

Technology-assisted Cohort Optimisation of Early-phase Multi-centre Patient Studies

The common aims of early-phase research centre around helping to define the safety, tolerability and pharmacokinetics of a drug at single or multiple doses (or even multiple formulations) typically administered in an ascending manner.

These early-phase studies are sometimes referred to as “cohort” studies as they are characterised by a relatively small number of subjects being enrolled at each dose or cohort across one or more sites. For example, a single ascending dose (SAD) study will classically enroll subjects in four to six independent cohorts in a sequential manner with each cohort being initiated following completion of data review at a certain time point of the current cohort; while a multiple ascending dose study may require even more cohorts. More recently, there has been an effort to ensure a seamless transition from single to multiple dose cohorts (SAD-MAD) within a single study often consisting of up to 10–12 cohorts across as many sites. Of note, some sites may be engaged early on in the enrollment process while others are activated in a staggered approach. Unlike studies seeking to enroll normal healthy volunteers at a single site, the majority of early-phase cohort studies in patient populations are conducted across multiple sites with the number of sites being dependent upon sample size, length and complexity of the study, and the recruitment potential of the indication of interest. For patient studies it is common for multiple sites to be engaged in the simultaneous enrolment of patients into a single cohort. Therefore, it is imperative to ensure the accurate and timely assignment of patients into each cohort while guaranteeing that all screened patients who are eligible for study participation are actually randomized, and that there is no chance of over-enrolment. This requires the centralised monitoring of rapidly changing recruitment efforts

and notifying sites of fluctuating accrual speed and limits in real time. This monitoring may involve moving some patients from screening to randomisation, holding others back, and opening/closing recruitment across multiple sites simultaneously. Tasks such as these lend themselves to a technological solution such as interactive response technology (IRT). Much like interactive voice response systems (IVRS), IRT, sometimes called IWR for interactive web technology, uses the internet instead of the phone to serve as a gatekeeper and data tracker, and has obvious advantages over IVRS in terms of speed, accuracy and ease of use.

Battling Recruitment Fatigue

In early-phase drug development there are multiple strategies which may be employed to help ensure successful cohort study conduct all requiring a high level of data tracking and operational acumen. In order to be both efficient and successful, a unified approach must be undertaken not only to ensure that timelines are met but also that the study enrolls appropriate patients and yields high-quality data. Each study therefore requires a well-defined and unique strategy which can leverage enhanced technology to ensure rapid and proper enrolment of patients, the seamless collection of data, and the timely scheduling of safety review meetings complete with relevant outcomes in the most efficient manner possible¹.

These strategies can also be utilized to help combat recruitment fatigue as cohort studies across numerous patient populations often suffer from sluggish enrolment as site staff can become resistant to sponsor demands to repeatedly commence and halt their recruitment efforts. Additionally, site staff are particularly sensitive to situations in which a potentially eligible patient is actually overlooked due solely to the timing of cohorts or other procedural delays. This interruption in recruitment and

inability to randomise every eligible patient may result in recruitment fatigue, with poor and variable enrolment at a site that cannot be forecasted accurately.

The Virtual Patient Waiting Room

In an effort to increase the predictability of timelines, stabilise enrolment fluctuations, master the timing and unpredictability of complex cohort designs, fight recruitment fatigue and ensure that all eligible patients who can be randomized actually are randomized, a technology-assisted “virtual patient waiting room” was created. This virtual waiting room permits investigators to recruit patients on an ongoing, rolling basis in a “next in line” approach that permits multiple sites to simultaneously enroll patients into a single cohort, while continuing to recruit for the upcoming cohorts. Patients recruited who meet eligibility criteria when randomisation is closed for a specific cohort are simply placed in the virtual patient waiting room while screening activities continue for the subsequent cohorts. This simple maneuver stabilises recruitment efforts and patterns such that sites do not have to be shut down and started back up multiple times. By utilising this strategy, the appropriate enrolment of each individual cohort can be more easily managed simply by proper programming of the IRT to ensure that all eligible patients are randomized, that there is no over-enrolment within the cohort, and that the time between cohorts is minimised. Importantly, forecasting important metrics such as last patient visit in each cohort can be easily achieved. As many sites requiring local IRB/EC approval take longer to start up, they are at a disadvantage in enrolment compared to sites who use central review; and utilising an IRT-assisted cohort optimisation strategy will permit an equal opportunity for all sites to enroll in a particular cohort despite regulatory disadvantages.

