RECRUITING THE STUDIED POPULATION IN A TIMELY MANNER

EARLY PHASE CLINICAL TRIALS – MAXIM #5

Recruitment and retention issues result in trial delays and costs and may potentially undermine trial results. Every clinical trial phase is facing its own specific hurdles. The fact that early phase trials do not offer therapeutic benefit for the subjects is a specific drawback. Phase 1 trials are typically performed in healthy volunteers, whereas from phase 2 onwards patient populations are needed. However, special populations and patient cohorts are increasingly included early on.

Subject enrollment is a key driver of clinical trial success but remains one of its biggest challenges. The exact challenges depend on the trial phase, the population specifics and study design details.

As phase 1 trials mainly involve healthy volunteers (HV), increasing general awareness, on safety for example, is paramount. Besides that, the incentive for HV to participate remains mainly a financial one.

For patients, the situation may slightly differ. Confronted with disease, they tend to be willing to help innovation. Nevertheless, fear of side effects and of getting a placebo (hence losing time to get treated) often deters them. As early phase studies typically contain frequent visits and assessments, the overall burden and time spent also becomes a decisive factor. Physicians play an important role in identifying and "convincing" eligible patients, but they are often dealing with similar constraints. In addition, eligibility criteria are more restrictive in early phase. Hence, finding participants may be a little like looking for a needle in a haystack.

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

- Simplify the protocol if possible to lower the burden for patients and physicians
- Evaluate eligibility criteria to identify overly restrictive components
- Identify factors that impact recruitment, both positively and negatively
- Foresee a realistic recruitment period, leave some flexibility
- Include experienced sites with demonstrated patient access and dedicated recruitment staff
- Foresee recruiting activities: advertising, social media, call centers
- Provide clear information to patients and physicians
- Keep close contact with sites in prescreening period
- Keep clinical trial investigators motivated by via frequent communication and assistance
- Ensure contingency measures that can be implemented quickly

CASE STUDY 1

How applying the right contingency measures can save patient recruitment

In a combined HV/patient study run by SGS, an experienced patient site was struggling with recruitment. By rapid implementation of a pre-study contingency plan, the study still met the initially agreed upon study timeline.

A European biotech company outsourced a combined single and multiple ascending dose study in HV and moderate-to-severe atopic dermatitis (AD) patients.

SGS Clinical Pharmacology Unit conducted the HV part as a single site. Two patient sites in Eastern Europe with experience in early AD trials, and reliable partners to SGS, estimated they could recruit the 24 patients in six months. As a pre-study contingency measure, SGS suggested to include their patient site in Hungary as a third site.

During the first patient cohort, one of the sites had unexpected recruitment difficulties, despite their proven track record in AD studies.

The project manager and operational team immediately undertook action:

- Follow-up with the site was intensified to investigate the patient pipeline and recruitment forecast
- The potential to increase the committed enrolment target was discussed with the other two patient sites
- The Hungarian site substantially increased their network through advertising in relevant patient groups and approaching additional collaborating specialists. Consequently, they could triple their initially committed enrolment
- The in-between cohort time was maximally compressed

As a result, the significant recruitment delay from the first cohort was entirely cleared. Having sites with dedicated recruitment staff proved to be an enormous added value to boost recruitment capability. The study ended within a week of the initially foreseen date.

We conclude that even experienced sites can encounter unexpected recruitment issues, especially in acute indications and indications with seasonal variations. Candid communication with all sites and implementation of contingency measures can be critical to rescue a trial.

CASE STUDY 2

Enrollment hurdles when looking for a "niche" population

SGS was contacted to assist in a phase 1b multicenter study in patients with Major Depressive Disorder (MDD).

The trial population consisted patients with early onset MDD that had to reach a certain level of symptom severity but were not allowed to take any antidepressant drugs.

While evaluating this request, the following challenges were identified:

- Many patients with early onset MDD would not yet have consulted a physician.
- Those seeking help are contacting their general practitioner, not a psychiatrist
- People are often reluctant to divulge their symptoms to others
- MDD represent a rather fragile population that might fear participation in a phase 1 trial
- Ethical considerations with the use of a placebo arm
- Availability of participants due to the need to two overnight stays of two consecutive nights

The following solutions were implemented:

- A public advertising campaign was set-up (social media, websites, newspapers) referring to a call center.
- An expert psychiatrist was involved from screening onwards to guide participants.
- Awareness was increased with accurate and accessible information
- The trial was executed at a first-rate medical facility
- Financial remuneration (for time spent and overnight stays) was provided to the "patient-volunteers"

Recruitment for this trial remained slow and difficult. The main reason being the required level of symptom severity (without any medication) which was often just not reached. Although 14% of the population faces depression, the patients needed in this trial represent only a very small niche.

This case study stresses the importance accessing "patient-volunteers" by making accurate, understandable information accessible.

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