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Overcoming Clinical Development Challenges in Oncology with Innovative, Adaptive Trial Design

Employing Adaptive Approaches to Reach Desired Clinical Objectives

The field of oncology is expanding and changing rapidly. With increasing advancements in genomics and interests in precision-based medicine, more biomarker-guided treatments are being tested for new indications at an increasing rate. Such research activity is dominating pharmaceutical pipelines, and is only growing in complexity and intensity. Oncology research now spans 450 immunotherapies and over 60 different mechanisms of action, with nearly 100 new next-generation biotherapeutics (NGBs) currently under investigation.

These complexities bring unique challenges. Oncology researchers struggle to source large enough patient populations for clinical trials, and there is often a lack of knowledge regarding a disease's natural history. This is especially true for rare cancers. The intricacy and changeability of endpoint analysis and clinical trials is growing, with the complexity of Phase I trials increasing by 20% in the past five years alone (measured as a combination of endpoints, eligibility criteria, and number of subjects). These problems are compounded for smaller companies that may lack the resources needed to plan and run clinical trials in an optimal and efficient way – a hurdle that is likely to worsen as trials become more complicated.

Given the environment of dynamic care in oncology, clinical development must be adaptable and dynamic, too. On top of this, there is a pressing need for earlier and longer-term planning that considers the entirety of a development plan, rather than individual trials that are planned and implemented on a step-by-step basis. Trial developers can achieve this by using innovative, adaptive trial and programme designs, and involving quantitative strategists – statisticians, clinical pharmacologists and data scientists – early in the design and development process. Early involvement can hugely impact not only a single trial, but an entire development programme, enabling researchers to plan effectively, manage data optimally, and react to difficulties that threaten trial success.

The Challenges Facing Oncology Researchers

Many of the difficulties prevalent in rare disease research are now evident for oncology trials, as more of these trials are now targeting specific subsets of the population with given biomarkers or characteristics. As a result, it is challenging to run randomised or larger-scale studies given that there is likely only a smaller pool of patients with biomarker targets to recruit. Many trials also have limited options in terms of comparator arms, making it challenging to compare and evaluate results. Due to scant knowledge of especially rare conditions, information on a disease's natural history is often lacking, leading to reduced clarity over the outcomes, results and likely roadblocks.

Additionally, trial sponsors are calling for shorter, faster, and more streamlined development paths. Combined with the competitive nature of the field, this pressure is having a significant effect: the median duration of the drug development process in oncology is declining, and some 'breakthrough' drugs are being approved at earlier stages of trials (Phase I, II, or combined II/III). Furthermore, while time-to-event endpoints still dominate in oncology, additional endpoints, such as best overall response, are being more widely used earlier on in development programmes. These capture different aspects of a disease and help characterise a product more accurately, facilitating its use and acceptance by stakeholders and authorities. While a variety of endpoints can capture more complete and detailed information, trial designers must be prepared to incorporate a more diverse, evolving range of endpoints and analyses than in the past, and at various stages of the trial.

With these challenges in mind, typical clinical development and regulatory pathways stand to benefit from new approaches that are optimised for the oncology research space — innovative, adaptive trial designs that offer new routes forward for organisations of any size. The development and use of such designs are encouraged and supported by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), and regulatory frameworks are evolving to reflect this[1,2].

From Phase to Plan: Towards a Holistic Approach

While clinical trials are traditionally separated into phases, this structure is becoming unsuitable for many rapidly evolving areas of research, with oncology being a standout example.

The different phases of trials are increasingly difficult to separate distinctly: initial studies in patients can often morph into dose escalations and expanded cohorts, and can provide evidence of both safety and efficacy in various specified sub-populations. While a science-based 'learn and confirm' mindset [3] remains present throughout the entire trial process, with a focus on understanding the functional relationships at hand, the delineation of distinct phases and stages of development is becoming less clear.

Rather than adopting a phased, study-by-study approach, oncology researchers now require a more overarching clinical development plan. Holistic perspectives enable a more adaptive, collaborative workflow within a fast-moving research and development environment, and offer flexible access to extensive complementary expertise and experience. This approach helps to identify and mitigate risk, which in turn leads to better preparedness and chances of long-term success. Compared to a phased approach, a holistic process can also help to cut clinical development timelines, lower the number of patients needed to address a research question, and reduce costs.

