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Patient Recruitment in Clinical Trials: Areas of Challenges and Success, a Practical Aspect at the Private Research Site

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Abstract

Enrolling in clinical trials could be time-sensitive and time-demanding tasks for the research site, especially if it is a private research organization compared to the research conducted at an academic or medical center. Every study differs in various aspects, such as phases, study indication, eligibility criteria, etc. In terms of meeting the enrollment deadline, typically, the study indication and availability of the patient's population at the geographical area of the research site would decide if the trial could be time-consuming. Patient recruitment and retention are critical for the success of every clinical trial; however, worldwide, this area is facing tremendous pressure and challenges. Globally 55% of clinical trials terminated due to low recruitment, with an average enrollment success rate of 40% for Phase III and IV trials. Over 80% of clinical trial attempts fail to enroll, extending the study and adding new study sites. In the United States, more than 80% of clinical trials fail to achieve targeted patient enrollment, and 30% of study participants discontinue participation. This article reviewed various factors hindering clinical trial recruitment and retention and suggested strategies to make the research site successful.

Keywords

Clinical Trial Recruitment, Clinical Trial Retention, Clinical Trial Participants, Clinical Trial Termination, Study Budget, Clinical Trial Enrollment Challenges

1. Introduction

A fundamental element of a successful clinical study is the quality conduct of the trial, which includes data quality, data integrity, efficient recruitment, and reten-

tion of sufficient study participants. Globally, this area is facing pressure and challenges leading to 55% trial terminations due to the most common reason for low enrollment rates and only 7% of enrolled patients completed the studies [1] [2]. In this article, we discussed various strategies that can help recruit and retain study participants and significantly reduce the dropout rate.

The clinical trial recruitment goals and associated efforts could differ from academia to a private research organization, so the strategies, their effectiveness, and the related performance pressure further differ from site to site. For example, self-supporting for-profit organization business models are highly demanding, requiring them to set up vigorous goals for the success of every clinical trial they have at their site. In contrast, enrollment in academia or university settings could be more lenient while considering the nature of their support system. Patient recruitment and retention are paramount to pharma, CROs, SMOs, and research sites as retention stimulates the chances of successful study completion, saving the money and time of all parties involved.

Although the study sponsor always aims to meet the enrollment deadline early, the research site often goes the extra mile to achieve the enrollment target as vigorously as possible. However, as mentioned earlier, the nature of the site could also decide how competitive and stressful the enrollment goal could be. The nature of clinical research work at private organizations is demanding, time-sensitive, competitive, and highly ambitious. Typically, the site begins enrollment as soon as it is activated and is persistent in achieving the higher enrollment goals throughout the open enrollment period. The site uses various successful enrollment strategies to make every clinical trial successful in terms of enrollment, patient retention, and quality to attract future research business opportunities. Comparatively, in studies open in an academic environment, enrollment and retention may or may not be time-sensitive, competitive, and stressful due to the goals, objectives, nature of research, and the amount of funding the department receives to conduct clinical trials [1] [2] [3].

2. Literature Review

In clinical trial endeavors, recruitment activity could invest up to 30% of development timelines and approximately 1.2 billion USD [4]. Having 11% of clinical research sites with no enrollment and up to 37% of sites below enrollment target requires ongoing recruitment and retention efforts, including robust strategies, plans, and deadlines with new ongoing updates during the study. In the United States, more than 80% of clinical trials fail to achieve targeted patient enrollment, and 30% of study participants discontinue participation. According to a survey of 1024 clinical research coordinators, the clinical trial duration is the 60% reason, and lack of efficacy is the 40% reason for low enrollment. A National Institutes of Health study reported the following primary reasons for study subjects' dropping out: "55% of researchers believe that lack of investigators' dedication toward subjects is the reason subjects drop out, whereas 44% of the re-

searchers believe subjects are afraid of possible study treatment side effects, 47% of researchers believe patients are afraid of the study procedures, 36% of researchers believe subjects' poor compliance is the reason subjects drop out, 27% of researchers reported insufficient support from family doctors and loved ones, and 9% of researchers reported a lack of awareness and incorrect understanding of the clinical trial process and drug inefficacy as the reason study subjects drop out" [5].

