International Journal of Clinical Trials
Gangurde N et al. Int J Clin Trials. 2024 Nov;11(4):305-309
http://www.ijclinicaltrials.com
pISSN 2349-3240 | eISSN 2349-3259
DOI: https://dx.doi.org/10.18203/2349-3259.ijct20243334

Review Article

From hurdles to high performance: overcoming day-to-day challenges for successful clinical trials at sites

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Received: 18 July 2024
Revised: 06 September 2024
Accepted: 13 September 2024

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ABSTRACT

Randomized clinical trials are fundamental in testing new drugs, medical devices and treatment protocols. They help to determine the efficacy and safety of new treatments, leading to medical innovations that can significantly improve treatment outcomes. Clinical trial sites are the engines that drive medical advancements, but they face numerous challenges in their day-to-day operations and impact the study outcome as well as data quality. Continuous improvement through research and innovation ensures that clinical trials are conducted more effectively, leading to better healthcare advancements and patient outcomes. Execution of clinical trial at the hospital site is a critical task and associated with the new challenges every day which may include patient recruitment, retention and compliance to the data collection. GCP compliance is a soul of clinical research and difficult task to comply with. GCP is a harmonized guideline accepted by most of the countries all across the globe.

Keywords: Quality assurance, ICH-GCP guidelines, Clinical trial sites

INTRODUCTION

Well-designed randomised clinical trials can benefit the participants as well as the investigators, the sponsors and the medical community.[1] Clinical trial sites are crucial for recruiting and retaining participants, collecting and managing data, ensuring compliance with protocols, monitoring patient safety and maintaining quality assurance. Their efforts ensure the generation of reliable data essential for advancing medical science and improving patient care. Clinical trials are indispensable for advancing healthcare, offering hope for better treatments and cures for various diseases. They provide the evidences needed to ensure that new medical interventions and diagnostic tools are both safe and effective, ultimately leading to improved patient care and health outcomes. Clinical research and clinical trials are important from the public health perspective.[2] Clinical trials play a crucial role in healthcare advancements, providing the foundation for developing new treatments, improving existing therapies and enhancing overall patient care. India is a potential hub for the execution of clinical trials, reason being the great hospital and healthcare infrastructure, pool of qualified investigators and the disease burden. English-speaking population and qualified manpower are an additional advantage. India clinical trial market is valued around 2.1 billion USD and expected CAGR is around 8.3%. The favourable regulatory environment and the expedite approval process is a growth engine for the clinical trial businesses in India. Central Drugs Standard Control Organization (CDSCO) centralised regulatory authority have come up with online approval processes and have set the timelines for the various regulatory approvals for the trials to be conducted in the India. The digitalization of clinical trials is expected to impact market growth positively. Digitalization has enabled streamlining several trial processes, such as data capture, regulatory compliance

logistics and supplies management. Furthermore, with the introduction of digital therapeutics, real-time data acquisition related to safety and toxicity is becoming increasingly easy, thereby promoting timely rectification in trial design, and facilitating market growth. The cost of clinical trials in India is nearly half that incurred in the U.S. and Europe. Thus, the cost efficiency and a large treatment-naïve patient pool offered by the county are anticipated to drive the market.[3]

METHODS

This is observational and retrospective study and the authors are professional clinical research experts. They are working with various clinical research sites. They have used the data and information/real-hands on experiences from Vedant Multispeciality Hospital, Pune and Pulse Multispeciality Hospital, Pune sites while studies execution for various indications.

The objective of this study is to enlist the date to day operational challenges while conducting the clinical trials and offering some solutions based on experiences and free literature available. The inputs also include the formal interactions with investigators, study participants and the study staff.

DISCUSSION

Clinical trial site faces day-to-day challenges. The biggest challenge is patient recruitment and their retention in the study. There may be difficulties in finding eligible participants who meet specific inclusion/exclusion criteria. Retaining participants throughout a clinical trial is crucial for generating reliable data and ensuring the success of the study. As Informed Consent process is a rigorous process, some patients get demoralised. Sometimes patients are willing to participate in the clinical trial, but kins are not willing. Investigational Product (IP) shipment gets delayed to reach to the site due to some logistic issues, sometimes. Patient might get irritated, if he does not receive his treatment in time.

