Clinical Trials of the Future

John F Tomera at WorldCare Clinical explains the impact that portfolio management, adaptive design, scheduled interim analysis and clinical imaging CROs can have on clinical trials

Portfolio management in the biopharmaceutical industry depends on a clear and careful balance between costs, risks, timing, options, revenue and fit within the strategic drug development model. The tools of adaptive design and scheduled interim analyses can help sponsors make better portfolio decisions when working with imaging CROs. A trial based on an adaptive design can also integrate a variety of international sites with domestic sites. While adaptive designs themselves are not new, they always require initial planning that may be unfamiliar to most sponsors.

The complexities of clinical trial management are well-known and are often unpredictable. Severe repercussions of stopping a trial early necessitate both statistical and clinical judgment. Methods that employ adaptive design and scheduled interim analyses can help inform this decision when used in a blended strategy. Some studies, particularly those which require greater sample sizes, will benefit from quicker adaptation or faster answers to crucial questions, while others may be designed more efficiently with a standard approach. Adaptive designs can be used to evaluate technical successes and can be instrumental in balancing the need for continued staff resourcing with trial costs. To this end, imaging CROs can help maintain portfolio value by curtailing superfluous costs, as well as assist in scaling up or down radiology reads more quickly and efficiently, according to the strategy of the sponsor, in order to help determine whether the trial should continue or not.

ADAPTIVE CLINICAL TRIAL DESIGN VERSUS TRADITIONAL APPROACHES

Put simply, an adaptive trial is a framework that aims to complete a trial faster, without compromising on the quality of the trial or safety of the drug. Imaging CROs can help facilitate the adaptive trial for sponsors beyond those issues and aspects presented within the FDA Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics (1). It promotes more efficient clinical trial activities that can decrease the overall time-to-market of the drug and is based on the 'learn and confirm' model, where a result is confirmed immediately through parallel studies, rather than waiting for the completion of the entire phase.

Additionally, adaptive trials focus on making the process more flexible to empower sponsors to make modifications in response to data collected during the trial. Empowerment is contingent upon the predefinition of sponsor response action and decision-making rules, and is deployed by the application of scientific study modification points (SSMPs) that can occur frequently (in a fully sequential design) or at other predetermined intervals. SSMPs are defined prospectively by the sponsor and include anticipated actions for handling decisions made downstream from trial initiation.

Conceptually, adaptive or flexible trial design allows for changes and amendments to take place after a trial has started without compromising the scientific method (2). This form of planning and implementation means that team and technology benefits can be realised at the front end of the adaptive trial design process and precludes a late-stage disaster from occurring. It is critical, however, that decision-making rules governing the adaptation are clearly stated in the study protocol for all forms of adaptive design. This is the most important distinction necessary for maintaining the research perspective in this type of trial compared to other more standard types.

The traditional approach to clinical development involves conducting modest-sized dose-ranging studies in Phase II. Once the results of Phase II trials have been analysed, they are followed by a larger confirmatory Phase III study (or studies). In contrast, an adaptive clinical trial strategy allows for midcourse adjustments to be made to ongoing trials without them stopping. The adaptive design uses the results of interim analyses to continuously 'fine-tune' dose selection, treatment duration, sample size, and potentially other key parameters while allowing the study to continue.

Usually, adaptive trials by design have a mid-study analysis and decision points that will change the way a study is conducted. As adaptive trial methodologies are relatively new to most pharmaceutical and biotech companies and their vendors, there is the potential that mid-study modifications to the study design could have a negative impact on the clinical trial if not properly executed. This is where the use of an imaging CRO can prove crucial.

THE ROLE OF THE IMAGING CRO

Imaging CROs manage medical images in clinical trials and work intimately with sponsors, investigative sites and other centralised CROs that may be handling other aspects of trial data management. Many pharmaceutical firms and related companies rely on imaging CROs for their expertise in clinical trial image acquisition and their quality assurance processes, attesting to both scan integrity and the objective assessments of independent radiologists.

The pharmaceutical industry recognises the strategic business benefits of portfolio management, but many companies face numerous challenges in implementing effective, results-oriented solutions. Imaging CROs have become an increasingly indispensable service in medical diagnosis and translational research, both of which are relevant to pharmacology and drug development. Therefore, imaging CROs remain a central intersection where many healthcare professionals collaborate.

By aligning their efforts with the goals of the FDA and its Critical Path Initiative (CPI), imaging CROs can play a pivotal role in advancing and streamlining clinical testing and drug development, especially when it comes to reducing R&D costs. Through their facilitation and management of the process for collecting scans and image interpretation for objective and independent end-point assessment, imaging CROs provide the key to more efficient and informative clinical research and can help determine whether or not a response to a test compound has been identified and confirmed. This process ultimately holds the promise of making many new medicines available and affordable for patients.

TECHNICAL BARRIERS

While the FDA is increasingly requesting that imaging studies be included in regulatory submissions for new drug approvals, a number of technology gaps and infrastructural needs still remain (3). Imaging CROs, however, are well-positioned to bridge these gaps and overcome many of the technical barriers that have impeded progress in this area to date.

One of these barriers involves internal standardisation efforts. Consistency in the processes of capturing imaging data is critical to the validity of imaging study results. Calibration procedures, consistent across multiple imaging devices, among images taken by the same device, and images taken across time, must be accurate. A Phase III medical imaging study, for example, may include 1,000 patients at 100 different clinical sites, and its dispersed data collection strategy will require strict adherence to study protocols for calibration of imaging equipment, as well as anatomical positioning of research subjects. An imaging CRO can provide clinical trial sponsors with guidance in designing an appropriate Independent Imaging Review Charter (imaging charter) for submission to the FDA. It is also responsible for the image acquisition protocol, typically as part of an image preparation and submission guide, developed before the study begins. The documents specify a standard manner for acquiring, managing and assessing images to ensure that data from multiple imaging sites is collected consistently.

