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Research Article

A Pilot Study to Understand an Impact During the COVID-19 Lockdown in Clinical Trial Monitoring Activities and its Management

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Abstract

COVID-19 pandemic has hit the global healthcare and research surface with a staggering blow, however, with some drawbacks and imperfections the clinical research fraternity worldwide has held up the principles of rights, safety and well-being of patients. Lack of logistical, transport permissions in different parts of the world alongside the severe infection capacity of the deadly virus had put intermittent pauses to clinical trials in the last two years. This survey based observational study focuses on the real-time experience and opinions of the clinical research associates (CRAs) who had been carrying on with their on-going clinical trials unperturbed with the apparent obstacles. The respondents faced different types of issues in the accountability of investigational product, accessibility to central laboratories, conformity review of informed consent of the subjects, and most importantly, complexities in the adapted new methods of source data verifications in their monitoring activities. The suggestions generated in the survey on how the existing loopholes can be addressed and what should be the focus on such changed model of monitoring, were highlighted. In the lines of ongoing initiatives by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), the various clinical trials strategic working groups, and regulatory authorities like USFDA, this survey-based study highlights the need of technology adoption. Going forward, remote and hybrid monitoring models can be cost-effective and possibly more efficient than onsite visit-based monitoring model.

Keywords: COVID-19; Remote Monitoring; Risk Based Monitoring; Hybrid Monitoring

Abbreviations

AI: Artificial Intelligence; COVID-19: Coronavirus Disease; CRA: Clinical Research Associates; CT: Clinical Trials; EWG: Expert Working Group; GCP: Good Clinical Practice; ICF: Informed Consent Form; IP: Investigational Product; RBM: Risk-Based Monitoring; SDV: Source Data Verification;

Introduction

The world has changed a lot since March 2020, and so has the perception and approach towards clinical trials. The pandemic and countrywide lockdown implemented in different parts of the world did make it difficult to conduct clinical trials (CT) in the conventional way in various cases. Trial participants enrolments plummeted, research staff in majority of hospitals were shifted to helping COVID-19 treatment efforts, few of the trials were postponed considering them too dangerous to conduct, and surgical intervention trials had to be paused as the operating rooms in many sites were converted into ICUs [1]. Needs no mention that the ICH good clinical practice (GCP) guidelines along with all the important regulatory authorities require design and conduct of trials to focus

on protection of trial participants and quality of the trial. Equal participation and involvement of each stakeholders of clinical research is essentials for such trial design. During the past two years, the clinical trial fraternity has experienced many difficulties to achieve these through conventional clinical practices involving checklists and generic standards. It was realized at every level that innovative and unconventional approaches to build quality into the trial designs and to minimize is the need of the hour. To achieve that, the ICH E6 (R3) Expert Working Group (EWG) discussed and considered the following key themes [2]:

- Facilitating the electronic informed consent process including the use of digital technology (e.g., remote consent process)
- Changing trial design and data sources – potential applicability of non-interventional trial designs, use of new sources for data viz. real-world data including electronic health records, wearable fitness devices, and the use of predictive algorithms and artificial intelligence (AI).
- Data management innovation such as remote source data verification and system validation.
- Monitoring aspect – Consider improving clarity on central monitoring, providing information on the process to distinguish between critical data and non-critical data for RBM (risk-based monitoring).
- Consider utilizing remote GCP inspections developed during COIVD pandemic.
- Improve ways to involve patients in the whole process from CT design to conduct, by welcoming suggestions and best practices.
- Changing the approach from retention of essential documents to retention of essential information.

Clinical trial monitoring in current times has evolved and adapted through the changing scenario of patient care and limited accessibility to healthcare system. The sole purpose of monitoring remains unchanged, i.e. ensuring 1. Protection of the rights and well-being of human participants, 2. Accuracy, completeness and verifiability of trial data from the source documents, and 3. Compliance of the conduct of the trial with the approved updated protocol, GCP and applicable regulatory requirements. Mainly three types of clinical trial monitoring are relevant in common knowledge — On-site monitoring, Remote monitoring, Centralized monitoring. Many of the trials had to migrate from on-site monitoring to remote monitoring to ensure unhindered and quality-focused conduct of those clinical trials. The current study will try to assess the impact of lockdown during COVID-19 pandemic on monitoring activities in trials wherein the subjects were already under treatment.

Materials and Methods

The current study was done to assess the impact of the lockdown during COVID-19 pandemic on monitoring operations in ongoing clinical trials in India. The study technique selected was questionnaire-based survey among working clinical research associates as the experience is crucial but understand the impact. The sampling was convenient sampling. The sampling method was convenient sampling in CRAs who were available at this time. In total, there were ten questions in the questionnaire, among which, in one question was open-ended and the remaining were closed-ended. The data was collected. The collected data was analyzed through percentage analysis with the help of Microsoft Excel. The survey was completed within one week in the first week of August 2022. Then there were 25 respondents in this survey we were available during their busy schedules of monitoring work. Note to 40 total respondents we could select these 25 based on there continuous monitoring experience.

Results and Discussion

The questionnaire was intended to understand the experience of the working CRAs while of shifting monitoring methods from onsite to remote monitoring. The data collected was listed in an excel spreadsheet and later analysis was done. We will not see how the collected data versus the cumulative experience of CRAs In shifting monitoring methods and achieving the compliance in their respective trials through this pandemic. Later in this section, also look at individual opinions on which were the key parameters considered during source data verification. Let us dive into the data analysis.

In the first question, these CRAs were asked whether they could successfully move from onsite monitoring to remote monitoring in their ongoing studies. 15 out of the 25 respondents felt it was a successful shift.

