Operational Challenges of Adaptive Trials:
Integrated Technology and Best Practices for Successful Implementation
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Operational Challenges of Adaptive Trials

Summary

Operational execution of adaptive trials has specific requirements that must be implemented to minimise operational bias. Neglecting any of them can compromise trial integrity.

This white paper provides a review of key operational challenges and best practices for conducting adaptive design trials based on ICON’s experience from developing and executing more than 200 adaptive trials. Furthermore, two industry examples of adaptive trials exposed to operational bias are assessed to identify how a study’s outcome and validity can be compromised, and how such issues can be prevented.

The Utility and Requirements of Adaptive Trials

Adaptive clinical trial designs provide an innovative approach to drug and device development that can enhance development efficiency and maximise portfolio value.

Regulators, including the U.S. FDA and the EMA, have provided guidance on the use of adaptive designs for clinical development [1, 2], which has accelerated industry adoption of adaptive trials [3].

The benefits of adaptive trials include the abilities to:

- Combine clinical trial phases to expedite clinical development
- Right-size study enrolment so a trial is neither underpowered nor overpowered
- Adjust the allocation of patients among trial arms, which provides a powerful and highly efficient strategy to assess a wider range of dosing regimens than traditionally possible
- Adjust a protocol’s inclusion/exclusion criteria to enrich for relevant patients for precision medicines
- Stop the trial early for futility or efficacy

These designs can eliminate months, if not years, from the traditional development cycle while also mitigating unexpected issues that often delay availability to patients of vital treatments and add millions of dollars in extra costs.

However, adaptive trials also present unique operational challenges. Chief among these are ensuring data quality and integrity, and maintaining blinding of interim data analyses and adaptive changes. Timely monitoring and cleaning of trial data are essential to ensure data used in interim analyses are reliable, and avoid incorrect adaptive changes that may result in trial failure.

Maintaining investigators’ and study teams’ blinding to interim decision and adaptive change criteria, timing and implementation are essential to avoid introducing operational bias that can invalidate study results.

Indeed, regulators require that steps to ensure data quality and blinding integrity are documented, and they will conduct additional statistical review of the data to check for operational bias.

These stringent operational requirements for adaptive trials are neither necessary for the success of traditional clinical trial designs, nor are they supported by traditional clinical trial infrastructure and practices.

Technology solutions, including automated data collection and in-stream cleaning, and remote site monitoring, can make adaptive clinical trials affordable and practical. However, these solutions must be implemented in accordance with best practices to be effective. Below we examine three of the most common operational challenges seen in adaptive clinical trials and how those should be addressed.

Three Critical Operational Challenges in Adaptive Trials

In reviewing adaptive trials, regulators carefully assess how trial design and execution minimise the risk and potential impact of data quality issues and operational bias on estimates of treatment effects and the interpretability of trial results. Therefore, successfully executing adaptive trials requires identifying the potential for these challenges in their varying manifestations, and proactively addressing their root causes.

1. Data quality

Adaptive interim analyses require quality data that are consistent and accurate up to the interim analysis cut-off date. Any subsequent change to the data used at the interim has the potential to invalidate any adaptive change based on it, which in turn can invalidate the entire trial. This includes, for example, the late detection of a major protocol deviation that would exclude several patients from statistical analysis, which led to trial failure in Case Study 1 below.

Real-time data collection, cleaning and monitoring are, therefore, essential because they drive the timely decisions at the heart of adaptive trials.

2. Operational bias and implementing adaptations

Operational bias can arise when unblinding information leaks out to study investigators, which can compromise trial data integrity. Even knowledge of adaptive choices and adaptation decision rules by investigators can introduce operational bias, as it may influence the way investigators treat, manage or evaluate patients.
As this bias cannot be overcome with statistical adjustments, individuals involved in the conduct of a study should remain blinded not only to the interim analysis results but also, as much as possible, to what interim adaptive decisions may be made during interim analyses. To mitigate this potential source of operational bias, steps should be taken at the design stage and throughout the trial.

Typically, Data Monitoring Committees (DMCs) are empowered to make adaptive decisions on behalf of sponsors. Whenever possible, decision criteria should be kept confidential and described in documents only available to DMC members and the unblinded statistical team supporting the DMC, such as the interim analysis plan and DMC charter. To avoid accidentally conveying adaptive criteria or decisions to trial investigators, sponsors also should be blinded.

