Challenges in Recruiting Early-phase Trial Populations

Any issues in the recruitment and retention of subjects for a clinical trial can result in delays and unnecessary costs, and may even potentially undermine its results. Each clinical phase faces its own specific recruitment challenges that need to be overcome: a specific drawback with early-phase trials is that they do not offer therapeutic benefit for the subjects; Phase I trials are typically dependent upon healthy volunteers; and Phase II trials onwards require patient populations. However, special populations and patient cohorts are increasingly included in early-phase studies to ensure the success of a therapy.

Irrespective of the clinical phase, the success of a trial relies heavily on the enrolment of subjects, and this may be made more challenging depending on the specific needs of the study design, the trial phase and the population's characteristics.

As Phase I trials mainly involve healthy volunteers, it is important for trial recruiters to increase the general awareness on what a study may entail and to ensure concerns about safety are well understood. That being said, the primary incentive for healthy volunteers to participate in a study remains mainly a financial one.

For patients, the situation and motivation to participate in a study may differ. Confronted with a disease, patients tend to be willing to help innovation; however, the fear of unpleasant and unknown side-effects, and the potential of being a placebo recipient – and potentially missing the opportunity to be treated with the active drug – often deters them. As early-phase studies typically contain frequent clinical visits and assessments, the overall burden and time spent being part of a trial also becomes a decisive factor. Physicians play an important role in identifying and "convincing" eligible patients, but like patients, their time is also limited. Treating patients is the primary role for doctors, and time spent working on clinical trials is an additional burden, made more challenging by the issues of potential side-effects or patients receiving placebo treatments – so in these ways, the constraints of both physician and patient are similar. With the eligibility criteria for subjects being more restrictive in early phase, finding participants can be incredibly challenging.

To assure recruitment in a timely manner, it is important to tackle these hurdles at all stages of trial preparation and execution and it is sensible to plan with the following measures in mind:

- **Simplify the protocol**

Is it possible to reduce the burden for patients and physicians? When planning the study design, discussion with specialists is vital to ensure the population targeted in the trial will find the commitment feasible. For some conditions, an overnight stay in a trial unit is comfortable, but in general, patients with chronic diseases that may already spend a lot of time in hospital may be more reluctant. For other diseases such as asthma, where patients may be relatively young and working, the time spent in the trial needs to work around other commitments. For physicians, any assessments undertaken in a trial is additional workload and needs to be carried out outside of normal practice, so they too need to be comfortable and agree to the feasibility of the proposed schedule.

- **Evaluate eligibility criteria**

Is it possible to identify and reduce overly restrictive components of the subject profile? Again, knowing the feasibility of the protocol against the target population is vital – for example, if looking at an older population, having a very stringent profile of concomitant medications and conditions is going to create difficulties. Many restrictions in criteria are used out of habit and may be overly-cautious. Some flexibility, of course not at the expense of potentially compromising safety, may be warranted if recruitment becomes overly challenging otherwise.

- **Identify factors that impact recruitment**

When looking to recruit specific patient populations, there are a number of impacting factors, both positive and negative. From a positive angle, a potential drug for a disease where there is currently an unmet need is a strong incentive for participation, even in early-phase trials that have no therapeutic benefit. It may be that a country's healthcare system is restrictive, meaning that second- and third-line treatments are not readily available to all patients, so by offering an experimental treatment to those and follow-up treatment afterwards, patients may welcome the additional assessments that come as part of the study and the innovative care for free. Financial compensation for participants needs to be considered; for example, payment to patients who may need to take time off work to participate in a study.

Negative factors that can affect recruitment that need to be considered include the previous treatment histories of subjects. Often any history of biological drugs, such as anti-tumour necrosis factor (TNF) medication, is not allowed in trials for auto-immune diseases. This makes finding treatment-naïve patients for drugs in this area very difficult in Western European countries.

- **Foresee a realistic recruitment period**

In early phase, everything needs to progress as fast as possible. As treatment periods are often short, a sponsor may wish to complete a study within a year or even earlier, often leading to a recruitment period of only three or six months, which may not always be feasible. Patient trials are not manageable within the same short timeframe as healthy volunteer studies are, nor can they be spread over the long time period that Phase III trials are. It is important to apply realistic estimates and allow some flexibility in the timing to ensure that the appropriate numbers can be met.

