

# Implementing and Managing Adaptive Designs for Clinical Trials

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The average expenditure related to development of a drug candidate has doubled over the last decade. Each day that informed decisions about a drug candidate are delayed carries with it opportunity costs, tangible costs and patient risk. One way to address these challenges – that is currently receiving significant attention from pharmaceutical companies and regulatory agencies – is adaptive trial design.

## **ADAPTIVE TRIAL DESIGN: AN OVERVIEW**

Adaptive trial design refers to a clinical trial methodology that allows trial design modifications to be made after patients have been enrolled in a study, without compromising the scientific method. In order to maintain the integrity of the trial, these modifications should be clearly defined in the protocol. When designed well, an adaptive trial empowers sponsors to respond to data collected during the trial. This is achieved by re-focusing the trial in a way that maximises the impact of each subject's contribution. Examples of adaptive trial designs include dropping a treatment arm, modifying the sample size, balancing treatment assignments using adaptive randomisation or simply stopping a study early for success or failure.

In a standard trial, safety and efficacy data are collected and reviewed by a monitoring board during scheduled interim analyses. However, aside from stopping a study for safety reasons, very little can be done in response to that data. Often, a whole new study must be designed to further investigate key trial findings.

In an adaptive trial, the sponsor might have the option of responding to interim safety and efficacy data in a number of different ways, including narrowing the trial focus or increasing the patient population. An example of narrowing the trial focus includes removal of one or more of the treatment arms based on predetermined futility rules. Alternatively, if the data available at the time of the review do not allow for a clear decision between utility and futility, it might be decided to expand the enrolment of patients on one or more treatment arms beyond the initially targeted sample size.

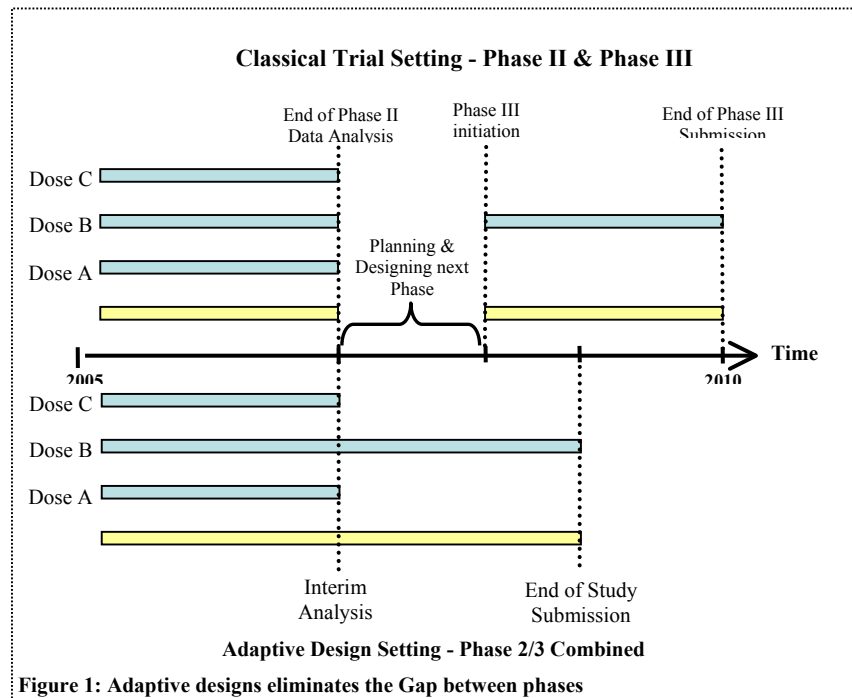
Another example of adaptive design is the response-adaptive. In a response-adaptive setting, patients are randomised to treatment arms based on the response to treatment of previous patients. In a response adaptive trial, real-time safety and efficacy data can be incorporated into the randomisation strategy in order to influence subsequent adaptive randomisation decisions on a patient-by-patient basis. An example of response-adaptive

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randomisation is ‘play-the-winner’, which assigns patients to treatment arms that have resulted in fewer adverse events or better efficacy.

