

Patient Recruitment and Retention in Clinical Trials



The clinical phase is a complex, expensive and lengthy phase in the drug development process. There are several challenges in conducting and managing clinical trials which are operational or medical/scientific in nature, of which the major ones are recruitment and retention of patients. Despite more than two decades of focused attention and improvement efforts, patient recruitment and retention are among the largest challenges facing clinical research enterprises, and are among the greatest contributors to delays in drug development¹. Delays in patient recruitment bring additional burdens to biopharmaceutical and medical device companies in terms of spending additional budget and losing vital time from the exclusive marketing phase of the patent period. Moreover, nowadays patient recruitment is becoming more challenging due to increased complexity of clinical trial design, stringent eligibility criteria and trends towards targeted patient populations to satisfy the labelling requirements. Timely patient enrolment and maximising retention are the key aspects in successful completion of the drug development cycle in today's competitive market.

There are various challenges with regard to patient recruitment and retention which can be related to diverse aspects like study protocol design, patients, disease, investigational sites and geographical areas where clinical trials are conducted.

Potential Challenges in Patient Recruitment and Retention

Protocol Barriers: In the last few years, the complexity of protocol design has been increasing to satisfy regulatory and intended label requirements. The data from the Tufts Center for the Study of Drug Development indicates a significant increase in the number of procedures, eligibility criteria, number of CRF pages and protocol amendments in the last few years². Greater complexity of a study protocol is directly proportional to more difficulties in recruiting and retaining patients on the study. In an oncology study, it is difficult to get treatment-naïve patients if it is one of the inclusion criteria. Some study protocols require patients to be present for long hours in the hospital for several tests to be carried out. Such a long wait may be really taxing for some patients and may limit their participation and retention in a study. Limitations on concomitant medications and a requirement for a wash-out period are the other aspects which limit patient recruitment and also affect patient retention. Complex study procedures and frequent protocol visits create additional burdens for patients and their family members. This becomes critical if it is a pediatric trial where children and their parents have to adjust to rigorous study schedules and school activities.

Use of placebo: Most of the study protocols designs involve use of placebo. If the placebo is one of the arms on a study, it becomes difficult to convince patients and their family members to participate in the study, especially for studies of psychiatric conditions, pain management and other critical intervention conditions where the real treatment is of utmost importance to patients for their conditions. Even if the protocol offers rescue medications and patients have the right to withdraw from the study at any time, it is becoming challenging to get patients and their family members to be willing to participate in the study. Use of placebo not only restricts patient recruitment in a study but also creates great challenges in terms of retaining patients on a study.

Disease-related challenges: Patients' disease conditions play a critical role in patient recruitment and retention. In the case of oncology clinical trials, most patients are often exhausted with the disease and from previous chemotherapy or radiotherapy, which compels them to keep away from clinical trial participation even if they are eligible for a study. In the case of psychiatry patients, lack of insight and awareness and cognitive impairments prohibit them from thinking about clinical trial participation even if that late-phase efficacy clinical trial may be a good option for them as far as treatment or drug efficacy is concerned. Also, it requires a different set of strategies to retain these kinds of patients on psychiatry clinical trials. The limited physical mobility and poor quality of life of patients due to disease prevents patients from participating in trials.

Patients' barriers: Diseases like Alzheimer's disease, arthritis, Parkinson's disease and prostate cancer are commonly seen in geriatric patients, and it is hard to recruit and retain these elderly patients on a clinical trial. The pediatric group poses altogether different and highly complex challenges, and therefore many clinical trials in this area like pediatric diabetes trials are open for recruitment for a long period of time, as they fail to recruit patients on time, and also retain them. Moreover, for conditions like diabetes, where the existing market offers good alternative treatments, parents are not willing to enroll their children in clinical trials where the efficacy and safety of the study drug have not been proved and established. Many times, the majority of patients are unaware of any kind of clinical trial happening in their vicinity. This becomes quite a disadvantage where a trial offers a unique treatment which is better than those available in the market, like in the case of rare disease indications e.g. carcinoid syndrome or acquired hemophilia. As clinical trials are experimental, there is always a fear in the minds

of patients and their family members that the test drug may not work or may produce undesirable side-effects. These kinds of apprehensions prevent patients considering clinical trials as an attractive option.