Clinical trial site personnel should provide participants with clear and understandable information about the study, including potential risks and benefits, before they enrol in the trial. They should get detailed information about the study. Patient counselling is very important to recruit and retain the patients in the study. Some studies May go on year-on-year and ask the participants to dedicate significant time for clinic visits, tests, procedures and follow-up appointments. Duration of study is one of the critical factors. This ongoing commitment may be difficult to manage alongside work, family and other personal obligations. Frequent travel to the clinical trial site can be burdensome, especially for participants who live far away or have limited transportation facilities. Additionally, scheduling clinic visits around work or childcare time can be hectic or challenging. To overcome this challenge, the sponsor, CROs or sites should offer fair compensation for time and travel and also consider implementing incentive programs to acknowledge participant commitment. Offer flexible appointment times and consider virtual visits and decentralise clinical trial model, when possible, to minimize travel burdens.

Participants assigned to the placebo group might feel discouraged when they don't experience any improvement. This lack of perceived benefit can lead to withdrawal from the study. Certain trials may involve invasive procedures, blood draws, medication adherence or dietary restrictions. These ongoing demands can become a burden for participants, impacting their willingness to continue participation in the trial. This lack of knowledge can lead to decreased motivation and commitment over time. The sites need to create a supportive and welcoming environment for participants, providing ongoing communication and addressing their concerns promptly. Frequent communication from the research team or providing updates on the study progress can make participants feel involved and in the trial which might help in patient retention in the study.

Even if a medication or treatment has been deemed safe in earlier stages of the clinical trials, participants in a clinical trial can experience unforeseen side effects. These side effects, ranging from mild discomfort to severe health complications, can be a major reason for dropping out. Participants may not receive adequate support or guidance on managing side effects, leading to frustration and a decision to discontinue the trial. To overcome the above challenges, clinical trial team, Principal investigators and Clinical research coordinators should develop a comprehensive plan for managing side effects, offer prompt support and provide guidance to participants experiencing discomforts.

Strict adherence to the clinical trial protocol and the compliance is a key of the successful clinical trial. Hence clinical trial sites should stick not only to protocol adherence but also to maintain data quality. Principal Investigator (PI) is sometimes overburdened during his service to patients. He/she could not focus on patients in clinical trials due to his/her hectic OPD and IPD patient schedule. To overcome this above problem, PI and site staff should be well trained with ICH-GCP guidelines. Quality assurance team can arrange GCP workshops, refresh trainings to PI, CRCs and site staff on quarterly basis. Sometimes non-compliant attitude and the approach of the trial participant is a critical challenge especially with the dose regimen and noting the same in the patient diary.

Frequent communication with the patients by clinical trial team/CRC can avoid the patient dropout rate. Proper training and counselling should be provided to the patients as well as their relatives about filling the diaries and entering the side effects in timely manner. Manual data entry in Electronic Data Capture (EDC) is prone to

errors such as typos, incorrect entries and misinterpretation of data. Clinical trials often have complex protocols, making data entry challenging and increasing the likelihood of errors. Large amounts of data need to be entered, especially in large-scale trials, which can overwhelm data entry personnel. There is a pressure and time constraint to meet deadlines from sponsors and monitors. It may lead to rushed data entry and higher error rates. Inadequate training and varying competency levels among staff can affect the accuracy of data entry. Insufficient training and lack of supervision can result in improper data collection practices. Ensuring that all staff strictly adheres to the trial protocol can be difficult, leading to protocol deviations and errors.