As these examples demonstrate, the adaptive design concept can be utilised in a number of different ways to increase trial flexibility. In a well-designed adaptive trial, that flexibility can result in lower drug development costs, reduced time to market and improved patient safety. Cost reduction is achieved by stopping unsuccessful trials earlier, identifying successful trials sooner, dropping unnecessary treatment arms or

determining effective dose regimens faster. Time to market can be accelerated by identifying successful trials sooner and reducing, or removing entirely, the lead time between trial phases, especially Phases II and III. Patient safety is improved because adaptive trials tend to reduce exposure to unsuccessful treatment arms (which are dropped early), and increase access to effective treatment arms (via response adaptive randomisation).



## ENABLING TECHNOLOGIES

While adaptive design thought leaders differ on a number of theoretical statistical issues, one issue they nearly all agree on is the critical role that technology plays in support of adaptive design implementation. Technology is critical because it empowers clinical teams with real-time information, and then enables them to plan and quickly implement seamless changes in response to that information. The key enabling technologies for adaptive trial design are interactive voice response (IVR), electronic data capture (EDC), and clinical trial material forecasting systems.

### IVRS

Interactive voice response systems are among the most widely used of technologies in the clinical trial industry. They are comprised of a phone-based user interface that is connected by a complex IT system to a central database. Within the clinical trial setting, IVR systems are used to perform a variety of patient and clinical trial material management related functions. The most common clinical uses of IVR technology are patient randomisation and dosing. IVR systems can be deployed in simple settings to perform functions like central randomisation, or they can be used to facilitate more complex services such as dynamic treatment allocation or automated dose titration. Since most modifications in an adaptive trial design setting involve sample size, dosing, and/or randomisation, IVRS is a key enabling technology for adaptive trials.

### EDC

Electronic data capture (EDC) is the concept of collecting patient clinical data directly from the investigative site electronically, and transmitting the data over the Internet, rather than using paper. Although EDC technologies for clinical trials have been used for 20 years, it is only in recent times that EDC use has become widespread. With EDC, sites are required to enter relevant patient information via an electronic interface – often a web-based application. Data are automatically checked against predefined rules when entered or saved, and can be immediately queried for data clarification when submitted. As a result, EDC systems typically generate higher quality data that is available much more quickly than paper-based alternatives. Since the ability to make

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informed decisions in an adaptive trial setting is directly dependent on the quality and speed of the data that is available, EDC is a key enabling technology for adaptive trials.

## Clinical Trial Material Forecasting Systems

Most IVRS vendors provide clinical supplies management services in support of studies that utilise their IVR systems. These services often include clinical supplies demand projection, inventory management from depot to site, tracking from depot to site to patient and expiry date management. Clinical supplies are usually managed in real-time based on patient enrolment rate, protocol specific information and supply inventory levels. This type of supply management strategy works adequately for projecting need over a short timeframe at the site or patient level. However, when the goal of utilising an adaptive design is to combine Phases (typically Phase II and Phase III), more powerful and proactive forecasting technologies may be necessary.

Clinical trial material forecasting systems provide clinical supply professionals a vehicle to analyse overall supply requirements on a study or programme level. Based upon protocol-specific information and clinical supply chain requirements, forecasting tools simulate patient enrolment and project time-phased patient demand of clinical supplies. These tools can be used to simulate a variety of clinical trial scenarios, including combined phase adaptive trials. As a result, forecasting technologies enable users to maximise clinical supplies utilisation, especially when multiple dose levels are being investigated. Since the ability to plan appropriate drug supply strategies, in support of potential treatment arm modifications and study samples size adjustments, is critical to the success of many adaptive trials, forecasting is a key enabling technology.