Technology solutions that control the dissemination of unblinded information, such as secure portals and secure communication platforms that provide access to data only to authorised DMC members have proven effective for appropriately controlling blinded information in adaptive trials.

Many adaptive decisions, such as arm dropping or randomisation ratio adaptation, can be implemented, using appropriate technology and processes, without being disclosed to the blinded study team. Blinding other adaptive decisions, such as an increase in sample size, can be more challenging. However, this, too, can be accomplished with appropriate planning.

3. Sample size reassessment

Sample size reassessment is a relatively common type of adaptive design in Phase III trials. One or more planned, unblinded interim analyses may be used to reassess sample size based on observed treatment effect size. The study sample size can be increased in the event that the observed treatment effect is smaller than anticipated but remains clinically relevant. Operational challenges associated with these type of designs include data quality and reliability, appropriate timing of interim analysis, and variability of observed results between interim looks.

Case Study 2 below provides an example of a design with two planned interim analyses with different recommendations between interim analysis 1 and interim analysis 2. In this case, a change in result trend after a decision to increase sample size at interim analysis 2 suggests that knowledge of the change may have introduced operational bias, which may have contributed to the study’s unnecessary oversizing. Blinding investigators to the total sample size and trial duration may have prevented any operational bias that occurred in this case.

### Integrated Technology Solutions

Statistical and operation biases can result from multiple overlapping causes. Since any one event can result in trial failure, best practice dictates that all potential biases should be mitigated. This can be done by using a range of validated technology platforms that address the entire range of operational challenges of adaptive design in an integrated fashion. Four crucial components of an integrated infrastructure required for adaptive designs are:

- A statistical platform for designing and analysing adaptive designs so that they remain valid across adaptive decision points and trial phases, such as ICON’s ADDPLAN (See sidebar 2)
- A real-time informatics platform for continuous data collection, cleaning, and analysis, thereby enabling interim analyses to be conducted at any time during a trial without compromising the trial’s integrity, such as ICON’s ICONIK
- A robust monitoring methodology to ensure any potential data errors or protocol violations are proactively identified and mitigated, so that the validity of decision-making at interim analysis is not undermined, such as ICON’s Patient-Centric Monitoring
- An adaptive study execution platform to ensure that appropriate firewalls are maintained to prevent exposure of blinded trial information, and that study adaptations (e.g., randomisation and drug supply changes) can be implemented efficiently without unblinding the nature or results of interim analyses, such as ICON’s FLEX ADVANTAGE

Implementing and executing an adaptive trial enabled by an integrated technology platform is best done by professionals experienced in adaptive trial design and execution. In fact, US FDA adaptive trial guidelines explicitly support this as a best practice. With powerful technology and established best practice implemented by knowledgeable staff, sponsors can reap substantial financial and human service benefits adaptive trials can provide.
Transforming Portfolio Success with Adaptive Designs

High attrition rate in Phase III trials, lengthy development programmes, and increasing development costs all demand a smarter approach to drug development. Adaptive design, identified in FDA’s critical path initiative, is a key way to improve trial efficiency.

Read ICON’s white papers on adaptive design to learn how trials in your portfolio may benefit.

ICON Adaptive Design Technology Platforms

Executing an adaptive trial requires specific, validated infrastructure. ICON has developed the most robust technology platforms for designing and executing adaptive trials.

– ADDPLAN is the industry-leading statistical platform for the robust design, simulation and analysis of adaptive trials from Phase 1 to Phase IV. The FDA, EMA, and PMDA have licensed the platform to analyse adaptive designs.

– ICONiK is ICON’s informatics platform to consolidate, standardise, and analyse the operational, clinical, and real-world data collected during clinical development in real time.

– Patient Centric Monitoring is a proprietary risk-based monitoring methodology that uses a root cause analysis technique, called Human Factors Analysis, to systematically classify and analyse the underlying causes of trial errors. This data helps CRAs deploy the right risk-mitigation resources to the sites that need them most. The approach is compliant with ICH G6 (R2) 2016 guidelines and enables proactive mitigation of issues to support interim analyses at any point in the trial.