Cost is key in drug development. As the average annual investment required to produce new medicines increases, with

per-product figures ranging up to US $300,000, sponsors are seeking ever-more streamlined production pipelines. Proving cost effectiveness is therefore essential to a product achieving a desired level of market access, coverage, value, and commercial success, as well as reaching the market in a timely, effective way.

Adaptations Bring Built-in Flexibility

Clinical development plans allow researchers to better prepare for the trial ahead. Clinical development plans that incorporate innovative design features such as adaptive trial designs and Bayesian statistics can help maximise performance and efficiency. Adaptive trial designs allow for ongoing and data-driven decision-making throughout the trial process using pre-specified adaptations to minimise potential risks while protecting trial integrity[4]. A Bayesian framework for analysis can offer more intuitive probabilistic interpretations of key clinical measures, formal incorporation of existing information, and flexibility in rules for adaptations[5,6].

This kind of flexibility is especially important in oncology. Given the absence of predecessor trials and data on many rare diseases and cancers, trials often lack the information needed to make accurate forecasts of expected outcomes. Even when agents being investigated in a trial are novel, or there is little information about characteristics or anticipated response[7], oncology trials can adapt and move fast, highlighting the need for flexible data collection and decision-making.

Importantly, adaptive designs offer the ability to react and adapt dynamically to new findings mid-course. For example, trials with small patient populations operating under an adaptive Bayesian design framework can 'borrow strength' from previous trials[8]. This approach combines trial data with prior information and predecessor results to obtain better estimates of safety and effectiveness, and ensures that trials will not fail due to lack of power. Prior data can potentially reduce the necessary size or duration of a trial, allowing the same decision to be reached faster or with fewer participants. From a regulatory perspective, the FDA's Center for Biologics Evaluation and Research (CBER) appears receptive to Bayesian approaches[9].

Adaptive designs can also allow for adaptive population enrichment, whereby eligibility criteria are adjusted throughout a trial using prospectively planned interim analyses so that, after an interim look at the data, only patients likely to benefit from a new treatment are enrolled. This can increase the power of a trial and allows trials to continue with smaller sample sizes and shorter durations than conventional approaches. Adaptive enrichment designs can overcome issues caused by differences in treatment effect between sub-populations[10] by involving multiple parallel trial arms, and enriching for biomarker characteristics likely to predict for clinical success[11].

One concern that is prevalent among trial participants, especially in oncology, is that they could be assigned to a placebo or a subpar treatment arm. This anxiety can delay patient enrolment and prevent trials from reaching ideal cohort sizes. Designs that incorporate external, synthetic or historical control arms can alleviate such fears. These designs leverage real-world data to model comparator arms based on previous studies, making them especially useful for early exploratory trials or other instances where the eligible size of the patient populations is low. Rather than needing to recruit real participants for control arms, trials can instead use synthetic arms based on health data gathered as part of routine care, records, claims, registries and historical trials. Historical control groups ensure that the baseline characteristics in a treatment arm are comparable to that in previous standard-of-care trials[12], reducing the risk of trial participants being exposed to a treatment that is inferior. When announcing its 2019 strategic framework[13], the FDA acknowledged the potential of real-word data in supporting the development of drugs and biologics, noting that such data can be used to advance medical research, generate evidence, and better analyse clinical outcomes.

Adaptations regarding changing endpoints are especially useful. Given the unknown nature of many of the diseases studied, oncology trials often rely on event-based endpoints on unknown timelines[14]. Selecting the right endpoints is crucial in bringing the right evidence when it comes to submission; complex endpoints must satisfy all stakeholders – patients, payers, prescribers, regulators – and must therefore be planned out at the early stages of conventional clinical development. Adaptive approaches, however, allow endpoints to be adapted and introduced at different stages of a trial. Multiple endpoints (for example, Overall Survival and Progression-free Survival) can also be combined to inform decision-making[15]. Reconsidering composite endpoints can help in overcoming the issue of scarce data and helping to better anticipate dynamic timelines and targets.

Quantitative Strategists Are Essential for Trial Success

Quantitative strategists – from statisticians to clinical pharmacologists and data scientists – are essential in trial design. This is especially true for adaptive clinical trials, where it is paramount to ensure that any changes in trial parameters do not compromise integrity and statistical validity.

