How to Minimize Low Enrolling Sites: A Case Study in Diabetes

Abby Abraham, Janet Jones, Sunitha Vikram

ABSTRACT

India is becoming one of the fast evolving destinations for conducting global clinical trials. This case study shows that, as expected, Indian sites have a higher subject recruitment rate than the global average there. However, there is scope to enhance subject recruitment performance by looking at the relative performance of the Indian sites. The case study looks at high and low performing Indian sites to define the attributes associated with performance. Clinical trial insight has been used to develop a series of steps to help facilitate in identification of sites and improve patient recruitment process. Tips are provided on how the CRA can review historical and competing study data, the importance of assessing the availability and interest of the PI and study team. With this knowledge, the CRA can pro actively help sites identify and resolve potential issues related to start up delays and recruitment by creating a site specific recruitment plan and lastly encourage and motivate sites to achieve the target as per the agreed plan. The importance of CRA-Investigator relationship is another critical element in achieving high recruitment performance. Analysis of these trends can serve as indicators for site performance and help to differentiate the low from high recruiting sites.

Key words: Site Performance, Patient Recruitment, Feasibility, Diabetes, India

INDIA, and Asia Pacific, are increasingly engaged in clinical trials to support accelerated recruitment and shorten clinical development timelines. This trend has been particularly important in western diseases, such as diabetes. As competition increases, it is important that Asia Pacific countries continue to be internationally recognized as reliable enrollers who meet our targets and deliver high quality patient data.

This case study examines four large global diabetes studies in which India made a significant contribution to the recruitment effort and performed above the global study average (Table 1). The characteristics of high and low enrolling sites have been identified as guidance to minimize low enrolling sites in the Indian patient recruitment lifecycle.

Table 1. Summary of the Indian contribution to the 4 completed complex global diabetes studies.

| Study | Indian contribution | Relative recruitment rate of the study in India compared to the global study |
|-------|---------------------|--------------------------------------------------------------------------------|
|       | # Sites | # Patients randomized |                                                                                     |
| 1     | 8      | 58                  | 1.7 times higher                                                                     |
| 2     | 14     | 97                  | 3.5 times higher                                                                     |
| 3     | 12     | 124                 | 3 times higher                                                                        |
| 4     | 35     | 523                 | 2.7 times higher                                                                     |

The relative recruitment rate was calculated by taking the mean average of the Indian recruitment rate / the mean average of the study.

Defining sites for their enrollment performance

The performance of each site has been compared to the performance across the study. Sites were classified as low, medium or high enrolers (Fig 1a). The Indian sites were high performers when compared to the global studies; only 15% of the Indian sites were low enrolers (Fig 1c). When performance was evaluated across the Indian sites, (Fig 1b),

Abby Abraham
Associate Director, Clinical Operations
ICON Clinical Research, India

Janet Jones
Senior Director, Project Information & Feasibility
ICON Clinical Research, India

Sunitha Vikram
Project Manager, ICON Clinical Research, India
the medium and high performing groups (61% of sites) produced 80% of the patients. This indicates that most sites contributed patients and made a cost effective contribution to the study which contrasts to the frequently quoted metric of 20% of the sites contributing 80% of patients.

**Low verses high performing sites**

During the study conduct, sites were characterized by the CRA against a list of positive and negative criteria (Fig 2a) to define what worked / did not work. A lack of PI and team engagement were the most common negative characteristics and low performing sites had more negative than positive characteristics (Fig 2b). The reverse was seen in high performing sites: the PI and team were highly engaged and available, they were organized, prepared to plan for the study and open to training if required. These characteristics translated into higher recruitment, productivity and quality. The sites were motivated and eager to learn with a plan of how they were going to conduct the study and manage the recruitment process.

Although the use of Site Management organization/ Clinical trial units was classified as a positive characteristic, this did not consistently translate into higher enrollment. Enrollment was only boosted when one SMO was managed with a recruitment plan.

The site setting can have an impact on enrollment, for example, the high level of attrition in private hospitals, with a PI working as a consultant, can result in a previously engaged and motivated PI leaving the study, resulting in ineffective and delayed enrollment.

