India's next challenge: Rebooting recruitment

India became one of the most attractive destinations for global clinical trials due to its potential for fast recruitment of patients. However, this premise is seriously challenged by the recent regulatory changes.[1] It is likely that some of the difficult regulations - compensation - may get amended and overall regulatory environment might improve. However, the challenge would be: how to reboot the recruitment? It would be worth reflecting on the past recruitment experience to develop effective strategies.

Based on marketing applications approved by US Food and drug Administration in 2008, Indian sites recruited an average of eight patients per site.[2] In contrast, the average number of patients per site was 13 for China and 16 for Brazil. In our study of recruitment performance of Indian sites, we found large variations in recruitment rates between the sites.[3] In three studies, 39% sites did not recruit any patients in the first month. Although few sites could recruit first patient within 1 day of site initiation visit, the delay at some sites was as long as 123 days. The recruitment was <50% of the target at nine of the 41 sites. It would be desirable to understand the challenges faced by Indian sites in recruiting patients.

Recruitment in clinical trials depends on two factors: protocol related factors and patient related factors.

During the time period, India became a clinical trial destination, the clinical trial protocols have become more complex, demanding, and burdensome for both sites and patients. Between 1999 and 2005,[4] the average number of inclusion criteria has increased threefold. The average number of procedures grew annually by 6.5%, reaching a median number of 35 procedures in 2005. In 2012, a typical phase III protocol included 50 eligibility criteria, 167 procedures, and 13 endpoints.[5]

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Such complex protocols impact the site performance.[4] The patient enrolment rates (i.e. the percentage of patients randomized following screening) dropped from 75% in 1999-2002 to 59% in 2003-06, and the study completion rates for patients fell from 69% to 48%.

Among the patient factors, the most important is informed consent. According to a study by Gitanjali, only 30% of Indian patients are likely to consent for a clinical trial.[6] Most patients withheld consent because they did not want to give blood or take a new drug or were afraid of tests.

There could be several barriers in patient's unwillingness to take part in a clinical trial.[7-9] The patients may be worried about uncertainty of treatment or trials, uncertainly of efficacy and safety of trials, loss of confidentiality and consent process. The patients may be concerned about trial burden, number and frequency of appointments and procedures, physical discomfort associated with procedures, travel problems and costs, and missing work. In addition, mistrust of trial organizations is a significant barrier[7] in trial participation. The legacy of past abuse in Tuskegee Study is reported to be a significant barrier in African Americans' participation in clinical research.[10] Current adverse media publicity and the public interest litigation on clinical trials could reinforce such mistrust. The large treatment naïve population is unlikely to be naïve in asserting their autonomy!

Let's see how this translates into recruitment numbers. If a site has 100 potential patients, 30 would consent. Of these nine (30%) may not agree for audio-visual recording of consent. From the available 21 patients, 14 could be enrolled and 7 could complete the study. Earlier, when the regulations were less difficult, the sponsor had freedom to select a large number of sites or add sites in case the planned recruitment was not achieved. However, considering the current rationing on number of trials per site and preference for 50% public hospitals, the recruitment will be a significant challenge in India. There is an urgent need to evolve strategies to reactivate the recruitment process.

The current crisis of confidence among clinical research patients requires a major public awareness campaign to allay fears of the patients by creating awareness about (a) the need for clinical research process and its value in improving public health (b) regulatory mechanisms for human patient protection and (c) compliance enforcement actions. The government has a major role to play in this effort. This has to be actively supported by the industry and the investigators.

The investigator sites need to develop a systematic approach to recruitment. An analysis of our data (unpublished data) showed that for a cardiac study, enrolment was 11% of the feasibility estimates. In oncology studies, the screen failure rate was 41% patients. Of these, 68% did not meet the selection criteria. This suggests that the sites do not have an up-to-date active data base of potential clinical trial patients. If a site plans to recruit one patient/month, it would require an active database of 14-15 patients. It is essential that the sites develop a good database of patient population, preferably electronic, which can provide realistic feasibility estimates, and improve screening process and expedite enrolment process. Of course, this has to be supplemented by training of the site team in understanding the protocol specific eligibility criteria and procedures, and regular discussions with the team about study status. It would be important to improve communication with the patient and the family, which could be reinforced by educational aids.

The site should also focus on strategies to retain the clinical trial patients till completion of all protocol related procedure and visits. The site should make efforts to make it easy for the patients to follow-up, reduce dropouts, and facilitate patient retention.[11] This could be achieved by practical measures, e.g. completing all protocol-required procedures during the time allotted for visit, solving transportation issues, providing the patient with easy-to-carry and easy-to-understand instructions. Contacting patient by phone, when there is a long interval between visits, can resolve any issues that might be bothering the patient. Treating the patient with respect and making him/her feel that his/her participation is important would go a long way in ensuring compliance to trial procedures and facilitating retention of the patient.

Last year's regulatory changes have diverted the attention of the industry and the investigator away from the practical issues in conduct of the clinical trials. While waiting for the regulatory scenario to improve, it would be desirable for the industry and the investigator to refocus on strategies to reboot the recruitment!

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