phase trials and the population studied. Some examples are given below.

1. For early phase trials in patients with a life-threatening or rare disease where several potential treatments exist it may be very important to find the most promising ones as quickly as possible.
2. For rare diseases, the use of adaptive designs may make a trial viable when a traditional design is not.
3. There is less information about an intervention in the early phase of trials and they could benefit from more flexible designs.
4. In confirmative trials the methods will need to convince the community at large as well as the study team. This may, therefore, influence the choice of approach.

## Implementation

It is important to recognize that every adaptive study is different and requires special attention. It is therefore crucial to involve a statistician with expertise in such studies. The Adaptive Designs Working Group (ADWG) offers consultation to trialists who wish to consider an adaptive design and support in implementing adaptive designs. For enquiries or further information please get in touch with ADWG outreach officer Philip Pallmann ([p.pallmann@lancaster.ac.uk](mailto:p.pallmann@lancaster.ac.uk)). Another option is to contact the Hub Network Methodology Advisory Service for Trials (MAST):

[http://www.methodologyhubs.mrc.ac.uk/methodology\\_advisory\\_service.aspx](http://www.methodologyhubs.mrc.ac.uk/methodology_advisory_service.aspx)

Some of the most important points to consider are:

1. A clear rationale of why an adaptive design is needed should be developed;
2. Designing an adaptive study is more time consuming (an industry benchmark is at least 3 months of planning) than fixed sample designs and so plenty of time should be scheduled prior to the grant submission deadline to explore these methods. This may require simulation based methods to check operating characteristics of the design, such as for example the significance level, the statistical power or, in a study with multiple doses, the frequency with which the correct dose is selected;
3. Phased periods of recruitment, rather than recruiting patients as fast as possible, may often be a more efficient approach when an adaptive design is being used and the merits should be contrasted with the impact on momentum at participating sites;
4. There can be substantial effort required to create and validate bespoke software (validation is challenging) to facilitate the adaptations, although dedicated software for this is increasingly becoming available;
5. Special methods are available for computing p-values and confidence intervals and avoiding the bias in estimation of treatment effects after the use of an adaptive design, and these should be used whenever possible;
6. Formal interim analyses should be reported to a trial IDMC, which should have the final responsibility for confirming any adaptation. The independence and expertise of the IDMC and TSC which will make recommendations for adaptation is critical, as is agreeing a detailed IDMC and TSC charter. It is desirable to be able to respond to unplanned analysis requests from the DMC to address unexpected issues identified by the DMC without requiring unblinding of other study team members;
7. Interim analyses may require unblinded assessments which can introduce bias when estimating the effect of an intervention;
8. Documentation of all processes and actions should be maintained, and may be required for regulatory and/or publication purposes;
9. To make timely and fully informed decisions requires efficient data collection and cleaning throughout the trial, which is resource intensive. However, this in turn should reduce the time required for the final analysis in preparing the data sets for database locking, unblinding and final analysis;
10. Given that an adaptive design may terminate accrual or treatment early or go on to a planned end, funding arrangements will need to be flexible. This may be challenging if, for example, staff are recruited on fixed term contracts;
11. Careful planning is necessary for the preparation of data for interim analyses and for the reporting of analyses to the IDMC and the reporting of conclusions from the IDMC to the TSC;
12. Other logistical issues may need to be considered, for example drug supply and distributions, randomisation and recruitment.