Navigating the Future of Oncology

Overcoming Four Critical Clinical Trial Challenges

Cytel

Introduction

Over recent years, oncology studies have vastly outnumbered all other areas of clinical research, with no indications of slowing down. This field is rapidly evolving, driven by advancements in genomics and a growing interest in precision medicine, leading to a significant increase in testing biomarker-guided treatments for novel indications. Such research activity now dominates pharmaceutical pipelines, with a rising complexity and intensity that presents unique challenges.

Oncology researchers struggle to recruit adequate patient populations for clinical trials, and there is often limited knowledge of the natural history of diseases, particularly for rare cancers. The intricacy and changeability of endpoint analysis and clinical trials are growing, especially with the increasing complexity of Phase I trials—measured as a combination of endpoints, eligibility criteria, and number of subjects needed. This hurdle is likely to worsen as trials become more complicated.

Given the dynamic care environment in oncology, clinical development too must be adaptable and dynamic. Moreover, there is a pressing need for comprehensive, proactive planning, considering the entire development strategies, rather than individual trial-by-trial approaches. Trial developers can achieve this by using innovative, adaptive trial and program designs and involving quantitative strategists—statisticians, clinical pharmacologists, and data scientists— at the outset of the design and development process. Early involvement of these experts can hugely impact both individual trials and entire development programs, enabling effective planning, optimal data management, and proactive resolution of challenges that may jeopardize trial success.

Addressing Four Critical Challenges in Oncology Trial Design

1 PATIENT RECRUITMENT AND SPECIFICITY OF TRIALS

Many of the difficulties prevalent in rare disease research are also evident for oncology trials, especially as more of these trials target specific subsets of the population with given biomarkers or characteristics. Conducting randomized or larger-scale studies has become challenging due to the limited availability of patients with specific biomarker targets for recruitment. Moreover, the limited understanding of rare conditions in oncology contributes to the lack of comprehensive information about the natural history of these diseases, further complicating patient selection and trial design.

A prevalent concern among potential trial participants, particularly in oncology, is the fear of being assigned to a placebo or suboptimal treatment arm. This anxiety often leads to delays in patient enrollment and may result in trials failing to reach the ideal cohort sizes necessary for robust statistical analysis and conclusive outcomes.

Innovative trial design approaches could be adopted to address these challenges, including synthetic control arms. Rather than recruiting real participants for control arms, trials can use synthetic arms based on health data gathered in routine care, records, claims, registries, and historical trials. Historical control groups ensure that the baseline characteristics of patients in the treatment arm are comparable to those in previous standard-of-care trials. This approach reduces the risk of trial participants receiving inferior treatments.

2 COMPLEXITY OF TRIAL DESIGN

The landscape of oncology clinical development is characterized by increasing pressure from trial sponsors for shorter, faster, and more streamlined development paths. This competitive environment has led to a decline in the median duration of drug development processes, with breakthrough drugs receiving approvals at earlier trial stages—Phase I, II, or combined II/III studies.

Traditionally, clinical trials are segmented into distinct phases, but this structure is becoming less suitable for rapidly evolving research areas like oncology. Trials often transition seamlessly from initial patient studies to dose escalations and expanded cohorts, providing evidence of safety and efficacy in specified sub-populations. While a science-based 'learn and confirm'[1] mindset remains present throughout the entire trial process, focusing 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. A holistic approach enables adaptive and collaborative workflows within the dynamic research and development environment, leveraging extensive expertise and experience to identify and mitigate risks effectively. It allows better preparedness, leading to higher chances of long-term success. Additionally, compared to a phased approach, a holistic process can streamline clinical development timelines, reduce the number of patients needed to address a research question, and eventually, lower costs associated with drug development.

Another important factor is the integration of quantitative strategists, including statisticians, clinical pharmacologists, and data scientists, which is crucial in optimizing trial design and overcoming statistical challenges in adaptive clinical trials. Early involvement of statisticians ensures proactive risk management and strategic decision-making throughout program development. By addressing trial complexities upfront and leveraging statistical expertise, organizations can enhance trial efficiency, reduce the likelihood of trial re-runs, and increase the probability of regulatory approval.

3 DATA MANAGEMENT AND INTEGRATION

Oncology drug development faces numerous data challenges that demand specialized expertise and processes for effective management. These studies have highly complex data utilization and analysis considerations, incorporating various external data categories, dose escalations, therapy cycles, and sophisticated endpoints.

Key data challenges and the potential solutions:

Addressing High Volume of Data:

Early-phase oncology studies often involve multiple treatment cycles, resulting in a high volume of data collection and variability in trial length for subjects. Collaboration between data management and statistics groups is crucial during Case Report Form (CRF) creation to avoid duplicate data collection and ensure accurate data capture. Data cleaning processes, including automated and manual checks, must be implemented consistently to prepare data for analysis efficiently.

