

## Short Communication

# Clinical data monitoring during COVID-19 pandemic: an experience from a regulatory trial in India

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## ABSTRACT

The essence of any clinical or healthcare related discovery is its methodologically sound clinical research and clinical data monitoring. This eventually helps the clinicians to understand the best possible clinical management pathways or patient management at all the levels of healthcare system. The pandemic has had an impact on clinical trial data monitoring as well. New or mixed approaches to routine monitoring have been introduced to ensure the quality of the overall research in these challenging times and are being tested for efficacy, cost-effectiveness while keeping ethical considerations as the main priority. This write up intends to highlight a few steps taken to ensure data integrity and participants' safety and rights.

**Keywords:** Clinical data monitoring, Source data verification, COVID-19, Pandemic, Remote or central monitoring

## INTRODUCTION

Clinical data monitoring in a clinical trial (CT) ensures the integrity of study data and protects the rights and well-being of study participants. Monitoring as a quality control measure is an ongoing process performed by a qualified and trained independent personnel assigned by the sponsor to perform the monitoring activity diligently. It commences with study preparedness at the site and, concludes with the end of the study at each site. In general, the routine monitoring ensures that the study conduct is as per the approved protocol, the good clinical practices (GCP) guidelines, standard operating procedures (SOPs), and applicable regulatory requirements.

There are several approaches to monitoring and a 100% source data verification (SDV) ensures capturing all critical and noncritical observations during onsite monitoring visits.<sup>1</sup> Another approach is remote or central monitoring, where the study monitor performs all the

study-monitoring processes remotely, using a secure online platform. However, in India, due to pragmatic reasons, the preference for central or remote monitoring is slowly and steadily attaining momentum.

A combination of onsite and remote monitoring will enable the monitor to focus on the challenges, by avoiding frequent travel and could use site visits more efficiently for source data verifications and process monitoring.

Various studies have highlighted that a major part of on-site monitoring is SDV which accounts for 46% of the study monitor's time. Source data verification assures better compliance and quality. Regulatory authorities do not define the extent of SDV to be performed or data to be verified in clinical trials. Even, food and drug administration (FDA) recommend review of a "representative" number of participant records and not all records.<sup>2,3</sup>

The recent COVID–19 pandemic has brought unforeseen challenges to clinical researches in India and across the world. This has an impact on clinical studies in India as well. Considering the safety of both study participants and the study team (including monitors), the sponsors have to decide upon suspending the fresh screening, and enrolment at the sites and on-site study-monitoring visits. Simultaneously, it has been a great challenge to ensure the protocol-driven follow-up activities and the investigations including continual treatment of the already enrolled participants.

The consequences of the COVID–19 pandemic forced to evolve implement and adapt at an astounding pace. The national lockdown followed by the pandemic allowed revisiting the plan of actions and adjust the monitoring strategy. As an initiative, the sponsor and the monitoring team developed a contingency plan to ensure that the study and the monitoring activities functioned smoothly.

As the impact of this pandemic on clinical trials cannot be addressed by a strategy of ‘one size fits all’, we propose to suggest a suitable strategy for this situation in our write up. This is based on our experience from an ongoing clinical trial being conducted at multiple sites for drug resistant tuberculosis.

## METHODS

### *Monitoring strategy before COVID–19 pandemic*

A multicentre clinical study to study the effectiveness of a combination of newer drugs for the management of drug-resistant tuberculosis is ongoing in five sites in India. As a regular or routine plan of action, the monitoring team developed a detailed study-monitoring strategy for clinical data monitoring and safety monitoring before the study and on-site monitoring initiation at the site level. This plan determines the extent, nature, and frequency of monitoring visits, and these considerations are based on the reflections from the protocol and the regulatory requirements. This includes the research goal, aim and objectives, study design and its complexity, the site’s experience in implementing a clinical trial, and the outcome to be measured at the end. This plan has been co-created in consultation with the sponsor. During the monitoring visit to the sites, the study monitor performed major tasks as listed below.