Advantages of IRT

In addition, IRT can be utilised to successfully manage the appropriate dosing and often complex timing/tracking requirements mandated per protocol. For instance, in a classic cohort study design which requires sentinel dosing, the first one to three patients dosed within each cohort are more strictly monitored to determine tolerability for a given time period prior to administration of the next dose. In this situation, the IRT can be designed to effectively halt enrolment not just within a site but across sites, to ensure that there is no additional enrolment until the requisite time period is met². Additional “breaks” may be implemented to ensure that all safety parameters are observed, i.e. no further dosing proceeds until a one-week period has occurred following the dose of the nth patient in each cohort, depending upon study specifications. The IRT can simply restrict further randomisation until this or any time parameter is met.

Cohort Modelling

Importantly, information that is typically used to generate enrolment curves across an entire study can also be modelled to reflect a specific cohort, and this model can vary from cohort to cohort. For example, enrolment rates may be very low in the first cohort but peak by cohort number three or four as the “virtual waiting room” fills with appropriate patients. Screen failure rates also vary with cohort succession with the highest rates usually evidenced in the first cohorts and then continually declining over successive cohorts or until the investigators’ patient database is exhausted. These cohort metrics can be used to estimate the number of sites needed to enroll at any one time period, noting that not all sites need to be actively recruiting at the same time. For example, in a common SAD-MAD study of 10 cohorts enrolling eight patients per cohort (six drug and two placebo) it may be necessary to launch at least 12-16 sites overall, although only six to eight would be active at one time with three to four utilised for the last two cohorts only, especially if the last cohort is expanded in terms of sample size or treatment duration. It is important to note, however, that

those sites activated last should not be viewed as “back-up” sites as it is imperative that they are initiated and fully ready to screen early on in the timeline.

Of course, using this IRT-assisted cohort optimisation strategy requires adding screen time for patients currently in the virtual waiting room, with an average screen time of 42-49 days recommended. The benefit of this increased screen time is that it allows patients to be in the virtual waiting room for longer periods of time and not be screen failed simply due to the screening time elapsing. Even though this recommendation of 42-49 days may be two to three times longer than the screen times in typical SAD/MAD studies, this time is more than recompensed over the length of the entire study conduct. In fact, our experience in a recent set of Alzheimer’s disease studies suggests that the use of the IRT-assisted cohort optimisation saves an average of 2.9 weeks per cohort. In a 10 cohort SAD-MAD study, the overall timelines were reduced by over six months compared to studies conducted using a standard approach to recruitment.

Increased Safety Data Vigilance

In addition to promoting continuous recruitment efforts across sites, IRT also permits increased data vigilance enabling more accurate and timely review of safety data. In cohort studies, a review of safety data is typically required prior to escalating to the next cohort and the parameters for the advancement to successive cohorts can be incorporated into the IRT specifications. For example, once the nth patient in a cohort completes a certain visit (nominally week four or six visit), the site is required to enter all data into the electronic data capture (EDC) system within 24 hours of the patient completing that visit. Haematology and chemistry lab results should be returned to the site minimally two days after being drawn and therefore would be available for monitoring by the designated site monitor and/or physician. The regional monitor could then plan their visit to the site two days after the patient completes the week four or six visit. This would ensure

that all relevant data is monitored, cleaned and available prior to the cohort safety review meeting. Once analysis of any pharmacokinetic, pharmacodynamics or biomarker variables have been completed, data management can run the appropriate patient profiles or listings required for the cohort safety review meeting.