According to the UK Harris Interactive Survey of eligible patients who are aware of the trials, 71% patients chose not to participate in the trial, out of 71% of patients, 37% thought the standard of care treatment was better, 31% of patients were afraid of getting a placebo, 22% patients were afraid of being used as an experimental subject, and 21% patients expressed long commute as the primary reason for the opt-out [6] [7]. According to a study by the Kaiser Family Foundation, a significant ratio of millennials does not have a steady primary care provider. The lack of a trusted relationship between Primary care providers and patients will restrict clinical trial recruitment, as primary care providers are considered the most trusted source for clinical trial recruitment.

3. Barriers to Study Recruitment and Retention

3.1. Challenges Related to Study Participants

Lack of enough time to attend frequent study visits. With a fixed or busy work schedule, patients do not want to use their paid time off (PTO) for study visit purposes or in the case of hourly wages workers PTO is not applicable. For single parents who live at a long-distance location or parents who need to arrange childcare to accommodate their research study visit, the burden of participating is high, even though enrolling in a research study is suitable for their health. Long-distance commutes to attend the study visits consume much of the subject's time. Inconvenient study schedules in terms of early morning study visits, extended duration study visits, or multiple blood draw study visits, lack of transportation or depending on friends and family for transportation assistance, availability of existing approved best treatment options for the study indication, these factors can create hesitancy among participants hindering the study recruitment and retention..

Study participants were concerned about the possibility of getting a placebo rather than the actual study drug treatment. Participants are concerned about possible side effects of investigational products as understood during the ICF process and listed in the ICF.

Discouragement by friends, family, relatives, primary care provider, or another health care specialist. Misunderstandings such as "approved available treatments are always better and safer for the health than a new investigational product". The chronic disease patient population is concerned about adding new study drugs to their daily medication regimen [8]. It has also been observed that longer-duration trials or trials with frequent study visits could face strong pa-

tient recruitment and retention challenges. Due to the study visit commitment, patients feel restricted from making their personal travel plans as their plans could fall at the same time as the study visits [9] [10]. Patients concern that their clinical trial participation will increase their caregiver responsibilities due to the additional health crisis if arise due to side effect of the investigational treatment. Large medical centers data reported that road traffic in metro areas, long commutes to research sites, and clashing schedules availability for the study treatment were the primary challenges for the study subjects. Association of Research Professionals data shows that over two-thirds of Americans live two hours from the leading medical research centers.

3.2. Challenges Pertaining to Sociocultural Factors, Budget, and Protocol Related Criteria

Sociocultural factors: Misunderstanding about clinical trial participation and compare it to a guinea pig experiment restrict clinical trial recruitment and retention efforts.

Budgetary restrictions: Sponsor provided study advertisement budget is minimal, considering the exorbitant cost of broadcasting on TV, radio, and newspaper media. Most of the time, sponsors provide a limited advertising budget, which quickly dries up in 1 - 3 months restricting patient recruitment. Many independent third-party companies provide dedicated site support for recruitment and retention efforts [1]. This includes finding patients, sharing contact information, scheduling patients and transportation, etc.; however, having a low study recruitment budget hinders these efforts [11].

Stringent protocol eligibility criteria: For example, a strict range of specific screening lab results can lead to 59% of screen failures in interventional studies as compared to observational studies [9] [12].

With the advancement of the drug development process and the related demands, there has been a significant development in clinical trial designs. Clinical trial designs are becoming more complex and revolutionized to find the best possible answer for complex, recurring health conditions which has no or limited current available treatment options. The protocol eligibility criteria are getting more specific and stringent, requiring intensive trial-related testing, restricting recruitment leading to extended recruitment periods, and eventually forcing protocol amendments to recruit patients or adding additional study sites [5]. Bioequivalence studies face extreme competition in finding healthy volunteers [9].

Competitive trials also slow the recruitment process, making the trial expensive. Some trials could be lengthier because they require study participants to undergo an extended follow-up or observation period. Without sufficient budgetary provision the ongoing maintenance of such studies burdens the sites [8].