Another technical barrier that requires consideration is internal evaluation and validation. This is particularly important in three-dimensional clinical imaging, where customised computational algorithms are used to interpret images and assess disease progression. While the software used to interpret images continues to evolve, some investigators argue that the time required for training is not cost-effective and the tasks are not user-friendly. Because of the unique niche of the imaging CRO, such customisation is performed more routinely and proficiently than at sites or institutions where there is only an episodic need.

Imaging CROs also play a role in performing quality control checks to verify administrative and interpretative details. For proficient use of the scans, imaging CROs align data definitions for interpretation in software relating to differing anatomical regions of images or adjudication criteria for radiologists to interpret them more easily.

When it comes to data transfer and archival systems, imaging CROs have circumvented the sponsor reliance on couriers to transfer digital imaging data from the clinical sites to their internal sites for analysis. The cost of courier services previously greatly inflated therapeutic development costs.

As with any regulatory environment, storage and retrieval systems are required to archive data for the long-term. The current range of image file sizes is generally between 500 megabytes (MBs) and 10 gigabytes (GBs), with file sizes expecting to move toward 120GB over the next few years. Therefore, storage capacity quickly becomes an issue when dealing with large files in such a heavily regulated environment. Image files that are changed or manipulated are always saved as new files to maintain transparency and documentation for FDA review, thereby multiplying storage requirements. Some imaging CROs now offer the ability to hold a sponsor's images in a secure database until it has been determined whether a central review of the imaging data will be required, thereby removing the burden from the sponsor.

Imaging CROs also help to preclude variability and comparability issues from plaguing scans by using data formats and transfer procedures via the Digital Imaging and Communications in Medicine (DICOM) industry standard. When DICOM is not used, differences in transfer procedures complicate comparability and integration during later analysis stages.

MUST-HAVES FOR SUCCESS

The communication and teamwork required for adaptive trials are very different from the linear approach taken in traditional trials. In an adaptive trial, communication requires that team members are brought together earlier and more often throughout the trial. Members need to be involved at the SSMPs to analyse the impact of modifications to their areas of study conduct. Once the analysis and decisions have been made, the predetermined logistics required are executed by the team members or automated systems.

In an adaptive trial setting, a monitoring board may have the option of responding to interim safety and efficacy data. This data can come from the trial itself or other new information in the drug development process that was not available at the start of the study. The Independent Safety and Monitoring

Board can respond to the new information in a number of different ways, including narrowing the trial focus or increasing the patient population. An example of narrowing the trial focus might include removal of one or more of the treatment arms based on predetermined futility rules. Alternatively, if the data available at the time of the review does not allow for a clear decision between utility and futility, it might be decided to expand the enrolment of patients on one or more of the treatment arms beyond the sample size targeted initially.

Options are available in an adaptive trial (such as patient allocation and their sampling in subsequent stages; when to drop an arm or stop the trial; and decisions affecting sample size, combining phases, and/or adaptive randomisation), unlike a standard trial, where safety and efficacy data may be reviewed by a monitoring board during scheduled interim analyses. The response to this data in a standard trial is generally either to amend the protocol or stop the trial and start a new one. Both responses are costly to timelines and budgets.

The ability to forecast and simulate gives greater confidence to the success of the adaptive design and, in many cases, will sort out problems before they happen. Simulations show different implications of patient recruitment, patient randomisation schemes, drug supply, product economic impact, clinical outcomes and sample size. Undercutting the costs of all of these anticipated entities to effective trial design will be the proficiency of clinical imaging services, based on both their expertise in technology as well as processes governed by quality assurance.

A BRIGHT FUTURE FOR ADAPTIVE STRATEGIES

Adaptive strategies offer several clear advantages, including the elimination of 'downtime' between trials. This allows investigators to continue to accrue patients and maintain the momentum established in Phase II through Phase III. Additionally, adaptive strategies help reduce the number of patients who receive ineffective or possibly unsafe doses of the study drug.

For fixed sample size trials, patients are currently enrolled to all treatment groups with little regard to emerging efficacy information obtained during the trial. Adaptive trial strategies could be designed to gradually favour higher performing treatments. Ethically, it is preferable to reduce patient exposure to doses that have demonstrated limited efficacy or potentially important safety signals. Adaptive trials allow for a 'go' or 'no-go' decision at a very early stage. This decision is addressed at each stage of adaptive clinical trial to help determine whether to continue or stop the study, helping sponsors save significant time, money and effort.

CONCLUSION

The culmination of a successful adaptive trial requires significant coordination of people, information and technology. Implementation of traditional clinical trials allows for more waterfall and stepwise manners, while an adaptive trial requires involvement from all disciplines, all the time. With pressures concerning patent expirations and revenue inflow sustainability, R&D has been the hardest-hit department within pharma companies. Consequently, companies are under intense pressure not only to increase the number of drugs in the pipeline, but also to shorten the time-to-market period, which is generally 10 to 12 years and can cost over a billion dollars. Among various innovative processes being implemented, adaptive clinical trials are one of the most promising to portfolio management, because these trials aim to advance a decision to either stop or continue with a trial at a very early stage. This allows the sponsors to decide whether or not to spend time and effort on trials that are more likely to be unsuccessful in the future. When adaptive clinical trials employ clinical imaging services, two very effective means of achieving a cost-effective end result have been set in place.

About the author

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