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The Need For Adaptive Trial Design

In Oncology Studies

Knowledge Sharing Series

Overview

The changing nature of clinical trials means studies in all therapeutic areas are rising in complexity.

But even with thousands of pharmaceutical trials currently underway across the globe, oncology trials are still presenting more difficulty to sponsors due to size and numerous changes in study protocols.

According to the May/June 2021 Impact Report from the ***Tufts Center*** for the Study of Drug Development (Tufts CSDD), each phase of a traditional oncology trial can last nearly two years longer than those of non-oncology trials [1].

The report also noted the following: "Clinical trial durations of oncology drugs are 30-40% longer than other drug trials, due to more complex designs and difficulty finding, enrolling, and retaining study volunteers" [1]. In addition to the expected complications that can arise from cancer studies, there are more sites, more countries, and more diverse patient populations involved than ever before.

Also, consider these additional findings from Tufts CSDD [1]:

- The number of oncology drugs in development grew at nearly double the pace of any other therapeutic area over the last decade
- Oncology phase II/III trials have higher average numbers of significant protocol amendments
- Oncology trials typically involve more countries and sites, but enroll fewer participants
- Oncology-focused protocols are more complex and associated with higher failure rates

1. Protocol complexity and patient enrollment intensify challenges in oncology trials, Tufts Center for the Study of Drug Development Impact Report, 23(3), 2021

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Overview

Trial research needs to account for increased complexity and competition when recruiting patients in cancer studies. Patients and oncologists have more choices than ever for the placement of qualified study participants. Not only are treatments more specialized, but the industry is finally beginning to see positive results from decades of research.

No longer do researchers have to rely solely on traditional approaches to existing cancer treatments, such as chemotherapy. Now, patients are being considered for immunotherapy as well as cell and gene therapy. According to the Alliance for Regenerative Medicine, at the outset of 2021, there were 1,220 active worldwide clinical trials in regenerative medicine and advanced and cell and gene therapies, with a majority (554) of them aimed at oncology [2].
While these therapies are still young, and there is much research left to conduct before they can be considered 'proven' treatments, they provide more options for researchers and patients alike. In parallel, researchers are finding more accurate, thorough cancer screening methods and ways to improve patient quality of life during and after treatment. Patient survival is no longer the only focus. As treatments become more and more successful, patients deserve to have fewer side effects and enjoy greater health after their oncology treatments have concluded.

No longer do researchers have to rely solely on traditional approaches to existing cancer treatments

2. Visit: alliancerm.org/arm-event/ sotibriefing

The Impact of Specificity and **Choice on Patients**

It's a significant understatement to say the human impact of delays can be serious if trials do not better facilitate the delivery of medicine to participants. With so many variables in play, traditional trial models – in which dosing levels and delivery cadence are rigid within the initial study protocol – are too limited to accommodate modern, more complex oncology studies.

With oncology trials making up roughly one-third of today's active studies across multiple countries, the drugs being tested are more targeted beyond just treatment. Rather, they're targeted at the specific mechanisms that fuel cancer growth and spread. While this is certainly an exciting development for oncology studies as a whole, finding and enrolling qualified trial participants is far more difficult, and delays are common.

Recruitment and retention present the most significant roadblocks to trials, especially in early-phase research. Oncologists have many studies from which to choose, and if there are numerous protocol amendments from the outset, which may force costly delays, it may dissuade oncologists from further enrolling patients into a study.

Enrollment rates for oncology trials are generally low from the outset of a study, with as few as one to two patients per site over the course of the study. This makes every testing modification crucial; if you spend too much time processing protocol amendments to add new dose levels you could lose a significant portion of your enrollment to other trials.

A More 'Personalized' Approach to **Oncology Treatment Strategy**

In a traditional trial model, researchers typically focus on one particular facet of the study and then move ahead once a successful outcome is achieved. These facets include but are not limited to dose level, dosing frequency, combination therapies, patient types that respond better to specific treatments.

Adaptive trials have the ability to make determinations on multiple facets of a trial at once, helping to move the trial forward – or back to the last safe baseline – more efficiently.

Perhaps more than any other therapeutic area, oncology trials demonstrate a need for less rigid models. From the outset, there are simply too many potential variants and treatments to accurately predict patient response, much less determine appropriate next steps within a blanket trial approach.

Oncology trials need to be more flexible (with more assertive treatment changes) because of the nature of cancer. When compared to other therapeutic areas, such as diabetes, the reward for innovative treatment is far greater.

Oncologists are accustomed to altering treatments per patient, such as when they adjust a chemotherapy regimen based on how the patient is faring that day. Other disciplines don't always have that flexibility.

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Benefits for Determining **Optimal Dosing**

For phase I oncology studies, adaptability is key for determining accurate dosage levels. In other words, protocol amendments are all but guaranteed. Oncology trials for high-toxicity pharmaceuticals can be extremely dangerous, necessitating numerous changes to dosage and cadence throughout a trial depending on each patient's ability to tolerate the treatment and the efficacy they experience.

Before efficacy can even be considered, trials need to demonstrate safe levels for:

- Dosing level
- Dosing frequency
- Potential combination therapies

Trial sponsors are typically prepared for frequent protocol changes for dosing prior to the beginning of a trial. However, when only the molecule or compound is consistent, there's a tremendous number of other changes to accommodate.