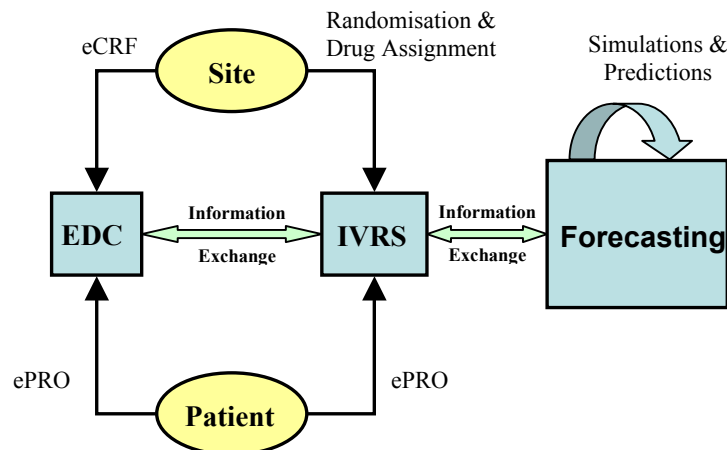


Figure 2: Interactive Clinical Systems integrated in an adaptive designs setting

## MAXIMISING THE BENEFIT

IVR systems are well suited for adaptive trials because they are simple to implement and use, and they provide the flexibility to easily implement adaptive modifications. In addition, the algorithms incorporated in IVR systems are transparent to users (including project personnel), and therefore allow adaptive changes to be implemented without compromising the study blind. For example, consider a design that employs an adaptive randomisation methodology to assign patients among four arms (three active dose arms and a placebo arm). Should an interim review reveal the futility of one of the treatment arms, an IVRS would allow for automated, immediate and transparent implementation of adaptive modifications, including removal of the futile treatment arm and adjustment of the enrolment targets for the remaining arms.

While IVRS plays a critical role in executing key interactive trial activities like patient randomisation and dosing, it is limited by its inability to collect and report efficacy and safety data. As a result, IVRS should be used in combination with EDC in the adaptive trial setting. EDC facilitates real-time data collection and review, therefore empowering sponsors to make informed decisions at interim assessment points.

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Adaptive trials are most successful when IVRS, EDC and clinical supplies forecasting systems are all used. However, merely using these technologies still falls short of maximizing the contribution that they can make in an adaptive trial. In order to reap the full benefit of adaptive trial design, these technologies should be designed and implemented in an integrated manner.

Imagine a trial in which subject number, patient randomization data and drug kit number generated by an IVR system flow immediately into an EDC system. Clinical site staff use the EDC system to enter safety data using a menu from the appropriate dictionary (such as MedDRA, COSTART, WHOART). Data from a central laboratory and an electronic patient diary are automatically imported to the EDC and IVR systems. Based on the lab values entered for the visit, the patient's next dose of the study drug is adjusted. Data related to a previously dispensed study drug, as well as the newly calculated dose, are used by the forecasting system, which adjusts the projected study drug need at the site, depot and global trial levels.

In this scenario, data is entered once via the most appropriate means and then supplied to other integrated systems that rely on that data. As a result, there is no need for duplicate entry of the same data and therefore no need to reconcile data. All of the patient's data is available through one system. Furthermore, with the data available in real-time, the status of study enrolment, patient safety and drug supply can be actively monitored and, when appropriate, decisions can be made in response to available information.

Successful implementation of integrated technologies provides real-time and automated data capture; real-time and automated data access, review and analysis; real-time reporting tools supporting an automated decision making process; and automated and seamless implementation of trial design. Also, and most importantly for adaptive trials, well-integrated systems allow for seamless change implementation during the course of a trial.

While statisticians will no doubt continue to debate the best approaches to adaptive trials, it is clear that the success of any adaptive trial is built upon careful planning and the integration of clinical technologies. As a result, a crucial consideration for sponsors is the technology vendor's integration capability with other systems. Choosing one vendor to provide all clinical trial technology support can eliminate tricky technology integration issues, and streamline project management as well as vendor management. The net effect of built-in integration is increased patient safety, decreased trial development timelines and decreased clinical trial costs.

Several sponsors have already moved forward with adaptive trials, and regulators are increasingly embracing the approach. Given the potential benefit for all parties involved in clinical trials, it is easy to see why momentum continues to build.

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