- **Include experienced sites**

Conducting a trial at a site which has experience allows access to a network of dedicated investigators with demonstrated patient access. Experienced sites will be able to provide more realistic recruitment estimates and will be aware of any conflicting trials which may affect recruitment, both within its facility itself, and in the broader area. Having sites with dedicated recruitment staff also reduces the burden on busy physicians to carry out recruitment of patients.

- **Plan recruiting activities**

The use of different advertising tools in recruitment is very important. Flyers, advertisements and posters within hospitals can encourage a patient to discuss enrolment on a trial with a physician during a consultation. Multimedia channels can be useful, especially when looking for people suffering from a condition such as an allergy, dietary intolerance or mild depression, who may not visit a physician on a regular basis. These channels can include newspapers, social media platforms and websites of patient organisations or support groups. There are a growing number of specialised companies that create smartphone apps to encourage recruitment, and allow patients to find trials, ask questions and provide feedback.

It is also important to bear in mind that the outlets used to advertise trials need to be allied with the demographics of the target population.

- **Provide clear information to patients and physicians**

It is understood that there is a general fear of clinical trials, especially in the early phase. As such, general information on how safety is guarded and the importance of drug research for a certain disease area is important.

Additionally, study-specific information is very important: participants need to know how the drug is working and what the potential side-effects are. Once a patient is willing to consider participation, all practical aspects must then be communicated, and it is important to listen to possible constraints – such as the time and travelling considerations, or fear of certain assessments – as it may be possible that some hurdles can be overcome with additional support or flexibility. This two-way conversation allows a patient to understand what is necessary from the start and avoids the potential drop-out during the study.

As explained above, many of these impacting factors may already be defined upfront by talking, and listening to physicians.

- **Maintain contact and support with sites**

Offering support to the sites during the (pre-) screening period via dedicated staff to increase recruitment efforts where necessary can reduce the burden on physicians and increase the chances of success. By maintaining frequent communication with clinical trial investigators, any issues can be identified early and acted upon, reducing the potential impact on the overall trial plan.

- **Ensure contingency measures that can be implemented quickly**

Despite a project being perfectly planned, unexpected setbacks can occur. Having back-up sites can add to the cost of a trial, but may help in overcoming recruitment challenges by reaching out to additional referring physicians. Concrete measures would depend upon the population needed, and where they could be found. A dedicated recruitment team can implement necessary steps quickly and efficiently to avoid any delay to a project's timeline.

Case Study: Recruitment of a Niche Population

There may be cases when a study relies upon a niche population, which brings about unforeseen challenges. One such example was a Phase Ib study looking to recruit patients with major depressive disorder (MDD).

The trial required patients with an early onset of MDD that had to reach a certain level of symptom severity but were not allowed to take any antidepressant drugs. The challenges in recruiting these included the fact that many patients with early onset MDD are often reluctant

to divulge their symptoms to others and would not yet have consulted a physician, and those that were seeking help would likely contact their general practitioner, not a psychiatrist. Patients with MDD also tend to have anxiety and would be naturally fearful of participation in a study, and there would be ethical considerations in how a trial would be run. These include the use of a placebo and the necessary length of stay within a facility, and how participants would react to being admitted to a medical unit.

Recruitment was carried out for this trial via an advertising campaign, and an expert psychiatrist was involved from the screening stage onwards to guide participants who were included. The "patient-volunteers" were financially remunerated for their participation, which necessitated a stay of two consecutive nights in a first-rate medical facility. The population needed for the study had to be without current medication and half of them would be assigned to the placebo arm. So the role of the psychiatrist was to monitor the psychiatric state of participants during the study, and to make the decision of withdrawing a patient if symptoms were aggravated. It was agreed by the ethics committee that the role, presence and expertise of this psychiatrist allowed for the use of a placebo on the patients undertaking the study.

As with all aspects of the drug development process, patient recruitment is greatly enhanced with proper planning and experience. Trials are expensive to undertake, and rely upon the success of recruitment to ensure that the carefully planned protocols can be delivered to develop the life-changing drugs of tomorrow. The use of teams of dedicated staff can assist in the process, and can ensure that challenging timelines and criteria can be met.

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