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Data Challenges in Adaptive Trials

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ABSTRACT

Adaptive trials are clinical studies where one or more parameters (e.g. sample size) can change as the study progresses, in a pre-specified manner, without compromising its scientific validity. Across the industry, simple adaptive designs are used on approximately 20% of clinical trials. Adaptive trial designs may save substantial time and resources by early study terminations due to futility; sample size re-estimation; and reduction of the number of protocol amendments. One of the main barriers to wider adoption of adaptive trials is operational concern, in particular delays and disruptions in trial execution. The objective of this work is to introduce adaptive trials and their data challenges, and to propose a possible data strategy.

INTRODUCTION

Unlike traditional studies, where all the elements are fixed (e.g. sample size, study duration, dose arms), adaptive trials incorporate the flexibility to change study elements while the trial in ongoing. The possible changes are usually agreed upon with the regulatory bodies, and predefined in the study documents (e.g. Clinical Investigational Plan, Statistical Analysis Plan). Adaptive trials involve one or more interim analyses, where the interim data (e.g. baseline, outcomes) is analyzed and interpreted, and drives the implementation of changes that reflect the preplanned adaptation strategy. Examples of adaptive trials include dose finding adaptive trials, where randomized arms are added or dropped after the interim look, and sample size re-estimation, where the sample size is re-assessed based on the observed treatment effect.

Across the industry, simple adaptive design trials are used on approximately one in five (20%) trials. The most common types are early study termination (for futility or efficacy) and sample size re-estimation. Regulatory bodies such as the FDA and EMA have expressed their views in a number of guidelines and non binding documents, and seem to be highly receptive of early phase adaptive trials (e.g. adaptive dose-finding studies in phase I/II).

The benefits of adaptive trials over traditional trials include i) cost and time savings, ii) better chances of finding optimal dose or population, iii) better understanding of treatment effect, and iv) reduction of patient exposure. Most of the cost and time savings derive from adaptive dose-finding studies in phase II and sample size adjustments and futility stopping in phase III, which allow sponsors to stop ineffective treatments or doses earlier. Dose finding studies allow sponsors to investigate more doses (often three to five) than with traditional studies (usually two), increasing the likelihood of finding a dose which is high enough to be effective whilst low enough not to be toxic. Likewise, trying out more doses means getting a better understanding of the dose-response curve, usually modeled as linear between the only two doses which are explored in traditional studies. As ineffective treatments or doses can be dropped earlier, the risk for the patients enrolled in the study can be lowered with an adaptive design.

Adaptive trials also yield additional risks over traditional studies, in terms of i) regulatory trust, ii) study planning and iii) study execution. Regulatory bodies are mostly concerned with those aspects which may prevent the investigators from getting the correct answer to the study question. In particular, they ask for statistical methodologies to control for type I error (false positives), warn against designs that could make the interpretation of the results too difficult or not possible, and emphasize that adaptive trials in phase III (or confirmatory) studies are not a replacement for lack of information that should have been obtained in phase II (or exploratory) studies. In terms of study planning, sponsors should keep in mind that adaptive trials are more complex than traditional trials and therefore take longer to plan, require a more skilled study team, and need adequate technology to support their data challenges. When it comes to study execution, adaptive trials are usually more demanding (especially wrt data management), and yield the risks of increased operational bias (e.g. breaking the blind) and logistical issues (e.g. delivering a new dose when adding a treatment arm).

It should be noted that adaptive trials are not always the best option, and its adoption should be assessed by a multi disciplinary team including clinical research and development, biostatistics, project management and clinical operations. The team should consider feasibility of the adaptive trials based on several aspects, including the nature

of the investigation (e.g. recruitment rate relative to treatment data availability) and the quality of the technology infrastructure.

In this work we illustrate data challenges that are common to most adaptive trials, and discuss at a high level an example of data architecture and data flow to deal with the additional complexities of this class of trials. Out of scope are the statistical methodologies and considerations involved in designing and analyzing an adaptive study (e.g. simulations in Bayesian studies, methods for control of type I error). We rather illustrate the data aspects of an adaptive trial, including data management and IT systems landscape.

DATA CHALLENGES

In this section, we will present a common study flow in adaptive trials, and then introduce the data challenges associated with the different stages of the trial.

STUDY FLOW

The schema in Figure 1 illustrates the adaptive study conduct. Study planning and execution are common to traditional studies. The new elements are the interim analysis and the decision that follows the interim analysis. These two steps can be repeated multiple times, as illustrated by the backwards arrow, until final analysis or early stop.