Examples of Cohort Optimisation

An example of the benefits of optimising cohort management via IRT is evidenced by the recent conduct of two separate Phase I, double-blind, placebo-controlled studies designed to establish the safety and tolerability of both single and multiple ascending dose(s) of blinded verum in patients with Alzheimer’s disease (AD) across similar SAD to MAD settings. A total of 80 patients for the first study, and a total of 57 patients for the second study, were enrolled across 10 dose-ascending cohorts for each study. Screen failure rates were 54% and 45%, respectively. For the first study, patients were enrolled across twelve sites in the US and Europe, while patients were recruited from nine clinical sites across five countries in Europe for the second study. For both studies, the main objective was to assess the safety and tolerability, and pharmacokinetics across SAD and MAD cohorts. Having appropriate Phase I facilities and experience, access to neurologic imaging centres, and familiarity with cerebrospinal fluid (CSF) sampling procedures were critical factors in the site selection process for both of these studies.

One primary challenge shared by both of these studies was related to the method of cohort management and escalation requirements. The complex design of two component sub-studies (SAD and MAD) resulted in the implementation of a unique strategy to support study screening and enrolment activities and direct escalation to subsequent cohorts. Importantly, in one of the studies, patients were able to roll over from the SAD to the MAD cohort; and in the other study, patients that discontinued early were replaced rendering accurate tracking via IRT obligatory. In both studies, the project team worked closely with the IRT staff

to program and successfully leverage the technology necessary to support these trials, permitting vigorous and competitive enrolment to occur across multiple site simultaneously, and importantly providing an equal opportunity to enroll patients across selected cohorts. Cohort transition was determined by a series of programmable criteria based upon the unique protocol requirements. Medical monitoring staff were responsible for authorising dosing of patients within a cohort via electronic approval, while the project management staff were responsible for the activation and closure of given cohorts based upon the outcome of each safety review meeting via IRT. The combined efforts across all functional groups and implementation of this technology facilitated continuous study management in which recruitment into a fixed cohort of patients could be controlled centrally across multiple site locations.

One key factor in the successful conduct of these cohort studies can be attributed to the speed and accuracy of data collection as well as efficient cohort management. The project team created a streamlined, effective process specifically tailored to these studies that was designed to facilitate an ongoing review of patient eligibility on the part of the study medical monitor.

Information was gathered from various data sources and compiled for easy review and confirmation of patient status. Ongoing details were provided to ensure patient wellbeing was maintained throughout the treatment period. Routine contact with sites coupled with a rolling data review resulted in the successful achievement of having over 90% of data clean at all times. This in turn permitted timely scheduling of the intra-cohort safety review meetings, saving even more time. Notably, a detailed written cohort management plan not only supported protocol compliance, the realistic opportunity for enrolment of eligible patients across sites, the consistency in patient visits, but also importantly the optimisation of the management of the various cohorts, saving time and costs while safeguarding patient safety and quality.

Conclusion

The ability to facilitate the uninterrupted recruitment of patients across multiple sites results in a continuous screening process, alleviating disruption in momentum and recruitment fatigue in cohort studies. This use of an IRT-assisted cohort optimisation strategy allows each site an equal opportunity to enroll patients, decreases burden upon sites by providing a tiered screening approach, and allows for more accurate study planning and



preparation for both patients and caregivers (i.e. accommodation for travel plans/vacations). Safety and data review committee functions are also managed within this technology driven methodology, yielding high quality data while minimising review timelines and transition between cohorts. In summary, the technology-assisted cohort optimisation strategy outlined above results in faster progression through cohorts while preserving study data integrity in early phase multi-centre studies saving both time and money.

REFERENCES

1. Morissey, M., Roberts, R., O’Gorman, B., Wells, D. Applying New Technology to Randomization, Cohort Management and Dosing in Multi-centre Early Phase Trials. Applied Clinical. Trials, Jan 15. 2015. www.appliedclinicaltrials.com
2. Byrom B. Using IVRS in clinical trial management. Applied Clinical Trials. 2002; 10: 36-42

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