Mitigating Risks of Block-enrolled Ophthalmology Studies

The use of block enrolment in ophthalmology trials helps enrolment keep up with the speed of these studies. However, the challenges inherent in their successful execution are numerous. Some studies complete enrolment in a single day, while others enroll in "blocks" over consecutive days or weeks to take advantage of this accelerated recruitment. These aggressive timelines create risks in the logistics of successful study completion. Therefore we, at Ora, Inc., have developed effective practices to mitigate these risks.

A standard, multi-person team contains a single technician per principal investigator (PI). Typical block-screening organisation sets up processes which allow for efficient movement of patients through the visit in a time and space-dependent manner. A waiting area is set up and logical, protocol-driven rooms are arranged to move the subjects through proficiently, allowing individual oversight at each test point by the PI and the study staff. This process ensures timeliness and most importantly, protocol adherence.

As mentioned above, block enrolment allows a site to efficiently fulfill its recruitment goals while theoretically minimising site disruption during trial progression.

Some of the advantages of block enrolment:

- Standardisation – with groups of patients being enrolled simultaneously, inclusion and exclusion criteria variance can be minimised, and protocol adherence policed
- Reduces bias – increasing the probability that each trial arm will be properly weighted – enrolment over a number of weeks can allow bias creep since real-time baseline comparison of enrollee demographics is not possible
- Consistency of data – since the data is entered in block format and thus reduces errors on transcription
- Site-to-site reproducibility – because the block model forms a single virtual construct, site-to-site variability is minimised
- Accelerates timelines – all of the above leads to a shortening of project timelines with concomitant gains for the sponsor and sites.

While the advantages of block enrolment are manifold, particularly for ophthalmic trials which may last only a few days, the risks and hurdles of block-enrolment are also plentiful and varied. It is critical to be aware of these risks and mitigate them at every stage of the project.

Some of the disadvantages and areas for oversight of block enrolment:

- Meeting recruitment targets – it is important to be aware of the date of enrolment and the travelling that patients must undergo. For instance, a Day 1 visit on a Saturday will have a detrimental effect on the enrolment efficiency if patients have weekend commitments. For other patients, weekend travel may be the only option if work-week commitments preclude them from visits during this time. Thus recruiters must be primed for flexibility in patient scheduling. Sites must also support this flexibility to mitigate any effect on enrolment.
- Maximum patient numbers – it is critical to be aware of the number of patients a clinic can realistically handle and customise the block size accordingly
- Effective advertising is tailored to site location, patient demographics and trial time commitment
- Paediatric population (i.e. recruitment and compliance)
- Lengthy clinic visits (sometimes >7 hours) – the availability of on-site comforts should not be underrated. Movies, hot and cold drinks, Wi-Fi and charging stations can all enhance the patient experience and therefore the patient enrolment and compliance
- Cumbersome paper diaries and EDC entry – perhaps the largest single risk for block enrolment is the diary and data entry. Without data, monitoring cannot be performed, and timeline creep with increased errors ensues. It is critical that the site staff can keep up with the data entry requirements of block enrolment, especially if paper diaries are used. Thus the block size must be tailored to site logistics. Ora has staff at the site initially to train and aid in this.

As shown above, Ora's strategy to overcome these hurdles has evolved and strengthened with our experience. Further to this, our responses to some of the critical factors in trial risk are discussed in detail below.

Recruiters

Ora has a team of recruiters who access an in-house database as the first step in recruitment. Site-specific patient databases are incorporated to enhance enrolment further. In our experience, a direct conversation with the patient which outlines realistic time commitments for study participation yields a greater likelihood of enrolment. Allowing time for the recruiter to describe the protocol in detail and answer any questions allows the patient or caregiver to make an informed decision about moving forward with a screening visit.

Sometimes, in ophthalmic studies, problem enrolment can be eased using referrals from opticians' offices, optometrists'/paediatricians' offices and University clinics. Patient-to-patient referrals can also be helpful, but it is the

responsibility of the recruiter to confirm patient suitability. Meeting the aggressive timelines of block-enrolled studies may be jeopardised by difficulty in scheduling follow-up clinic visits within window, especially those visits which are lengthy (>3 hours). To accommodate work schedules and help overcome this type of protocol deviation, we routinely offer visits in the evening and on the weekends, in addition to the standard visiting hours during the week, which we have found leads to greater compliance. Another important factor that is often overlooked is the clinical environment. By making the environment as comfortable and stress-free as possible, the longer study visits, and, by extension, patient compliance, are enhanced. In this regard, the clinics are supplied with snacks, movies, current magazines, device chargers, and toys/games for our paediatric patients. Lunch and dinner are also provided, and the all-important Wi-Fi should be made available at all times.

Advertising

Advertising often supports recruitment by producing a previously untapped patient population. The key to effective advertising is correctly targeting that population. In ophthalmic drug development, the patients often have reduced visual acuity. Thus radio and local TV adverts may be more effective than printed media. Another question to ask is whether the required demographic is an older patient group. If so, then advertising on an "oldies" radio station might yield more interest than advertising on a "pop music" station. If the target is a 21-year-old+ population, then advertising on social media may generate the best response. In a recent study which included a paediatric population, we found patient-to-patient referrals attributed to about 5% of enrolment.

The success of an advertising campaign should be an ongoing process. Our experience with block enrolment supports continuous reassessment during the trial to allow for the ability to redirect efforts when results are subpar, which is crucial to continued recruitment success.

Monitoring

Monitoring for these studies is also performed in blocks, creating travel and schedule headaches. Often monitors are away from home for 2-3 weeks at a time, which does not support a healthy work-life balance. To manage this, we set realistic expectations up front, before the study begins, mapping out a tentative calendar schedule. Allowing the monitors to return to their home base on weekends is paramount. To cope with the rigorous schedule and potential "burn-out" rate, we have co-monitors trained on the study who can back up the primary monitor, as needed. A weekly check-in from Monitoring Management continually assesses the pulse of the on-site monitor and lends support, when needed.

Ora's COO, Donna Welch, was integral in the initial design and implementation of the block-enrolled model. "With proper controls and execution, block-enrolled studies have enhanced efficiency and consistently deliver quality data while reducing timelines."

In summary, block enrolment is crucial for accelerated trial designs. The advantages include data integrity and reduction in demographic variability. However, care must be taken in monitoring and managing the risks inherent in this model.

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