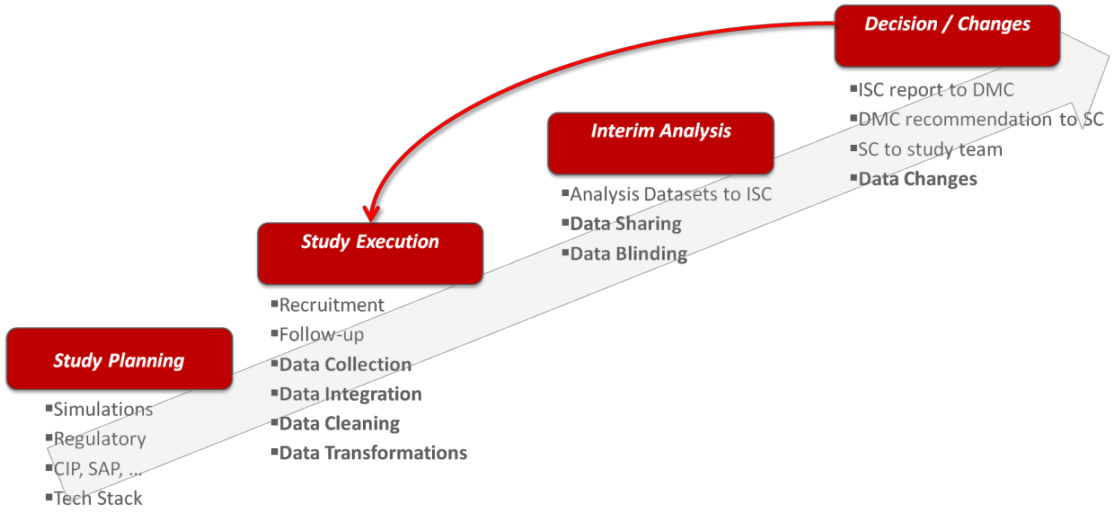

Figure 1 - Example of study flow in adaptive trials.

During study planning, simulations are carried out to explore the space of possible outcomes and associated decisions at interim analysis. This step requires a statistician with experience in simulations and advanced analytics (e.g. Bayesian methods). Study planning also involves communication with Regulatory bodies, which may have additional questions over new or less well understood aspects of the adaptive trial. The adaptive aspects of the study impact all the operational aspects of planning, from the study documents (Clinical Investigational Plan, Statistical Analysis Plan) to the choice of the technology. As changes in an adaptive study are pre-planned, it is good practice to plan beforehand for the changes that may be implemented after the interim look. Examples of possible changes impacting IT systems are Case Report Forms (CRFs) design, data models, and drug doses in the supply chain management system.

Most data challenges occur during study execution, when patients are enrolled and followed up. At this stage, data is collected from the investigators and entered into a database, either converting paper based forms or directly in an Electronic Data Capture system. Most trials involved multiple data sources (e.g. Case Report Forms, core lab tests, medical device data) which need to be integrated, cleaned and transformed into analysis datasets.

At interim analysis, the organization running the study shares the analysis datasets with an Independent Statistical Committee (ISC), which runs the analysis and produces the interim report. The ISC is usually unblinded to the randomization assignment, whereas the study team and Steering Committee are kept blinded.

The report from the ISC goes to the Data Monitoring Board (DMC), a multi-disciplinary panel including physicians with experience in the therapy and/or disease area. The DMC, unblinded to the treatment assignment, provides a

recommendation to the Steering Committee, which is then translated in study changes, such as early termination for efficacy met / futility, adding / dropping a randomized arm, or others.

In the following paragraph we discuss more in details the data challenges in Figure 1.

DATA COLLECTION

Data collection at the clinic may happen through paper based forms, or directly in an Electronic Data Capture (EDC) system. Paper based data collection yields more risks than use of an EDC when running an adaptive trial, because of the additional time it takes to transfer the paper form in a database. The risks are delays in study execution, and biased estimate of treatment effect at interim analysis. We illustrate the latter with an example. Let's assume that placebo and drug XYZ have the same adverse event rate (e.g. 10% bleeding at 1-year), and that the same number of 1-year visits has been performed for both arms. If more follow-ups reporting bleeding have been entered in the system for drug XYZ than for placebo, drug XYZ may look more harmful than placebo, when it fact it is just as safe. An incorrect estimate at interim analysis may trigger the wrong decision, such as stopping early the investigation of a beneficial treatment. The use of an EDC mitigates this risk by minimizing the time from patient visit to data available for downstream processing.

DATA INTEGRATION / CLEANING / TRANSFORMATION

Patient data originates from multiple sources. CRFs collect data on patient visits. Core labs return blood test results. Implantable medical devices such as insulin pumps collect continuous patient data. Other examples include electrocardiograms, gene sequencing, and wireless technology. All this data needs to be integrated, cleaned and transformed from raw data to analysis datasets.