Informed Consent: If the informed consent form (ICF) is not appropriately designed and fails to provide study-related information to patients and their family members in simple and easy to understand language, it leads to a lack of interest towards clinical trials. Also, getting a correct translation of the ICF is also essential, so it provides accurate information as per the original ICF, and also translation should provide the right meaning in context to culture. Again, it is also very important how the consenting process is carried out by site staff. If sufficient time is not given to patients and their family members and if they are not encouraged to ask questions in an open environment, it does not build trust between patients and site staff, which further leads to non-participation. The ICF process becomes harder in a psychiatric trial, where sites have to deal with patients affected with insight, awareness, mood and cognitive abilities thus influencing the consent capacity of patients, which can limit patient recruitment on these studies.

Geographic location: Country selection is very important in any clinical trial. Apart from sponsor requirements for country selection, one has to understand epidemiology, prevalence and incidence of disease pattern, country regulatory requirements, ethical needs, standard of care, clinical practice and experience of PI/sites in handling the specific clinical trial under question. The country should offer an adequate number of potential patients in that indication to complete the recruitment on time. In a few countries, there exist strong physician-patient relationships, where patients treat physicians as very important people in the healthcare ecosystem. In such countries, on physicians' advice patients can participate in a clinical trial. In some countries, family structure plays a crucial role and can influence patient participation in a trial. In developing countries, mainly sites from urban areas are selected for clinical trials for varied reasons, however they are many potential patients in rural areas who do not get access to these clinical trials. Again, selection of the right investigator based on speciality is also essential to ensure a good pool of patients at sites, e.g. in some countries headache and migraine patients are predominantly treated by neurologists and some countries they are treated by consulting physicians. In some countries rheumatoid arthritis patients are treated by consulting physicians, and in most developed countries, they are treated by specialists like rheumatologists.

Site staff: Inadequately trained site staff with regard to managing study subjects can hinder study participation. The site staff should be well trained in approaching and managing patients, especially for consent processes. They should be able to respond to patients' and their family members' questions and concerns very effectively, and need to provide the confidence to facilitate patient enrolment. This is required more so in trials involving

pediatric and elderly populations. The lack of study-related knowledge would definitely hinder patient recruitment and retention. Also, site staff need to take care of timely reimbursement of patients and their family members with regard to travel and sustenance to keep them motivated throughout the study. This is helpful in maximising patient retention.

Patient Recruitment and Retention Strategies

In order to take care of these various types of challenges in patient recruitment and retention, it requires study-specific, country-specific and site-specific result-oriented customised strategies to accelerate patient enrolment on clinical trials. As per facts and figures given by the Center for Information and Study on Clinical Research Participation (CISCRP), six per cent of clinical trials are completed on time, and 72 % of trials run over schedule by more than one month³. The complex, 'difficult to recruit' kind of clinical trials warrant a more systematic approach to patient recruitment. Most of the time, investigational sites provide their total patient enrolment by reaching into their own database of patients. However, due to the complexity of the current protocols, rigorous eligibility criteria and rarity of the disease condition, sites need to go beyond their practice to achieve their recruitment targets on time. The longer it takes to complete the recruitment, the more money and resources sponsors have to spend to complete a clinical trial. Moreover, due to delays in patient recruitment, sponsors can fail to achieve their important, planned milestone of "time to reach market", and each day's delay in reaching market costs a lot to sponsors.

The patient recruitment strategies currently used in practice can be broadly classified as in-reach and outreach activities. In-reach activities are mainly site-based activities where one can work within a site to optimise the patient pool and accelerate enrolment, whereas outreach activities are the activities carried on outside, around a given site - i.e. nearby areas and communities - to identify potential patients.

After assessing a site's capability, best practices, study-specific challenges, needs and willingness to recruit patients, one has to decide a site-specific patient recruitment plan which can be a combination of various in-reach and outreach activities. The sole purpose behind these strategies is to create study awareness to attract potential patients to investigational sites. These in-reach and outreach patient recruitment activities are carried out mainly as:

- Field-based activities by dedicated trained resources who work within and around investigational sites to identify potential patients;
- Advertising media outreach where one can use a compelling and ethical message to target study-specific population; and
- Call centre support for initial screening and patient follow-up.