Integration of Biomarker and Treatment Data:

Oncology trials require integrating diverse external data sources, including biomarkers and concomitant active treatments while maintaining data integrity and blinding protocols. Additionally, certain data undergoes adjudication or confirmation processes. This complex data-handling process necessitates collaboration with statisticians to ensure data availability and optimal decision-making throughout the trial.

High Volume of Adverse Events (AEs) and Serious Adverse Events (SAEs):

Oncology trials often encounter a high volume of AEs and SAEs. SAE data, typically stored separately in safety databases, must be regularly reconciled with clinical trial data to ensure consistency. The sheer volume of AE data can overwhelm trial teams without effective planning and automated solutions. Implementing automated reconciliation listings using software like SAS streamlines the process and enhances efficiency. Additionally, increasing the frequency of reconciliations ensures timely identification and resolution of discrepancies, minimizing data inconsistencies and ensuring accurate reporting based on trial protocols.

Limited Historical Insights:

Oncology trials face significant challenges due to the absence of predecessor trials and limited data availability. This lack of historical data impairs the ability to forecast expected outcomes accurately. Even when novel agents are under investigation in a trial, or there is little information about characteristics or anticipated response,[2] oncology trials can adapt and move fast, highlighting the need for flexible data collection and decision-making.

Data Management Challenges in Adaptive Oncology Trials:

In oncology, the ability to design early-phase trials to support combination therapies is crucial. Leading pharmaceutical companies are incorporating Bayesian and adaptive methods to make their trials more flexible. However, adaptive designs introduce complexities in data management, particularly when trial parameters need midstream adjustments. To fully harness the benefits of adaptive trials while addressing data management challenges, it is essential to have the expertise of experienced biostatisticians. Biostatisticians play a pivotal role in preserving the trial's integrity, ensuring accurate interpretation of findings, and effectively reporting results.[3]

4 REGULATORY METHODOLOGICAL ADAPTATIONS

Regulatory bodies like the US Food and Drug Administration (FDA) and European Medicines Agency (EMA)[4] have increasingly endorsed innovative approaches such as adaptive trial designs and the integration of real-world data (RWD) to enhance efficiency and flexibility in drug development, particularly in areas with high unmet medical needs such as oncology. While precise adoption rates are not commonly disclosed in public communications, the agencies' support is evident through various guidance documents and regulatory frameworks.[5] Despite this endorsement, navigating the implementation of these methodologies within regulatory frameworks can be complex.

Staying updated on regulatory developments and refining strategies to incorporate adaptive methodologies and real-world evidence enables sponsors to navigate regulatory challenges confidently and adeptly in oncology clinical development.

Conclusion

Oncology clinical development presents unique challenges that demand innovative solutions and collaborative strategies. The fast-paced nature of oncology study programs requires rapid validation and optimal data quality, necessitating a departure from siloed approaches where clinical operations and statistical discussions are segregated. Close collaboration between data management and statistics groups is essential to ensure efficient presentation of clinical data to regulators and meet the rigorous demands of oncology programs.

To overcome the challenges, stakeholders in oncology clinical development should leverage experience in designing innovative trials using synthetic control arms, head-to-head comparisons, and trial emulation methods. All these trial designs have distinct regulatory requirements, shaping data collection, storage, and deployment strategies throughout the trial journey. By embracing these innovative approaches and fostering inter-department collaboration, oncology clinical development can enhance efficiency, accelerate drug development timelines, and ultimately improve patient outcomes.

Emerging Trends and Predictions

PRECISION ONCOLOGY FOR PERSONALIZED CARE

Precision medicine in oncology is evolving rapidly, propelled by advancements in molecular profiling technologies such as genomics and proteomics. These methods enable tailored therapies that target specific cancer characteristics, promising improved treatment efficacy, minimized safety concerns, and reduced economic burden. The shift from one-size-fits-all approaches to precision oncology necessitates innovations in diagnostic techniques and clinical trial designs to enhance response rates and ensure global access to these novel therapies. This approach is instrumental in uncovering unique disease hallmarks and driving the development of effective, targeted drug regimens.[6]

The outlook for precision medicine in oncology appears promising, with advancements expected to refine identifying and targeting specific disease markers. This progress will enable increased personalized treatments tailored to each patient's unique cancer profile. These developments could enhance clinical outcomes and optimize treatment costs by reducing unnecessary therapies and prioritizing those with the highest likelihood of success.