Figure 1

The next question was regarding maintaining of subject confidentiality while shifting to remote monitoring in these trials. The responses revealed that in over 75% of cases the confidentiality were maintained successfully, while a considerable 25% said that there had been eventual breaches.

Figure 2

The third question tries to understand the level of difficulty faced during investigational product (IP) accountability during remote monitoring. IP accountability is a crucial factor during monitoring as it gives a primary idea of protocol adherence of each subject at the investigation site. The responses suggest that a significant 44% of the CRAs did find it very complex to handle IP accountability on shifting to remote monitoring. However, the leading 48% responses said the IP accountability was a manageable task remotely.

In the next topic, the CRAs were asked whether trial participant samples were managed with the central laboratory, and if not, what backup plan was implemented. 80% of the survey participants responded in positive, and 8 out of them assured that they did not need any back-up plan. 5 of the 25 survey participants said they only considered local laboratories within this period and samples were not managed by central labs. We will discuss in detail about the options implemented by CRAs in this parameter, in the discussion section.

Figure 3

When enquired about the intricate operational parameters subject rights were considered as priority. Seventeen out of twenty-five CRAs could comfortably conduct informed consent form (ICF) review remotely. It was a significant percentage of participants and that leads us to the next question.

Figure 4

Which key parameters were taken into consideration during source data verification (SDV) was the most important question in this survey as this depicts the tactical approach of ensuring protocol compliance while carrying out remote monitoring. Turned out that patient confidentiality and data integrity was maintained by focusing on validity of the ICFs through presence of subject's age, initials and signature, signature by impartial witness or legally acceptable representative (if applicable), alongside the principal investigator's signature, date and time, on each of the consent. Digital accessibility played an important role in this process as a number of the respondents used screen sharing methods while reviewing ICFs, while a few others felt more confident on using GxP compliant remote source data verification platforms.

Next, the participants were asked whether they could identify any loopholes for SDV or other monitoring activities in the existing approaches while shifting from onsite to remote monitoring. Here, 19 out of all participants (over 75%) did admit that there are still a few loopholes/issues to be addressed.

Figure 5

Three out of the 6 CRAs who responded that there were no loopholes identified, had given conflicting response in the next question i.e., whether loopholes could be addressed and closed once onsite monitoring was resumed. These three responses were excluded from the analysis to avoid confusion. Out of the remaining nineteen respondents

Finally, the respondents were asked a vital question on their individual preference of monitoring approach or model. None of the respondents were relying on remote monitoring alone, on this aspect of preference. A competitive 48% of the responses were in favor of conventional approach i.e., onsite monitoring, whereas, 52% (majority, 13 out 25) were in favor of adopting a hybrid model where both onsite and remote approaches can be implemented in a combined way.

Figure 6

Figure 7

Discussion

The study makes a path for further introspection into the most appropriate model of monitoring in globally affecting incidents like pandemic and sheds some light on the way forward. As we have seen in the past studies, misinformation or inappropriate data can generate through lack of participant compliance [9]. Definitely, in scenarios such as a global viral pandemic, patient safety and the safety of the research staff are majorly affected [8,12]. Shortage of healthcare staff and equipment made it economically staggering to continue even the basic medical care in optimal manner [14,15]; eventually clinical trial monitoring was affected. The current

survey-based research reflects equivocally on these discrepancies and drawbacks, and shows how the clinical trial monitoring was maintained in its best possible shape. CRAs who had ongoing trials under their workflow, around the world started using unconventional approaches to maintain data integrity and subject compliance without affecting patent safety, which is crucial in good clinical practice. Adoption of digital data capture methods as considered important by the 2021 EWG of ICH E6 (R3) was carried out meticulously for SDV. In addition, in case the trial subjects' samples could not be managed by the central labs, owing to logistical issues, respondents mentioned they have asked patients to get the tests done by themselves. However, in a few unique responses, samples were stored for bulk shipments as well. The responses show that there were complexities in IP accountability process while the approach had to be shifted from onsite to online. It was also mentioned that source data verification could not be foolproof in current pandemic period when the remote monitoring model had to be implemented. However, all the leading regulatory authorities are currently addressing these issues by applying the same method of our study – acquiring suggestions and opinions from all the stakeholders of clinical research. Active participation from patients (subjects), investigators, and the clinical research operations personnel will lead to error-proof digital and algorithmic system aiding to remote or hybrid monitoring. The study shows a trend, suggesting the inevitable paradigm shift towards a hybrid model of monitoring in the future with ever-increasing number of clinical trials. Many of the active CRAs in their on-going studies are familiar and comfortable with the on-site monitoring visits as it gives the access to the source data immediately, however, on a day-to-day basis technology and digital intermediates can aid to this purpose going forward.

Conclusion

Remote monitoring in clinical trials played a crucial role during the time of the global pandemic. These methods are cost-effective, reduce exposure, address shortages of resources and provide safety to the investigators, while achieving satisfaction with the majority of patients. This makes remote monitoring of particular importance. Our study reiterates the fact that in future, technology-enabled systems for day-to-day monitoring activities shall be implemented, considering their compliance and cost-effectiveness. Of course, the path is going to be long and arduous and shall need numerous research where GCP guidelines will remain the primary points of adherence while devising new models and methods for efficient hybrid monitoring model. The adaptive nature of human civilization and science must consider the factors that human resources can be preserved and unnecessary traveling can be minimized through adoption of technology such as, digital applications compatible with smartphones, data from patients' digital wearables, GxP compliant remote data capture platforms, and remote SDV platforms. During the pandemic, meetings and discussion panels have also evolved in the virtual mode in a large portion of the world which indicates a few more aspects of the clinical trial processes might be on the way to change gradually.

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Conflict of Interest

None.

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