*Allowing **flexibility to adjust the dosing regimen** patient by patient **can save lives,** and oncologists need that flexibility not only with commercial products but with experimental therapies.*

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How Master Protocols Can Help

Oncology trials can benefit from master protocols, which allow for multiple sub-studies that investigate treatments for one or more disease subtypes within an overall trial structure. In many ways, it's like a map detailing different paths to the desired outcome, even though the trial sponsors don't necessarily know which direction their study will evolve.

They work to improve efficiencies in clinical trials; Deloitte estimates master protocols reduce timelines by 12-15% on average [3].

There are two types of master protocols currently used. First, a basket trial involves a single investigational drug or combination therapy that is studied across multiple cancer populations defined by disease stage, histology, number of prior therapies, genetic or other biomarkers, or demographic characteristics. In basket trials, all patients receive the same treatment, targeting the marker found in their specific cancer type. An umbrella trial is designed to evaluate multiple drugs administered as single drugs or as combination drugs in a single disease population. For oncology studies, patients receive treatment based on specific markers identified, on a patient-by-patient basis. The drugs being tested may change if new markers are found, or if new treatments become available for that type of cancer.

> Deloitte estimates master protocols reduce timelines by 12-15% on average.

3. Visit: www2.deloitte.com/content/ dam/insights/us/articles/4509_ Master-protocols/DI_Master- protocols.pdf

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How a Modern RTSM **Can Better Support Complex Master Protocols**

Traditional randomization and trial supply management (RTSM) setups are typically not built to support the level of flexibility and agility needed for the complexity of oncology trials. With modern RTSMs, not only can you build in flexibility from the onset, but midstudy changes and amendments can occur as frequently as needed without sacrificing quality.

Though older, more rigid RTSMs are technically capable of handling such flexibility, it often requires sites to either pause treatment for weeks or months or to manually handle these changes, creating a risk of inaccurate data or other human error. By contrast, a modern RTSM that is built to enable flexibility, regardless of how many amendments or supply changes occur, can dramatically reduce the administrative burden.

Building a flexible oncology trial design within a modern RTSM allows investigators to see what's working and expand upon it, without disrupting other facets of the trial. These smaller sub-studies still funnel results into the larger study, without having to wait for the conclusion of the trial to determine if endpoints were met. Instead, a smaller, 'patient-by-patient' approach gives them near-immediate data to help inform later phases of the trial.

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Managing Cohorts **With an RTSM Within Frequently Amended Protocols**

As discussed, finding optimal dosage in oncology studies can be a moving target. As dose levels are added to the process patients in lower-dose cohorts may need to increase their treatment level. For others, new dosing cadences or even combination therapies may be introduced to the study. All of it needs to be accounted for, with zero margins for error.

This level of efficiency can be achieved, in part, through realtime management of cohorts, handled by the sites themselves using a capable RTSM. This not only improves the speed at which dosing changes are made but also centralizes the documentation of these changes, giving users a detailed audit trail for each protocol.

Ability to support creative designs

As trial designs follow the science, your RTSM needs to enable different methods of assigning, opening/closing and overall managing cohorts. Not every possible outcome is known at the beginning of a study, so the system must beable to allow for changes without waiting for custom coding.

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Conclusion

Clinical trial sponsors are often required to adjust treatment regimens fairly regularly until they determine what works for their patients. But, with limited enrolment pools and high competition between studies it has never been more important for trials to be operationalized in an agile fashion.

*Moving to **adaptive design optimizes the time and resources** needed to accommodate frequent, increasingly complex changes without risking costly delays.*

*For **highly varied oncology trials,** which often see multiple iterations of combination therapies designed for rapid treatment of patients, **time and resource efficiency is paramount** for studies, and the patients they serve.*

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Meet **Kathleen Greenough**

About the Author

Kathleen Greenough, VP Biotech Operations at 4G Clinical, has 19 years of experience in life sciences spanning Clinical Operations, Finance, and IT. Her wide range of solutions implementation expertise includes RTSM, CTMS, trial costing tools, OLAP financial suites and patient enrollment planning.

Kathleen has also spent many years as a Clinical Financial Planner and Analyst at a major biotech in Cambridge, MA, gaining a broad and deep understanding of the challenges inherent in Clinical Development. Specializing in software adoption and a frequent speaker at industry conferences, Kathleen is most in her element when working within a user community to facilitate solutions that are insightful and truly helpful.

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Still have questions?
Contact us today to start a conversation.

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About 4G Clinical

We reduce the time it takes to commercialize vital medications by delivering validated, easily extendable RTSM capabilities to Pharma and CROs faster than anyone in the world.

4G Clinical is driven by a single purpose: bring crucial medicines to those who need them, faster. 4G Clinical believes that the way to accelerate clinical research is by disrupting the way trials are executed. That's why we have revolutionized RTSM (randomization and trial supply management) and supply forecasting capabilities and services from the ground up.

4G Clinical is committed to helping sponsors and CROs follow the science, wherever it may lead, as quickly and as safely as we can. While we will not discover the next novel compound in the lab, we are doing our part by leveraging our extensive experience and technological innovations to bring speed and agility to clinical trials.

Prancer RTSM®

Our 100% configurable and agile RTSM is built for the clinical trials of today and tomorrow.

4G's RTSM platform, Prancer RTSM®, utilizes natural language processing alongside integrated clinical supplies forecasting and management functionality to slash development timelines, increase operational efficiencies and offer exceptional quality.

Bringing crucial medicines to those who need them, ***faster.***

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