THE PREDICTIVE POTENTIAL OF AI AND ML

Leveraging Artificial Intelligence (AI) and Machine Learning (ML) in clinical trials, particularly for drug discovery, represents a transformative shift towards more predictive and efficient research methodologies.[7] The Hierarchical Interaction Network (HINT) significantly advances clinical trial designs by forecasting outcomes based on drug molecules, target diseases, and patient eligibility criteria.[8] Enhanced by SPOT (sequential predictive modelling of clinical trial outcome), which emphasizes recent trial data, these AI tools streamline trial processes, including patient recruitment and maintenance. Systems like Trial Pathfinder, developed by researchers at Stanford, modify eligibility criteria to safely enlarge participant pools, potentially doubling recruitment without increasing risks.[9]

AI applications in clinical trials encompass patient retention by predicting dropout probabilities and customizing interventions, optimizing trial efficiency and accuracy. These innovations underscore the pivotal role of AI in modernizing clinical trials, making them more adaptable and patient-centric.

Healthcare stakeholders are expressing a growing interest in machine learning, leveraging this technology for various purposes. At Cytel, we harness real-world data to inform adaptive trials, using machine learning to analyze this data to guide clinical trial design. As these technologies evolve, they are poised to revolutionize oncology trials.

REGULATORY AGENCIES' INITIATIVES FOR INTEGRATING RWE

The FDA is actively pursuing future-focused initiatives to integrate real-world evidence (RWE) into oncology drug development. One prominent example is the Oncology Center of Excellence Real World Evidence Program, which seeks to modernize evidence development through strategic collaborations and policy enhancements. This initiative underscores the FDA's commitment to using real-world data to inform regulatory decisions, accelerating the advancement of oncology therapies in pre- and post-approval phases.[10]

Similarly, the European Medicines Agency (EMA) is actively pursuing the integration of RWE into its regulatory framework. The EMA's strategic approach includes the establishment of DARWIN EU (Data Analytics and Real World Interrogation Network), which aims to enhance the regulatory assessment of medicinal products across Europe. This network facilitates real-world data usage from healthcare databases to inform clinical and regulatory decisions. By improving access to and analysis of health data across member states, DARWIN EU supports the EMA's mission to ensure that regulatory processes adapt to the evolving landscape of medical research and product development. This forward-looking initiative reflects a broader commitment within the EMA to harness RWE for more dynamic and patient-centered regulatory decision-making, enhancing the responsiveness and effectiveness of health interventions across Europe.[11,12]

DECENTRALIZED CLINICAL TRIALS FOR PATIENT ACCESSIBILITY

Decentralized clinical trials (DCTs) are transforming the oncology research landscape by enhancing patient accessibility and streamlining trial processes. The FDA's Oncology Center of Excellence has emphasized the role of DCTs in advancing cancer research, promoting patient-centric strategies and incorporating digital health technologies to facilitate trial participation from diverse locations.[13] Recent studies highlight that DCTs can significantly reduce participant burden, potentially increasing enrollment and diversity in clinical trials.[14] Moreover, these trials leverage digital tools and real-time data collection to enhance the efficiency and effectiveness of oncology studies.[15]

The future of oncology trials likely involves a greater integration of DCTs, driven by technological advancements and regulatory support. This shift promises to improve the scale and scope of research and make clinical trials more adaptable and patient-friendly. The successful implementation and expansion of decentralized trials in oncology will rely significantly on the ongoing development of supportive regulatory frameworks and innovative digital solutions.

NAVIGATING ECONOMIC CHALLENGES

Economic considerations are increasingly important in oncology drug development. New treatments must demonstrate not only clinical efficacy but also cost-effectiveness. Despite the large number of cancer treatments (approximately 1600) in clinical development in 2023,[16] the development of oncology treatments remains relatively expensive compared to several other therapeutic areas, particularly evident in Phase I trials. This ongoing challenge for sponsors underscores the importance of identifying cost-saving measures.

Adaptive trial designs allow mid-trial adjustments like sample size re-estimation, stratification, or other protocol updates, taking advantage of emerging positive data (illustrated by the Champion Trial case study). These planned modifications not only provide strategic benefits but also ensure safety. They enable dosage changes and other crucial adjustments, helping maintain the trial integrity and success while optimizing resource utilization and reducing risks.

In a strategic effort to refine their Phase III oncology study, a prominent pharmaceutical sponsor partnered with Cytel to explore an adaptive Sample Size Reassessment (SSR) design, aiming to enhance efficiency compared to their existing Group Sequential Design (GSD). Through this collaboration, it was revealed that the SSR design, developed using Cytel's pioneering software, could potentially reduce the trial's sample size significantly—by 700 patients—and expedite study completion by 12 months if efficacy were proven. This optimization could lead to a 20% reduction in study duration and a cost reduction of 28 million USD, highlighting the potential impact of innovative trial designs on cost management in oncology drug development.