– FLEX ADVANTAGE is ICON’s proprietary Interactive Response Technology platform for managing patient randomisation, investigator sites and clinical supplies specifically for adaptive trials. The platform also ensures permissions-based access to data so as to maintain trial integrity and support efficient interim analyses.
Ending trials early when evidence of efficacy is strong is a major advantage of adaptive trial design. However, adaptive decisions always must be based on reliable data. To ensure that IA results and decisions are statistically robust, a sensitivity analysis should be planned as part of the decision making process.

In this study, protocol violations in a handful of patients early in the trial were not detected until after the trial was halted for presumed success. Ultimately, these undetected quality issues led to the trial’s failure. When the invalidated data were excluded from the final analysis, the results were no longer statistically significant.

This case study highlights how critical data quality and study conduct quality are to the success of adaptive design studies, particularly for studies with planned early stopping for success. Continuous central data monitoring and data cleaning might have prevented this failure.

**Study Design**

The study was a double-blind, randomised, placebo-controlled, multi-centre, comparative, Phase III clinical study in patients with chronic graft-versus-host disease. The primary objective was to demonstrate superiority of the test treatment compared to placebo in terms of the proportion of patients showing objective response at the final/withdrawal visit. Statistical hypothesis testing was conducted using a recursive testing strategy based on Brannath, Posch and Bauer [4] and Müller and Schäfer [5].

The study was planned as an adaptive two-stage group sequential design with possible sample size adjustments after a planned interim analysis beyond a first stage. Most importantly, the study could be stopped in case of significant superiority. The initial sample size estimate for the first stage was 70 patients, with 35 treated and 35 placebo. For the second stage, an estimated 56 additional patients were to be enrolled, for a total of 126 patients. The trial proceeded as noted in the timeline, Figure 1.

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**Case Study 1: Multiple Factors Undermine an Early Stop for Efficacy**

**Week 1:** Trial Begins Enrolment

**Week XX-XX:** First Interim Analysis

73 patients: 35 treated vs. 38 placebo

Critical value to confirm efficacy calculated at 2.676. The value achieved, 1.240, was promising, but below the level of significance.

The DMC:

– Recommended that the study continue
– Increased Stage 2 sample size to 152, for total of 225 patients
– Scheduled a second interim analysis, and documents this addition to the initial trial plan

**Week XX-XX:** Second Interim Analysis

175 patients: 86 treated vs. 89 placebo

Critical value to confirm efficacy dropped to 2.032. The value achieved, 2.048, is barely above threshold of statistical significance.

The DMC recommended stopping trial for success without recruiting the previously specified 225 patients. The sponsor concurs.

**Week XX + Y Days:** Trial Recruitment Halted

At the time of the interim analysis, an additional nine patients were enrolled. All patients continue in the study.

**Week XX + Z Days:** Protocol Deviation Identified

Data errors due to a major protocol deviation affected five patients. Correcting these errors resulted in the reversal of one patient’s outcome, as assessed during the first interim analysis.

**Week XX:** Final Analysis

183 patients

The critical confirmation value dropped to 1.726. The value achieved also falls to 0.739, far below significance. The study fails.

Were the final analysis conducted without the overrun subjects, for a total of 174 patients, the confirmation value achieved would have been 1.521, still below the threshold of significance. Notably, the last nine patients recruited displayed a negative trend.

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Why the Trial Failed

The unplanned interim analysis 2 was based on what turned out to be incorrect data.

The data changes seen in this case reflect significant issues with data quality and real-time monitoring during the study, and specifically at the time of the second interim analysis. Halting the trial early based on a barely significant result left no room for error when the final results changed due to data quality issues and recruitment overrun, leading to trial failure.

What Can Be Done to Avoid Failure

This case study highlights the criticality of data quality and study conduct quality for adaptive design studies, and more specifically for studies with planned early stopping for success.

In traditional trials, data are fully cleaned toward study end, a process that may take several weeks. For adaptive trials, adequate data cleaning must be done at a frequency high enough to enable interim analyses to be completed over the course of a few days.