Data integration, data cleaning and data reconciliation are time consuming tasks, which are critical for the successful conduct of an adaptive trial. Any ISC/DMC/Steering Committee meeting at interim analysis will include a thorough discussion on the data quality: amount of missing data, number of open queries, number of patients with clean and complete data, and so on. High data quality is a key factor for making sure the data assessed at interim analysis is reliable. For example, if diabetes is an exclusion criterion but lab tests indicate HbA1c at 7% (non-diabetic range is 4-5.9%), then the patient should not have been part of the trial to begin with, and the Steering Committee may decide to exclude the patient from the study. Not being able to identify this case in a timely manner may give interim results that refer to a different patient population than the one originally intended. Similar considerations hold for outcome data as well. Say that the primary endpoint is myocardial infarction (MI). As MI is difficult to assess directly, it is usually diagnosed as a combination of conditions, including clinical history and values of blood biomarkers. In this case, integration of CRF data and lab data is crucial to assess whether a patient has MI or not.

Frequent interim analyses mean intensive data cleaning activities, and the Data Managers and Statistical Programmers will often spend most of their time in a collaborating effort to improve data quality. As data management is an operational bottleneck in adaptive trials, the study team may benefit from platforms designed to integrate, clean and transform data, like a Clinical Data Repository (CDR). We will discuss the benefits of a CDR for data management in section "Data Architecture and Data Flows".

DATA SHARING / BLINDING / CHANGES

Once the data is integrated, cleaned and transformed, it needs to be shared with the ISC and/or the DMC. If the decision at interim analysis involves a comparison of the randomized groups, as it is often the case in adaptive trials, then the ISC needs to receive the unblinded datasets. This poses the challenge on how the blinded study team can provide unblinded analysis datasets to an external user. The main risk here is operational bias, i.e. influencing the study outcome by knowing the randomization assignments. Operational bias is one of the main concerns of regulatory bodies and should be addressed by a mechanism that ensures that only the correct people are unblinded. This can best be addressed by a platform like a CDR where data access is traced and where the type of access can be defined at the level of user group (e.g. study team, ISC, DMC).

Finally, once the DMC has expressed its recommendation to the Steering Committee based on the report from the ISC, then the planned changes need to be implemented. Some changes may not require any technology adaptation (e.g. early termination), whereas others (e.g. adding randomization arm) will have an impact on study components, such as CRF design, data management operations, drug supply management system, and others. The risk of not having a technology that supports these changes are delays in trial execution, and operational bias, as changes implementation if not carefully planned may disclose the randomization assignment.

DATA ARCHITECTURE AND DATA FLOWS

Now that we have discussed the main data challenges in adaptive trials, let's have a look at the same challenges in the context of data architecture and data flow. Figure 2 shows the same study setting of Figure 1, now organized from a data centric perspective.

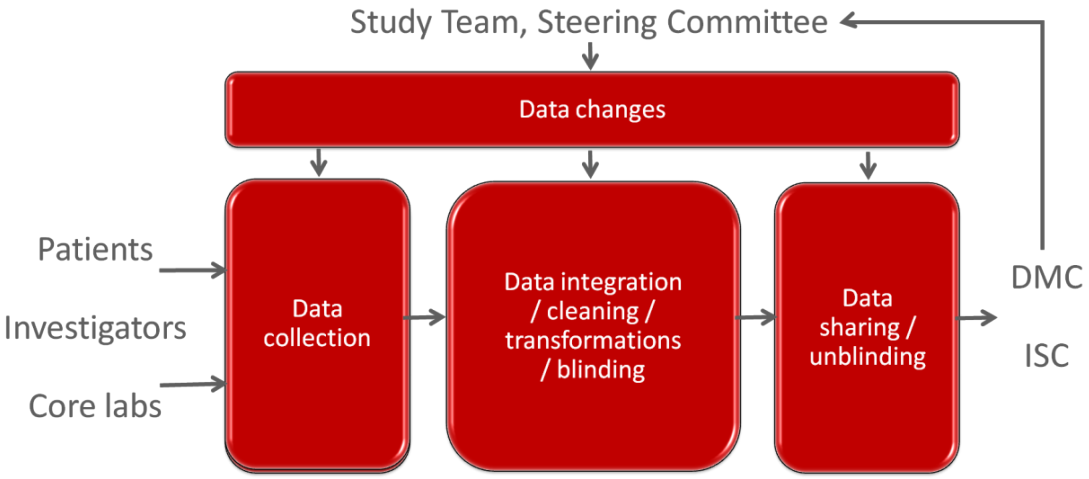

Figure 2 – Data architecture and data flow: challenges

Data from patients, investigators and core labs is collected, integrated, cleaned and transformed to analysis dataset, while keeping the study team and Steering Committee blinded to the randomization assignment. The analysis datasets are then shared with the ISC and possibly the DMC. The two committees will often need the unblinded datasets. The study team needs to provide the unblinded datasets without breaking the blind on their side. The DMC reports its recommendations to the Steering Committee and Study team, who implements the changes.

