Recruitment and retention of participants in clinical studies: Critical issues and challenges

A key determinant of a successful clinical study is to efficiently recruit and retain an adequate number of the study population. However, worldwide the clinical trial professionals experience pressure and several challenges with respect to recruitment and retention of participants. Surprisingly, participant enrollment issues are the major reasons for trial terminations. Global data analysis of all terminated trials within Clinical Trials Database reported 55% of trials were terminated due to the single highest reason of low accrual rate.[1] The average enrolment efficiency is also reported to be <40% for Phase III and IV trials.[1] Globally, more than 80% of trials fail to enroll on time resulting into an extension of study and or addition of new study sites.[2] Similarly, insufficient retention of the participants till study closeout is also a matter of concern. The remaining number of patients will be too small to answer the original research questions appropriately. Besides this, it has several ethical, financial consequences and delays the study.

With the recent revision of clinical trial regulations in India, the scenario of clinical research is all set to bring global clinical studies and promote indigenous drug development. The utter presence of a huge potential clinical trial population is perceived as an advantage for fast screening and enrolment by sponsors. Despite this, the major challenge for study sites is to achieve and maintain high rates for patient recruitment and retention.[3-5]

In this issue of the journal, Bose *et al*. conducted 5 years' audit (2014–2018) of all regulatory and academic clinical studies (n = 19) to evaluate the recruitment and retention of participants.[6] Screen ledgers and study trackers were used for screen failures and dropouts. The screen failures were high in interventional studies (Phase II, III, and pharmacokinetic) as compared to observational studies. Majority (59%) of the screen failures were due to abnormal laboratory values followed by postscreening consent withdrawal. Surprisingly, majority of consent withdrawal were healthy participants. While high dropout rate (88%) was due to lost to followup, non-adherence to protocol and consent withdrawal. The authors observed that high risk and interventional studies were the predictors for both screen failure and dropouts. Overall, the 5% screen failure and 4% dropout rates are remarkably low as compared to world literature, albeit, due to single academic study setting and relatively small sample size the results cannot be generalized. In view of the lack of publish information on national data in this regard, let us introspect the issue with various perspectives.

With changing times and advancing health care, there has been a paradigm shift in clinical trials designs. At present, clinical trial designs are "*complex, sophisticated and modernized*" to find the right answer for third or fourth line therapy for advanced clinical conditions having no treatment options or treatment-resistant/refractory cases. For example, the straightforward study design to enroll all patients with Stage II breast cancers has been replaced by specific genetic biomarkers. The inclusion criteria are more specific, stringent, and narrowed that requires intensive trial-related testing and restricts eligible participants. This may lead to longer recruitment period and eventually force protocol amendment to recruit more patients or additional study sites. It has been reported that more than 40% of the trials amend the protocol before the first subject visit; delaying the trials by 4 months.[7] Another constraint in recruitment is stiff competition for potential patients with multiple studies simultaneously recruiting patients at the same center. For example, docetaxel and paclitaxel trials for breast cancer patients, risperidone and paliperidone trials for refractory schizophrenia at the same study site and often with same investigator. For bioequivalence studies, there is an intense competition for healthy volunteers among clinical research organizations.

Further, several multi-country studies demand the use of central laboratory with its normal reference range (biochemical and hematological tests) for standardization and to minimize error. These reference ranges are adopted from textbooks written by western authors and do not match with the domestic study population resulting in high screen failure rate. Mismatch of hemoglobin levels in the Indian population is one of the common causes for screen failure as observed by Bose *et al*.[6] The best approach is to use "acceptable range" identified from population of participants beforehand. Similarly, the clinical trials using international treatment guidelines being

at variance with national guidelines/standard of practice may also experience recruitment challenges. Clinical trial feasibility tests will help in identifying country-specific or even institution-specific practices which can have an impact on overall study. With increasing popularity of the country on the global stage, the competing trials are likely to increase. The longer it takes to enroll patients, the trials become more expensive. Several trials demand long follow-up, the endpoint being either 5 years' survival or death. The retention of participants through study without adequate returns is not easy. In fact, it has been observed that trial participation of more than 6 months is a strong barrier to patient participation.[8] The study can be designed taking into account "India specific factors" to facilitate recruitment.