The PI and site staff together play a key role in patient recruitment. Therefore, it is important to keep the PI and site staff engaged and motivated in patient recruitment activities throughout the recruitment period, and make

them important partners to drive the whole process. It is necessary to establish a collaborative working relationship with the study sites to accelerate recruitment at sites. The various in-reach and outreach activities which can be performed to identify potential patients for a given study include:

In-reach activities	Outreach activities
<ul style="list-style-type: none"> ○ chart review from site patient database ○ establishing internal referral networks with physicians or other relevant specialities within site ○ co-ordination with site local laboratory for patient identification ○ educational meetings with relevant healthcare providers and physicians to create awareness of a study ○ educational meetings for patients/family members/care-givers ○ training to site staff to facilitate ICF process <ul style="list-style-type: none"> ○ effectively conveying risks and benefits of participating in a study ○ developing trust with patients/care-givers/family members about participation by taking care of all their concerns effectively ○ creating an open environment with patients/family members/care-givers where they are encouraged to speak freely and ask questions ➢ Arranging monthly conference call with all sites' Site Coordinators (SCs) for sharing success stories <ul style="list-style-type: none"> ○ meetings should not only be motivational, but should include listening to the site staff, learning what they see as problems, and offering solutions ○ Involving sites in peer-to-peer sharing of best practices 	<ul style="list-style-type: none"> ○ establishing physicians' referral network with other hospitals and clinics nearby to investigational sites 1. community outreach by participating in community events, community education and outreach programmes to create study awareness 2. co-ordination with advocacy groups and patient support groups for patient identification <ul style="list-style-type: none"> ➢ establishing key points of intersections where potential patients can be reached based on clinical profiling of a given study indication and disease as per a selected country's clinical practice ➢ traditional media outreach to target large populations and accelerate enrolment by using compelling and ethical message ➢ television advertising ➢ radio advertising ➢ print advertising ➢ direct mail 3. current other targeted, cost-effective media outreach <ul style="list-style-type: none"> a. social media b. online/web media 4. call centres support:

The above activities are supported by development of patient recruitment materials like:

- Advertisement materials for print, TV, radio or online ads
- Patient pre-screening chart
- Education materials for patients/care-givers/family members
- Monthly newsletters for sites
- Study-branded tools to build awareness at the site and for outreach activities

Social media like Facebook offer powerful and cost-effective tools for recruiting patients, as they encourage participation interactions where patients like to share their experiences and stories about their medical conditions, and also like to seek help. As per an ISR (Industry Standard Research) report, sixty-two per cent of the global population are somehow engaged in social media, and use of such media will grow drastically between now and 2015 for patient recruitment activities to take advantage of the pool of potential subjects for clinical trials⁴.

Some of the long-term, complex studies which require frequent protocol visits do require retention support. By carrying out some of the retention activities given

below, one can facilitate patient retention and ensure good patient compliance on a study. Call centre support and simple tools like text messaging can be used effectively to carry out retention activities.

- Planning appointments with sites for initial/follow-up visits and providing flexible/convenient appointment times
- Spending extra time with patients to understand their concerns and address them effectively
- Providing a summary of laboratory results to patients to demonstrate progress
- Appointment reminder services
- Travel assistance for patients/family members/care-givers, and patient compensation services
- Identifying the warning signals for potential drop-outs and working closely with these patients to support them to continue on the study
- Lost-to-follow-up recovery

Conclusion:

Patient recruitment and retention are challenges that the industry has been facing for many years, and they warrant a systemic, practical approach, especially for some complex and 'difficult to recruit' kinds of studies to ensure successful completion of the clinical development phase. The challenges with regard to patient recruitment and retention should be anticipated thoroughly during study planning and the protocol development phase itself. Accordingly, proactive planning can be done to ensure patient recruitment on time and to maximise retention. The success lies in effectively addressing study challenges and hurdles in patient recruitment and retention with country- and site-specific, innovative, practical and result-oriented strategies within the framework of regulations to provide timely and cost-effective results.

References

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