To avoid problems with data quality and analysis in such short time frames, ICON has implemented a systematic approach to adaptive designs data quality in its standard processes. These are:

- Use of risk-based monitoring enabled technology for real-time data monitoring and cleaning, including protocol deviations reporting, through the ICONIK suite
- Interim analysis with planned early stopping using fully monitored and clean data, including protocol deviations
- Interim analysis plans include the same scope of key efficacy and safety analyses, including sensitivity analyses, as for the final analysis
- Use of ADDPLAN for the required simulations and analyses to support a robust interim analysis decision
- Interim database locks adhere to the same quality standard as final database lock
- Protocol deviations are monitored and incorporated into the analysis using the same process and scope as for final analysis
- Addressing these issues would have increased the chances of a successful trial.
Blinding investigators to the treatment patients are given has been traditionally used to prevent operational bias, whether conscious or unconscious. In adaptive trials, pre-planned treatment changes are made based on ongoing results. The mere fact that a change has been made may influence investigator behaviour. For example, knowing that the trial plan allows dropping an ineffective treatment arm at a specific date might cause investigators to hold back patients who they think might benefit from the remaining treatment until that change is made.

In this case, physicians’ decision-making may have been similarly influenced. Specifically, physicians’ decisions regarding patient selection and data recording may have been influenced by the knowledge of the adaptive decisions. That the trial sample was first deemed sufficient suggested the study drug was performing as expected, while the later sample enlargement suggested that the treatment might not have been as effective. Such operational bias often shows up as a sharp change in results trends following an adaptive change, which was observed after both these changes. Lacking evidence that blinding was maintained, regulators would likely interpret sharp trend reversals as evidence of operational bias, leading to trial failure.

**Study Design**

This study was a randomised, double-blind, double-dummy, multi-centre, comparative, non-inferiority, Phase III clinical trial in patients with acute infectious diarrhoea. The primary objective of the study was to demonstrate the non-inferiority of test treatment versus active comparator in terms of time to clinical cure. The primary efficacy variable was to be subjected to a confirmatory statistical analysis using the O’Brien and Fleming $\alpha$-spending function.

The study was designed as an adaptive trial with two interim analyses. Initial trial size was calculated at 776 patients, based on an exclusion rate of 10% from the per-protocol population. Patients were equally divided into the two treatment arms. This could be revised during an interim analysis. The trial proceeded according to the timeline in Figure 2.

**Case Study 2: Operational Bias Introduced by a Sample Size Adjustment Disclosure**

Blinding investigators to the treatment patients are given has been traditionally used to prevent operational bias, whether conscious or unconscious. In adaptive trials, pre-planned treatment changes are made based on ongoing results. The mere fact that a change has been made may influence investigator behaviour. For example, knowing that the trial plan allows dropping an ineffective treatment arm at a specific date might cause investigators to hold back patients who they think might benefit from the remaining treatment until that change is made.

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Why the Trial Failed
The sharp reversal of results trend after the second interim analysis suggested operational bias occurred in this trial. Since the opportunity for bias existed and statistical analysis confirmed it, the trial results were questioned and required additional sensitivity analyses and justification.

What Can Be Done to Avoid Failure
To minimise operational bias associated with the dissemination of DMC recommendations for sample size adjustments, ICON has established a standard approach to protocol designs and conduct for studies with planned adaptive sample size re-estimation that maintain blinding from site investigators.

– Study protocols refer to the study maximum sample size only and DMC recommendations are disseminated to limited sponsor personnel excluding study conduct teams and investigator site staff

– Use adaptive design compatible Interactive Randomisation Technology, such as ICON’s FLEX ADVANTAGE

Moving Ahead with Adaptive Design
Several preventable, but significant risks exist when executing adaptive trials. Namely, operational biases can arise from the unblinding of study adaptations, which might influence investigator behaviour. Additionally, biases can arise from poor data quality at interim analysis or from insufficiently conservative design parameters. Regulators look close for these types of errors, which can result in trial failure.

To ensure that valid scientific inferences can be drawn, adaptive design clinical trials must be carefully designed and executed. Technology platforms are critical to prevent common risks that could unnecessarily lead to the failure of an adaptive trial. ICON’s technology platforms, including ICONIK, FLEX ADVANTAGE, and ADDPLAN, provide validated and immediately deployable infrastructure for executing successful adaptive trials.

To learn more, please contact us at adaptivedesign@ICONplc.com
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