3.3. Challenges in Recruitment: Observations from the Field

While working in the field, we found the following barriers to clinical trial re-

cruitment:

As described in the earlier section, stringent protocol eligibility criteria are often significant barriers to enrollment. For example, most of the clinical trials for non-dialysis patient population require a specific urine albumin-creatinine ratio value (UACR). The value of UACR could fluctuate quickly within months, days or even hours, and it may not be a reliable, consistent indicator; in addition, UACR testing is not a regular standard of care lab a nephrologist could order for a regular clinic visit. To avoid screen failures a site may want to test this lab locally prior they screen prospective subjects for the study. The site must bear the cost of this additional test if they do not want to be billed to the patient's health insurance. In addition, this testing requires extra coordination efforts by the research coordinators, which adds an extra burden to their tight work schedule. Strict protocol eligibility criteria is a long-standing recruitment barrier from time to time, and it could require further study evaluation and a subsequent protocol amendment. Another example is, protocol-exclusionary medications, which are many times are the most used medications in specific patient populations, for example, NSAIDs, blood thinners are prohibited in many chronic kidney disease area clinical trials. Another recruitment challenge is, study indication, a specific medical condition with a specific severity which may not be so commonly found in the patient population. It has also been observed that patients having specific medical condition and severity commonly take medications that also appears to be protocol-listed prohibited medications making recruitment efforts more tedious.

We also experienced some additional challenges such as, patients fear being placed in a placebo-controlled group instead of the active treatment group. As a result, they believe that they will not get the best available treatment and care. We found that patients' noncompliance with study protocol requirements and study procedures due to the commitment of time, transportation, their dependability on others or due to the unexpressed unknown reasons are the significant barriers to patient recruitment and retention in the clinical trials. We observed that lack of research awareness, the negative influence of social media, and discouragement by friends and families play a significant role in low study recruitment and retention.

4. A Personal Perspective on Proposed Solutions for Recruitment and Retention

We recognized that the most common method to recruit study participants was from the daily clinic schedule of physicians, advertisements, and outside patient referrals. Having a sound, viable recruitment plan while learning from the mistakes of previous studies, assigning qualified, dedicated research staff to do ongoing prescreening activities, study recruitment advertisements on effective social media, can make clinical trial recruitment successful. The recruitment plan is influenced by socioeconomic and geographical situations, protocol require-

ments, the patient population, and the enrollment time window. Developing a trial participants database using a clinical trial management system that includes all previous study participants can significantly help. In addition, contacting earlier study participants for suitable future trials is a fantastic way to boost enrollment. PI's and site staff's rapport with the study subjects while demonstrating knowledge and pleasant, courteous, honest communication is the key to building an efficient research site. The study staff must also be vigilant about subject noncompliance issues, address the subject's concern promptly, and be available to them and to their point of contact to answer any study-related questions not only at the time of informed consent but also during the entire duration of the trial. Well-mannered, professional study staff with friendly, approachable attitudes and a focus on listening, mentoring, and motivating study participants not only reduce the dropout rate but also bring substantial improvements [13]. Addressing following factors in advance can lead to successful conduct of the trial.

Advance Recruitment and Retention Strategies

Protocol-building phase: While designing the study protocol, the sponsor should take input from the research sites. This approach could address many clinical, scientific, recruitment, and retention issues and concerns in advance and proves beneficial to both pharma and the research site once the study is executed. Many times, at the time of protocol development, the study team needs to be made aware of the prospective challenges to conducting the trial at the site level, so an initial discussion with the research site at the beginning stage is a great start [14] [15]. Experienced PIs, site staff, and practical communication skills make much difference in study recruitment and retention. Compassionate study staff who understand participants' various challenges to attend the study visits such as, time management and transportation issues, long commute travel distance etc. Study staff make necessary arrangements to assist participants and ensure that the budget is negotiated or amended with the study sponsor accordingly.

Dedicated site staff can watch any missed calls or concerning calls from the study subjects and take proactive steps to reduce the likelihood that the participants will drop out of the study. Having a well-qualified site staff prescreen potential subjects so further communication between the PI and prospective subjects could be scheduled for the appropriate trial. It is crucial that the site is well prepared and prospectively asked to the study sponsor answers for most of the scientific, critical questions in advance, so recruitment can start booming as soon as site gets activated and go on without interruption until the study meets the enrollment goal. An adequate study budget is crucial for the sites to hire, mentor, motivate, and retain qualified and experienced staff throughout the study. By ensuring recruitment targets and milestones and by conducting site performance monitoring, the recruitment and retention goals can realistically be ensured.

The recruitment materials available in the clinics and in the research offices

can catch clinic patients' attention. Similarly having the study eligibility criterias handy can make the investigators to have a discussion with the patients in the real time manner. Having a counseling system in place reduces misconceptions regarding the clinical trial and explains the patients' study purpose, objectives, and procedures in simplistic language. A thank you note to patients for their time and contribution to the trial, reminder phone calls for the study visits, and follow-up phone calls between onsite study visits make patients feel valuable and show that they are being cared for their well-being. As a part of study subject retention sponsors should add the provision of additional phone calls in between onsite study visits regardless of the study schema and data requirement. Study budgets need to have provisions for reimbursement for this additional time research staff could spend as a part of study subject retention. Feeling appreciative and caring can retain patients' interest in the current and all prospective future trials. Research experts suggested incorporating machine learning and artificial intelligence for effective recruitment and retention, better implementation of trial design selection, and monitoring of patients [16] [17] [18] [19] [20].