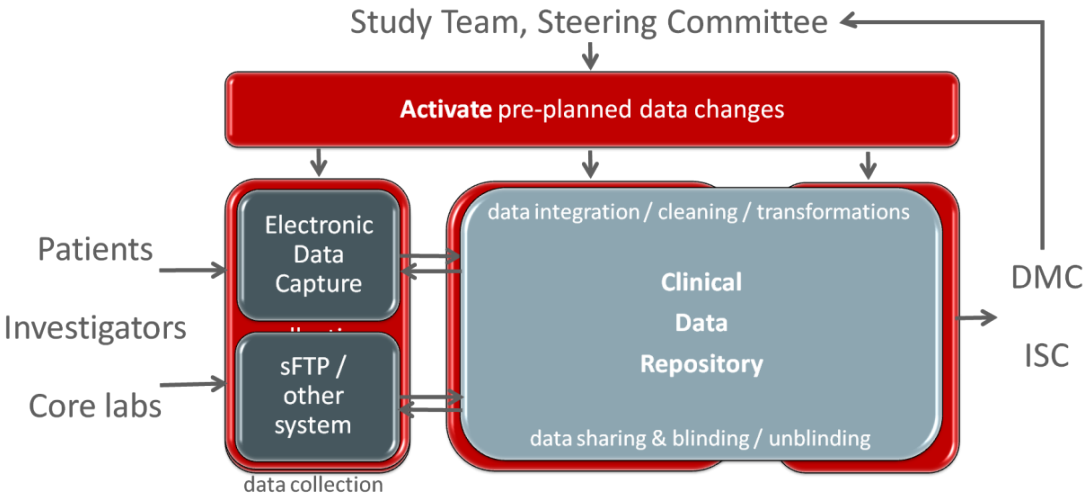

Figure 3 - Data architecture and data flow: IT systems landscape

If we look at Figure 3, the same data centric representation now contains the IT systems. We already discussed the benefits of an EDC system in section "Data Challenges". Other systems will be used to collect data from other sources. For example, labs tests are often delivered from the core lab to the sponsor as datasets in a shared sFTP server. After data collection, the data needs to be elaborated to produce the analysis datasets. We propose a Clinical Data Repository (CDR) as the IT system of choice for integrating, cleaning and transforming the data, as well as sharing the unblinded datasets while keeping the study team blinded. The CDR should be able to pull data from different data sources, in different formats, for data integration. It should pull the data in a timely manner, ideally in near-real time, to minimize delays in trial execution, critical for adaptive trials. Additionally, the CDR should enable

users to generate queries on the combined datasets (e.g. lab tests indicating high HbA1c and no history of diabetes in CRFs) and to push the queries back to the source systems (e.g. EDC), for timely query resolution. Transformations are then performed in the CDR which provides traceability of data points, version control of data and programs, access control to data and programs. Access can be regulated by user group, so that ISC and DMC can have unblinded access while the rest of the study team can perform their business operations while staying blinded. From an operational perspective, the CDR should have the capability to support a high volume of data and high number of users, and reliable security mechanisms. In terms of productivity tools to facilitate data management work, other desirable properties of a CDR are libraries of data models, libraries of data checks and transformations, and automatic execution of checks and transformations as the data is refreshed. Overall, the CDR has a central role in pulling together data from all the trial sources, and in reducing the burden on Data Managers and Statistical Programmers in the conduct of adaptive trials, especially when approaching an interim analysis.

As a last remark, changes on the study conduct requested by the Steering Committee need a downstream set of IT systems that is capable of pre-planning possible changes. For example, an EDC system that has the option of creating dynamic forms may enable changes implementation much faster than one that doesn't. Another example is a CDR that can handle multiple data models, including ones that are not part of the initial trial setting.

CONCLUSION

One in five trials is adaptive. Benefits of adaptive trials include cost and time savings, as well as higher chances of finding optimal dose or population and understanding the treatment effect, while reducing unnecessary patient exposure. The risks associated with adaptive trials include possibly more work to get regulatory trust, and risks associated with study planning and study execution. A number of these risks come from data challenges, such as data collection, data integration / cleaning / transformation, and data sharing / blinding / changes. We recommend the use of Electronic Data Capture (EDC) and Clinical Data Repository (CDR) systems when running adaptive trials, as they mitigate a number of risks associated with data handling.

As future development, we signal the rise in use of wireless technology in clinical trials (e.g. sensors, wearable devices). Wireless technology can be used for automatic data capture, with the benefit of reducing the number of errors associated with manual entry, and of collecting trial data in real-time (e.g. patient adherence, physiological parameters, patient activity).

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