#### *Routine on-site study monitoring activities*

Routine on-site study monitoring activities included: verify storage and accountability of the investigational product; verify proper adherence and conduct of the protocol (schedule of events); verify compliance with the written informed consent document; ensure that the study staffs are adequately trained about the trial; verify that the site is enrolling only eligible participants; report participant recruitment rate; verify regulatory compliance and site-specific ethics committee compliances; determine

appropriate reporting of adverse events; communicate protocol deviations and recommend an appropriate plan to prevent their recurrence; and ensure accuracy and completeness of the case report form (CRF) entries through SDV.

### *Monitoring strategy during COVID 19 pandemic*

Given the COVID–19 pandemic situation, the monitoring team restricted their on-site monitoring visits to the minimal in agreement with the sponsor. However, we proposed to conduct remote monitoring during this phase with the site team support to combat the anticipated backlog of SDV and informed consent document review. This was not there in the initial monitoring plan.

At first, the monitoring team sought support from the site for scanning and sharing the source documents with the monitoring team to resume the SDV during lock-down. However, scanning of source documents was not practical due to the limited staff strength at the sites. Travel restrictions across the country and within the city made it difficult for the site staff to reach the facility daily. Additionally, we also anticipated that due to the increased workload of the site staff, it may be difficult to track the documents shared, and eventually, it may create a lot of confusion among the team. Hence, we have decided to withhold physical or on-site monitoring until the situation normalizes. As the pandemic progresses, the following guidelines were finalized for the safe conduct of the study: suspended in-person study-related activities without a personal protection equipment (PPE) kit; suspended active screening of participants, as it may involve the participants coming to the center more than once; ensured a steady supply of study drugs (investigational product) to the enrolled participants at their doorstep to avoid their traveling to the study facility for drugs; ensure drug compliance by the site staff through a daily telephonic follow-up with the participants; the site team to file protocol deviations in the prescribed format for the missed or delayed (out of window period) activities during this phase; the site has provided the authority to facilitate electrocardiography (ECG) and complete blood count (CBC) at nearby health facilities of the participant in coordination with the medical officer in-charge; as the study involve utmost patient care and management, the sites prioritized the follow-up activities including clinical and laboratory investigations; monthly virtual meetings with the site team, sponsor, and the monitoring team identified and resolved the challenges faced by the site during this pandemic situation; the study team to ensure the limited exposure of the current COVID–19 pandemic to both the participant and the study staff; and the site team to manage the documentation of the study activities for future reference.

### *Study monitoring outlined*

Study monitoring was done by: the monitoring team initiated remote monitoring with site staff support; remote

monitoring included CRF completion and missing fields of the data entered concurrently; the remote monitoring observations were compiled and weekly reports were generated and shared with the sites for necessary action; the eligibility of the potential participants was confirmed through telephonic or email contact with the site team; safety monitoring continued through remote access to ECRF and SAE reporting support through email communications and telephonically as and when required or requested and; once the situation normalizes, the team will perform frequent visits and this includes updating site files at every participating site including sponsor and monitoring agency, review site master files, and resume SDV at study sites.

### ***Monitoring strategy after COVID–19 pandemic***

Even though the remote monitoring has the potential to reduce the number and frequency of site visits and subsequent costs attached, the need to explore the proficiency of the same in already established on-site monitoring studies. Besides, remote or on-site monitoring is not mutually exclusive. Hence, once the pandemic situation normalizes, we have decided to follow a mixed approach systematically for the study, mapped out for deployment of monitoring activities. It has also been observed that remote monitoring allows comparatively more frequent SDV than on-site monitoring. Eventually, this will support the team in recommending and considering the mitigation action sooner. This will further support the study sponsor to evaluate safety events, identify early safety signals, and check protocol compliance issues, etc. concurrently and more frequently.<sup>4</sup>

The monitoring team will focus on the following activities to improve this mixed approach to monitoring the study: identifying available options to conduct remote monitoring within the established system or database; explore the feasibility of uploading masked study documents mainly related to safety and efficacy (e.g. lab tests, imaging reports, any documents directly linked to primary study endpoints, safety data/reports, etc.) through a remote source–data-verification platform; set up the storage or archival of study documents at the site and the bio-specimen samples at the sponsor for future studies; revise the current monitoring plan with an addendum, detailing the plan of actions, remote SDV, labelling of documents, access permissions, and documentation of remote monitoring activity; training and retraining of the monitoring team, and the site staff; site files will have an overarching note to file (NTF) detailing the requirement for deviating from the existing monitoring plan; execution of data query resolution through electronic data capturing platform; and develop a tool to minimize the time of monitoring of each visit (especially during treatment and follow up) and resume the onsite monitoring more frequently and rigorously.