Similarly, it is essential to realize the characteristics of the patient population especially literacy level, sociocultural, and awareness about clinical research which plays a vital role in decision-making to participate in clinical trials. Even in the most developed countries with high literacy level, the awareness about clinical trials and the option/opportunity of participating in a trial in general population, family members, and caregivers is almost low to nil. Unlike western countries, display of poster or advertisement or recruitment campaign for public exposure to clinical research is not practiced in government institutions or corporate hospitals in India. It is perceived that such exposure may be twisted by sensational media reports. The patients may be reluctant to participate due to the perceived risk of harm and side effects of research. In India, during the festival times, the attendance of patients at the hospital tends to be less that affects recruitment rate. Fasting during the religious festival time is commonly practiced; that may affect the adherence to treatment and retention. The inconvenience cause due to hospital admission (pharmacokinetic end points) or additional study procedure or followup visits and travel distance from study site to patient residence can influence enrolment and drop outs. It has been experienced that the initial enthusiasm of participation and incentives gets diluted after first few visits, the burden due to follow-up visits, travel time, and waiting hours results in consent withdrawal and dropouts. The authors found substantial number of dropouts due to consent withdrawal, highest being healthy volunteers. This is alarming and may create low spirits among the study team members. It implies the importance of frequent engagement of the study site staff with the participant and leading family member for mentoring and compliance prior to informed consent. However, there is wide variation across academic institutions and public hospitals in the availability of clinical research department with dedicated space, infrastructure, trained, experienced staff, and secluded place to make the participant and caretaker comfortable and free for dialogues for various in-house trial-related activities.

The contribution of the study staff and site characteristics in enrolment and retaining participants cannot be undermined. The type of staff especially their involvement and forthcoming attitude, understanding of the study protocol, ability to effectively communicate with patients, awareness of the stress the patient undergoes during the trial (long waiting hours, frequent hospital visit, adverse effects, travel time, etc.), motivation and enthusiasm of investigator does influence the recruitment and retention. Frequent communication with the participant through proper coaching, guidance, explaining the nature of risk as well as risk mitigation plan, etc., in lucid local languages that can be understood by the participant and their relatives facilitate enrolment and avoid dropouts. More importantly, friendly and approachable study coordinator, giving sufficient quality time to carefully listen and mentor the patients not only improves recruitment but also lower dropout rate. If the trial design demands additional visits for tests and procedures, providing additional compensation for the inconvenience and discomfort, loss of daily wages for the subject and caretaker as well as incidental expenses may act as motivation and improves compliance. While frequent turnover of the study staff can hinder the recruitment. Thus, the positive environment and approach at study site would be easier to overcome the challenges of enrollment and retention in clinical trial and overall success.

It is time to explore and fully utilize electronic technology to determine the "feasibility" of conducting a trial and patient population. Targeted database population, social media and electronic health records, insurance database, prescriptions, prescribers, and payers data to find eligible patients for a specific trial, information about ongoing clinical trial and connect with resources to reach out to the desired patient population. In India, almost all the participant's recruitment is through doctors. It is therefore essential and most practical effort is networking with investigators and referring physicians. Professional associations websites and patient registries can share information about ongoing clinical trials (without disclosing the details) to facilitate participants recruitments. The study can be designed taking into account "India specific factors" to facilitate recruitment. Adaptive designs for clinical trials are expected to require less number of patients and reduce the duration of trial simultaneously, thereby ensuring the high chance of getting the right answer may be considered. The use of artificial intelligence tools has been proposed for trial design, selection, and monitoring of patients to improve

outcome.[9] Eventually, what really matters is recruiting right patients at right time and retaining them throughout the study to provide accurate, complete data for meaningful scientific and regulatory decisions. A "participant centric" approach by clinical researchers will go a long way.

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