Some research experienced academic and scientifically orientated PIs were not engaged but the PI’s did develop and coach an engaged and motivated team, which contributed to enrollment. Sites with prior clinical research did not necessarily yield higher enrollment over clinical research naive sites. In some cases this was due to an informal recruitment policy in which they would participate in more studies with modest patient numbers per study. This was off-set by the enthusiasm of inexperienced study teams. Their willingness to learn and execute correctly led to high performance.
In India, there is not normally a problem accessing diabetic patients consequently most recruitment efforts involve identifying clinic patients. One of the top recruiting sites used a referral network and to create informal links with GPs and other hospitals with a very positive effect. A successful approach is to increase awareness across the hospital and with colleagues, for example by making other colleagues aware of the study. In the large diabetic study involving treatment naïve patients it was possible to access the information and database that emanated from institutional health camps.

Positive characteristics, such as high commitment, dedicated and motivated team, etc. provide an indication of site performance. The kind of hospital (tertiary care), size of potential study patient pool and the ability to handle protocol related tasks contributed to higher levels of recruitment.

Steps to reduce low enrolling sites

Successful, patient recruitment needs to be considered as a cycle of events which begins with the right sites from previous study data and using them to conduct robust feasibility and planning and ends with a full evaluation of site performance and the factors that influenced the high and low recruiters. The Indian recruitment cycle is shown in Figure 3.

1. Enrollment planning starts with feasibility & planning
   - Examine previous performance / track record. Be aware of sites that have reliable but modest recruitment due to their recruitment policy.
   - Look at the competing study landscape, in fields such as diabetes, engage and evaluate new sites. These can be high performers if the are given adequate training and support.

2. Validate reality at the Pre-study stage
   - Validate competing studies and the impact they will have on recruitment. Use this and the recruitment policy to define expectations.
   - Assess PI interest, staff turnover and assess engagement and commitment. Understand the plan for resourcing the study team.
   - Validate the feasibility data to assess the size of the likely patient consenting pool, look at the impact of protocol related limitations / potential challenges.
   - Examine the source of patients and how patients will be engaged. Does a patient database exist?
   - Determine hospital administration issues that may delay start up.
   - For inexperienced sites assess the willingness to comply and learn.

3. Getting ready for the initiation visit by defining expectations
   - Map the data collected (eg interaction during the pre-study visit, speed of providing documentation and responsiveness) against the site to define the expected site characteristics.
   - Define the expectations of the site eg their planned enrollment numbers.
   - Arrange for pre-screening tests to validate the patient population. if needed.
   - Ensure that the site are ready to start pre-screening.
   - Get the site ready to start enrolling when they are activated.

4. Ensure that the site have the high performance characteristics at the Site Initiation visit
   - Ensure the PI and team are to be engaged in the study and confirm resourcing at the site.
   - Review the patient pathway, eg the patient database, referral network and identify any possible challenges seen by the site and enforce the commitment to enrollment.
   - Discuss and formulate the site specific recruitment plan. Sites may need help with this.

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**Fig 3 Indian Recruitment Lifecycle**
How to minimize low enrolling sites

5. Work in partnership with the site to get the most out of their recruitment plan

- Have shared understanding of the expectations and goals. Even if the site is to recruit as highly as possible and not be restricted by a target
- Encourage the sites to treat recruitment as an organized exercise, with a plan. Use short term goals, recognizing when milestones are reached.
- Constantly review against the plan, identifying reasons for recruitment slow downs. Define the intervention and resolution plan, eg a motivational visit, training visit, resource needs, alternative approaches
- Review the patient pathway and explore
  - Engaging others in the same institute
  - A referral network
  - The involvement of institutional medial camp

6. Share best practices that have worked in other sites to help motivate low performing sites

- This can be by ongoing newsletters or informal motivation sessions
- Understand and document the reason for low performance, to help make informed decisions for the next study.

In summary, from the case study presented very few Indian sites under-performed relative to the whole study and several key characteristics of high performing sites have been identified that can be used to maximize site performance. A missing component in this discussion is the CRA, who is the key to developing and maintaining site relationships. It is essential that the CRA is seen to be competent by the investigator and able to give the site the guidance and support that they need. Providing CRAs with the training, skills and support that they need to identify low performing sites, manage the relationships with investigators can be a key and critical component in converting low performing sites to high enrollers.