To reduce subjects' time for the onsite study visit, a hybrid model mix approach of a decentralized model and onsite study visits could be the best option; however, there are technology-related challenges, such as the uncomfortability of subjects while dealing with connected medical devices during telehealth visits cannot be ignored, and these factors can subsequently affect the study data. A stepwise, flexible, familiar, patient-centric technology could be the best thing to do. Some studies pay an additional mileage amount to the subjects to attend study visits in addition to the standard reimbursement study visit payment, while some studies do not have this additional provision. The commute itself is a big deal, as it could take half a day or an entire day of the patient's time, depending on the distance and length of the study visit. Study visits during weekdays during office hours are an additional burden on top of the commute distance. Unlike short-distance study patients who attend the study visit while taking a short break during office hours, long-distance study patients need to take the entire day off. Therefore, additional assistance such as reimbursement for lack of wages, transportation help, availability of the weekends to attend study visits, additional provision for mileage, food, and related expenses, having satellite offices, provision of home health services, and a decentralized clinical trial approach for extended study visits could be beneficial.

The information listed in the clinical trial advertisements, consent documents, and patient-facing material should be easily understood by the people with various educational levels. It must be ensured that patients understand all the details about clinical trials and their roles without any doubt. Unfortunately, the average American reads at the seventh or eighth-grade level; hence, a difficult-to-understand consent document appears to cause approximately 35% of study dropouts [21] [22].

Patients' trust in the treating physician and associated research team is an ef-

fective measure in recruitment and retention; hence, gaining and maintaining this trust throughout the clinical trial conduct process is critical.

The trust can be established by ensuring that the patient and their close relatives have an unbiased, solid knowledge of the process and their participation in the trial. By engaging them throughout the trial duration feels them valuable members and not just a medium of the experiment.

The most common observation in the chronic disease patient population who are participating in clinical trials is that there is a ray of hope for them to feel better and get better. Patient populations that need to be made aware of biomedical research will not be encouraged by the convenience of technology. Incorporating decentralized clinical trials, therefore, requires spreading research knowledge and awareness through various meetings at the individual and community levels. In addition, such a get-together can build trust between healthcare providers, researchers, and patient populations [22].

The research study could be designed while looking at country-precise factors for successful recruitment. Adaptive designs for the clinical trials are becoming popular among many pharmaceutical companies as they achieve the target of getting the correct answer while using fewer patients and with a reduced trial duration [9].

Completing the study feasibility survey is part of the study start-up activity. The most crucial thing the site must do is ensure all promising strategies that were portrayed at the beginning of the trial have been attempted for effective implementation while using technology such as electronic health records, social media, doctor referrals, and connecting with resources to find eligible patients with the goal of providing complete, accurate data for the regulatory approval. Establishing initiative-taking recruitment and retention strategies while acknowledging and understanding the barrier and successfully implementing various solutions is paramount. The sponsor's assistance in this matter is crucially needed. Reporting standards development assists clinical researchers in taking on evidence-based recruitment tactics by implementing prime recruitment methods to lessen costs and timelines Just like patient rights and safety are essential in clinical research, similarly "participant-centric" methodology is crucial to the success of the clinical trial [23] [24] [25] [26].

5. Conclusions

In the clinical trial endeavor, patient recruitment is an ongoing major challenge. The termination and slowdown of clinical trials have a significant scientific and financial impact on researchers, society, and patients as it obstruct the development and subsequent availability of promising new therapies to current and future patients. Termination and delay in the drug development impact patients who need new drug therapy, cause loss of time for all parties involved, such as patients, researchers, key stakeholder groups, and pharma, and specifically result in significant economic loss for the study sponsors and the public.

Terminated projects impact the motivations and morals of scientists and researchers and increase society's concern about participating in future clinical trials. Patients' participation in clinical trials is the critical element of the drug development process, which is time-consuming and beneficial to society. This article discussed key factors hindering patient recruitment and retention and reviewed the best possible long-term solutions to make every clinical trial and pertaining research site successful.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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