Glossary

Adaptive trial design:

A method in clinical trials that allows for modifications to the trial or its statistical procedures as it progresses based on interim data. This approach enhances flexibility and efficiency, potentially reducing the time and cost associated with traditional fixed designs.

Artificial Intelligence (AI):

The simulation of human intelligence processes by machines, especially computer systems, which can include learning, reasoning, and self-correction. In oncology research, AI applications can streamline the drug discovery process, enhance data analysis, and improve clinical trial efficiencies.

Bayesian methods:

A statistical framework that incorporates prior knowledge or beliefs, along with new data, to update the probability for a hypothesis as more evidence becomes available. This method is particularly useful in adaptive trial designs, allowing for continuous learning and decision-making throughout the trial.

Biomarkers:

Biological markers are used to measure and evaluate physiological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. Biomarkers are essential in oncology for diagnosing diseases, predicting therapeutic responses, and monitoring the effectiveness of treatments.

Machine Learning (ML):

A subset of artificial intelligence that uses algorithms to parse data, learn from it, and then make a determination or prediction about something in the world. In clinical trials, ML can be used to optimize study design, improve patient selection, and predict outcomes based on historical data.

Precision medicine:

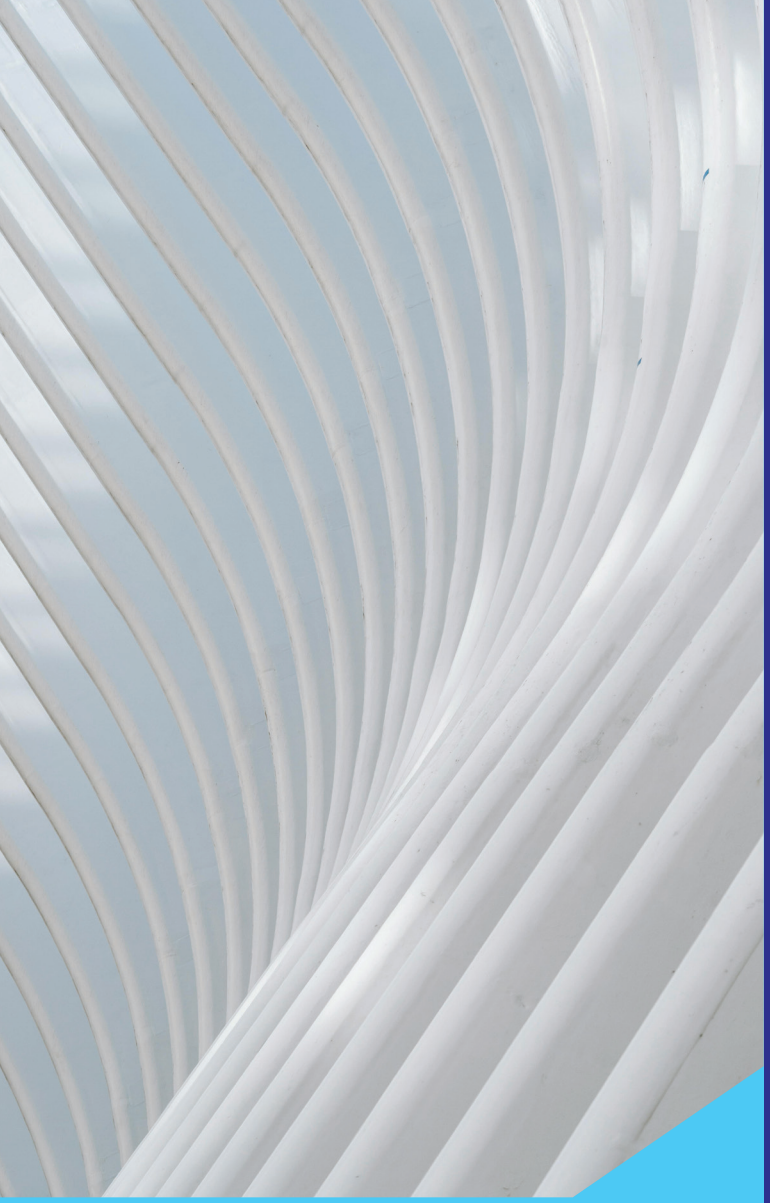
A medical model that proposes the customization of healthcare, with medical decisions, practices, and/or products being tailored to the individual patient based on their predicted response or risk of disease. Precision medicine often relies on genetic, genomic, and clinical data to make more accurate treatments possible.

Real-World Data (RWD) and Real-World Evidence (RWE):

RWD refers to the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. RWE is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

Synthetic control arms:

An approach in clinical trials where existing data from previous trials or real-world evidence is used to create a control group, rather than recruiting new patients to serve as the control. This method can expedite trials and is particularly useful in situations where patient recruitment is challenging or unethical.



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