The sites need to utilize EDC systems to reduce manual data entry errors. Comprehensive training programs for staff can be implemented on data entry. Develop and enforce Site SOPs (Site Operating Procedures) to ensure consistency and standardization in data entry and record maintenance. The sites need to establish robust quality assurance processes, including regular audits and reviews, to maintain data integrity. Quality assurance (QA) has become a major factor over recent years in the management and analysis of clinical trials.[4]

Implement feedback mechanisms for continuous improvement in data collection and entry practices. Regularly review practices to be followed to ensure compliance with regulatory requirements and ICH-GCP guidelines.[5]

Regulatory and ethical challenges in clinical trials include ensuring strict compliance with complex and evolving regulations, which can vary by region and trial type. Ethical challenges involve protecting participant rights, obtaining informed consent and maintaining confidentiality and data integrity. Addressing these issues requires meticulous documentation, robust informed consent processes, regular ethical training for staff and continuous monitoring and auditing to uphold high ethical standards and regulatory compliance. Balancing the need for rigorous oversight with the practicalities of conducting efficient and effective trials is a constant challenge.

Establishment of multinational collaborations among investigators and funding and regulatory agencies is indispensable to the advancement of science and the improvement of patient outcomes on a global scale.[6]

Ensuring informed consent and protecting patient rights are critical and challenging aspects of clinical trials. Informed consent requires that participants fully understand the trial's purpose, procedures, risks and benefits before agreeing to participate, which can be difficult to achieve due to complex medical and legal information. Protecting patient rights involves maintaining confidentiality, ensuring voluntary participation and providing appropriate care and support throughout the trial. These tasks demand meticulous attention to detail, clear communication and strict adherence to ethical and regulatory standards to safeguard participant's welfare and autonomy.

To maintain high ethical standards in clinical trials, it involves robust informed consent processes and regular ethical training as per NDCT Rules 2019.[7] For informed consent, ensure clear communication with simple language and visual aids, provide comprehensive and transparent information, treat consent as an ongoing process and also verify whether the participant is understanding it well. Keep thorough documentation.

Regular ethical training includes comprehensive and continuous education programs, practical workshops, ethical leadership, refresher courses, feedback mechanisms and utilizing ethics committees. Additional strategies include engaging participants, fostering transparency and accountability, regular monitoring and auditing and managing conflicts of interest. These strategies ensure participant's rights are protected and the integrity of research is maintained.

Staffing and training

There is great need to appoint qualified and well-trained staff to manage clinical trials effectively at the sites. Inadequate educational and training institutions can result in a shortage of well-trained professionals. Lack of awareness about career opportunities in clinical research can result in low interest among potential candidates. Limited financial and human resources for recruitment efforts can hinder the ability to attract skilled personnel. In small research settings, they may offer very less salaries and benefits, leading to higher turnover rates. Limited opportunities for professional growth and advancement can result in dissatisfaction and attrition.

Inadequate facilities, resources and support can create a challenging work environment, reducing job satisfaction. High workloads and stress levels, particularly in resource-limited settings, can contribute to burnout and turnover. Uncertain funding and job insecurity can make it difficult to retain skilled personnel.

Training and development programs should be provided to develop local talent, including partnerships with educational institutions to create tailored courses. Offer competitive salaries and benefits to attract and retain skilled personnel, possibly through grants and external funding. Create clear career pathways and provide opportunities for professional growth and advancement within the organization.

Improve the work environment by providing adequate resources, facilities and support to reduce stress and enhance job satisfaction. Implement flexible work arrangements to improve work-life balance and reduce burnout. Recognize and reward the contributions of staff

through incentives, awards, and other forms of recognition. Partner with local educational and professional organizations to build a pipeline of skilled personnel. Develop retention programs that focus on employee engagement, satisfaction and long-term career development.

Communication and collaboration

Clear communication between investigators, sponsors, CROs and regulatory bodies is vital for the success and integrity of clinical trials. It ensures that all parties are aligned on trial objectives, protocols and regulatory requirements, reducing the risk of misunderstandings and errors. Effective communication facilitates timely reporting and resolution of issues, enhances coordination and ensures compliance with ethical and regulatory standards. This collaboration supports the efficient management of trials, fosters trust among stakeholders, and ultimately contributes to the safety and well-being of participants and the reliability of trial outcomes.