In addition, the team will adopt the need-based approach for this mixed monitoring strategy for each site. This will

include the site’s performance and the level of risk and the number and level of protocol deviations/violations reported as the study progresses. The sites assessed as high risk will be visited more often than the sites deemed low risk. This balanced combination approach with a well-defined communication plan among the study team including sponsors, sites, and monitoring throughout the study period will result in high-quality data and securing compliance.<sup>5</sup>

We could explore the possibility of performing the most time-consuming on-site task through secure remote access. We hypothesized that performing SDV using existing technologies is a feasible strategy. The time at on-site visits can be utilized to ensure IP accountability, participant eligibility, and compliance with the written informed consent process.<sup>6</sup>

COVID–19 pandemic posed a serious concern about the recruitment challenges in the targeted study duration, data collection, and participant management. Eventually, these will lead to an extension of the study beyond the committed time points and subsequently raise budgetary concerns. Additionally, uncertain generalizability to clinical practice due to the deviations that occurred as per the approved protocol is also an important concern.<sup>7</sup>

### ***Impact of pandemic on clinical study***

The impact of pandemic on clinical study was as follows: suspension of screening activities; drastic reduction in the enrolment rate per month; protocol deviations increased due to out of window period activities filed as participants are being called for follow-up after spacing them out and are being called on dates when investigations are to be done; delay in concurrent data entry followed by the sites; prioritization of the participant management and patient care by the site staff more vigilant; limitation in ensuring drug compliance at a supervised way to daily telephonic calls with the enrolled participants; restricted coordination among the team in documenting the source data; reduced on-site monitoring visits and in-person patient visits to minimize potential viral exposure and spread; the supply of IP was restricted at the site as courier service was stopped; and delay in transporting bio-specimen to testing labs for further investigations as courier services was unavailable.

## **DISCUSSION**

This pandemic has alerted us to be prepared with well-planned meticulous and vigilant clinical research approaches, which ensure data integrity, and participant protection. A robust institutional platform and governance structure specific to the clinical study being implemented can translate the quantum of regulatory, ethical, operational, and clinical research knowledge to evidence. This pre-defined dynamic organizational structure will have involvement from all stakeholders including researchers, support study staff, and participants.

The major portion of on-site monitoring is for SDV where the monitor has to physically present at the clinical site to verify the source documents and essential site master file (SMF). Considering the geographical distribution and cultural disparities across India, the investigators tend to identify sites for their clinical studies to have a generalised representation. Sharing of source documents and clinical study files through any file sharing systems, or email platforms pose a serious compliance risk. A well-designed and secure remote SDV (rSDV) application can support the clinical sites and study monitors perform their routine tasks remotely. Exploring such a system would be another cost-effective strategy for clinical studies. The systematic application of these quality assurance approaches which include intensive on-site monitoring and remote or central monitoring via review of the database would lead to noticeable benefits. Sponsors may prefer 100% SDV due to regulatory requirements then; remote monitoring could be a cost-effective alternative. There is a sheer lack of unequivocal direction in conducting clinical data monitoring in our country. This may affect the safety of participants or may introduce bias in the outcome directly or indirectly or compromise the interpretation of study results.

Monitoring can capture failures in recording critical or non-critical parameters, which may influence the study outcome or participant safety. Monitoring could also capture the lacunae in following the study protocol or an SOP. A monitor can identify inaccurate or incomplete data entry in CRF or in a study-specific database, which has the potential to create criticality in data and eventually analysis and interpretation of study outcome.<sup>8</sup> Various studies have concluded that the monitoring team or the sponsor should anticipate and prepare adaptive approaches in monitoring.<sup>9</sup>

## CONCLUSION

Now, the intense and challenging environment in operationalizing clinical research has led to the questioning of the essentiality of the traditional approach to clinical data monitoring. The remote monitoring approach, customized as per the site requirements or based on the risk level can complement on-site monitoring.

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