Often, statisticians are only involved when trial developers want to answer a specific question in the design process – when calculating required sample size, for example. However, it is difficult to know when statistical expertise is needed[12], and to know what is unknown or unaccounted for. If a statistician is unaware that a trial faces a particular issue (defining the population, for example) they cannot suggest a solution (such as adapting for sample enrichment or using adaptive design to reduce the sample size needed). Involving a statistician from the start of programme development ensures they know the risks and can advise on how to address and mitigate them. For smaller organisations, this is even more important, where biostatisticians often need to pose questions that would come from elsewhere, such as outcomes research, data science, and clinical pharmacology in a larger organisation.

Additionally, as research trends towards precision medicine, an increasing number of trials select or stratify patients based on pharmacogenomics – where genetics is used to help determine or predict how an individual will respond to a drug. Statistical genetics experts thus have a potentially invaluable role to play in ensuring that clinical development plans are prepared for and navigating this emerging field appropriately and effectively.

Rather than just applying traditional biostatistics responses to specific queries, a collaborative, statistician-first workflow proactively identifies and avoids pitfalls and potential risks, ensuring that Statistical Analysis Plans are followed correctly – especially where adaptive methods are used in the study design. This kind of approach also synthesises existing information to identify the potential for innovative design features that are data-driven.

Early involvement of quantitative strategists helps to provide information and clarity, and to determine and evaluate different

ways to address key challenges. This reduces the risk of trials having to be re-run, saving time and money, and can help increase the likelihood of regulatory approval. For instance, the FDA and the EMA have approved approaches in which sample size is re-estimated following interim analysis; these designs are proven not to undermine a study's integrity and statistical validity, and they enable sponsors to confidently proceed with expensive late-stage studies[1,2].

Data Considerations and Complexity

Oncology trials have highly complex considerations around data use and analysis. Trials utilize various categories and sets of external data, include elements such as dose escalations and cycles of therapy, and involve intricate data derivations and endpoints.

Data related to biomarkers and concomitant active treatments come from various sources, is stored across disparate external databases, and must be blinded to ensure trial and data integrity. Some data is also subject to adjudication or confirmation. All of this complicates data handling processes, as it is crucial that data is blinded, aggregated, and accessible on a coordinated, transparent timeline. Here, statisticians can help – they can ensure that data is available throughout the development path as needed, and forecast the optimal timing for decision points through the trial process.

Trials require streamlined, clean, fit-for-purpose datasets that meet their specialised requirements, and researchers need constant, up-to-date knowledge of their data and its metadata to stay aware of data quality, accessibility, location, and status. Standardised approaches built around Data Management Plans can streamline workflows, bring preparedness and efficiency, and support pathways such as fast-track approval or data pooling[16]. This not only makes development plans more efficient but can improve their performance. Data pooling, for instance, brings together data from population-based or clinical settings for use in trials where sample sizes are inadequate. Given that large trials are not always possible, this enables a wider range of research questions to be addressed as accurately and effectively as possible.

Making considerations for adaptive trial design and other innovative trial design methods require technical capabilities. Some organisations, including smaller ones with fewer or limited resources, may find it beneficial to work with a collaborative CRO partner who can help them design and implement a robust data consolidation and analysis strategy. Combined with other services, such as historical or real-world evidence provision, this approach can ensure a trial is asking the right research questions, with the right data, for the right analysis.

Conclusion

To keep pace with the rapidly changing landscape and abundance of new therapies emerging in oncology, researchers must think ahead – and think differently.

Oncology trials face numerous challenges, ranging from small patient populations to evolving endpoints to complex data handling and analysis. Overcoming these requires a holistic approach that considers an entire clinical development plan rather than fragmented trial phases. Trial design must be able to adapt and targeted changes be made in real time that maintain the statistical integrity of the analysis of data. Here, quantitative strategists are essential to ensure that, as a trial adapts, it remains focused on its objectives and does not compromise its integrity or statistical validity.

By involving statistical expertise from step one, oncology can now employ innovative, adaptive ways of reaching a whole host of desired clinical objectives. Small and large organisations alike can benefit from adaptive trial design. These innovative designs can reduce the inherent risk in clinical trial development and implementation, and target the populations who would benefit most from a new agent or therapy[6] in order to bring products to market, and to patients, faster and more cost-effectively. After all, bringing benefit to the patient is the aim of any trial – and the more efficient and effective the trial, the better for patient health.

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