There may be Budgetary Constraints and Resource limitations at clinical trial sites which can significantly impact resources and infrastructure. These constraints may lead to insufficient staffing, inadequate training and lack of advanced technology and equipment. Limited funding can hinder patient recruitment and retention efforts as well as the ability to conduct comprehensive quality control and compliance checks. Overall, these financial challenges can compromise the efficiency, quality and success of clinical trials. Limited financial resources can make it difficult to cover essential personnel costs, such as hiring and retaining skilled staff and providing necessary trainings.

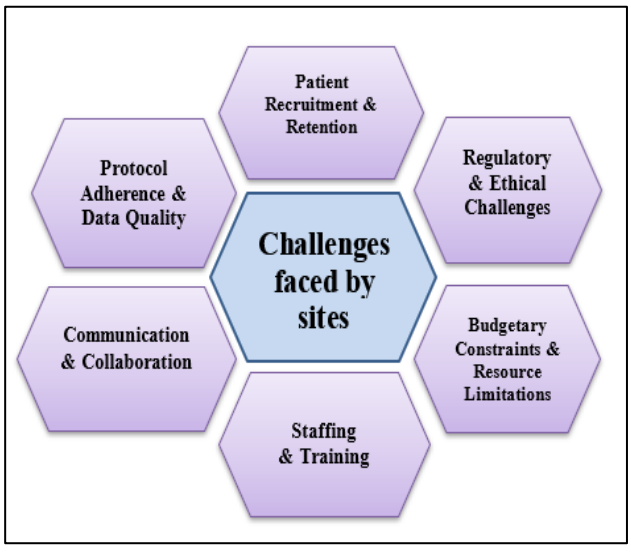

Figure 1: Challenges faced by clinical trial sites.

To overcome this challenge, the sponsor should provide sufficient funding to the clinical trials sites so that the studies can be conducted smoothly. Site can procure necessary supplies for study conduct. This financial sufficiency can help in successful trial execution and maintain integrity of clinical trials.

CONCLUSION

Clinical trial sites face day-to-day challenges that impact their operations and effectiveness. One significant challenge is patient recruitment and retention, as finding and enrolling eligible participants can be time-consuming and retaining difficult tasks and keeping them engaged throughout the trial can be equally challenging. Regulatory compliance is another critical issue, requiring strict adherence to trial protocols and meticulous documentation to meet regulatory guidelines.

Data management also poses challenges, including ensuring accurate and consistent data entry in source templates, maintaining data integrity in all logs provided by the sponsor and protecting confidentiality. Resource allocation is a persistent problem, with sites needing to ensure they have sufficient and adequately trained staff while managing budget constraints.

Effective communication and coordination both are essential within the trial team and with external entities such as sponsors, CROs and regulatory bodies. Ensuring participant's safety and care through regular monitoring and coordinated medical support is paramount. Logistical challenges include managing the supply of necessary materials and efficiently scheduling participant visits and assessments. Quality control is critical, requiring preparation for audits and inspections and adherence to standard operating procedures. Additionally, obtaining informed consent and keeping participants informed and engaged throughout the trial are vital to ensure compliance and retention. Managing these challenges effectively is crucial for clinical trial sites to operate efficiently, ensure compliance and contribute to the success of clinical trials.

Academic establishments like universities and colleges can design the courses which will bridge the gap between industry and academia. They can also include the clinical research activity related course curriculum in their degree courses. Industry should allow the youngsters to join them as intern / trainee. Industry and Academy can collectively revise the curriculum of the bachelor courses which may help the clinical research industry to get the trained resources. Career counselling from the industry expert for the upcoming batches will be great initiative to attract great talent towards the clinical research industry. It will also create a trustworthy, ethical environment for foreign clients and Indian industry would get phase I studies on a large scale to conduct.

These trends and solutions hold promise for making clinical trials more efficient, cost-effective and accessible.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Gangurde N, Bagde D. From hurdles to high performance: overcoming day-to-day challenges for successful clinical trials at sites. Int J Clin Trials 2024;11(4):305-9.