Review Article

Remote Monitoring and its Avail During Covid-19

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ABSTRACT

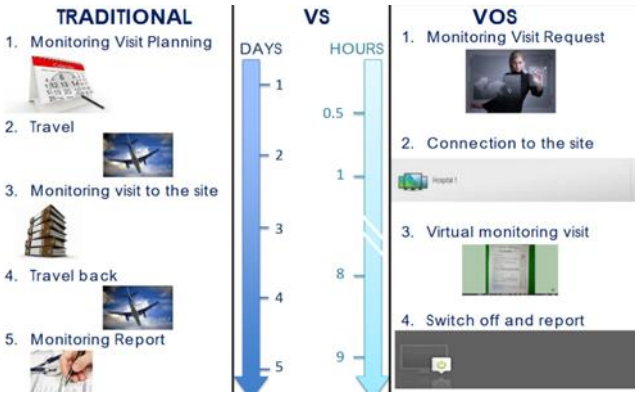
Remote monitoring has been a boon to the clinical research industry for a few years. According to ICH_GCP, the monitoring of the ongoing trails is the responsibility of the sponsor. The monitoring of the trials has become quite easy for CRA (a person appointed by the sponsor to monitor the ongoing trials) due to the evolution of the remote monitoring or centralized monitoring. The remote monitoring mainly reduces the time for preparation of the final reports of trails, thereby enhancing the work to be done on time. Majorly, it reduces the travel expenses for the sponsor. Remote monitoring is one of the innovative methods which can be used for the production of quality data and maintain the work-life balance of monitors. It involves the verification of the site documents from the remote place and should be electronically certified copies. Due to the unfolding COVID-19 pandemic, clinical trial sites and sponsors are facing circumstances that are decreasing potential of clinical research. With many monitors restricted from travel, sites and sponsors are reassessing ways to share information and collaborate virtually. As a result, sites and sponsors are exploring the potential of remote monitoring solutions. COVID-19 ramifications on clinical trial conduct continue to evolve at an astounding pace, requiring rapid adaptation, mitigation, and innovation. I believe the most valuable way to start that journey is by working together to forge ahead.

Keywords: Remote monitoring, centralized monitoring, CRA, Sponsor, ICH_GCP, source data verification, HIPAA, electronic data, FDA, MHRA.

INTRODUCTION

The monitoring of the clinical trial site is a crucial aspect in clinical trials to make sure that the information and procedures are followed as per protocol. The clinical trials where a clinical research associate (CRA) never physically goes to the research site to conduct their monitoring visits but reviews the data through secure online workspaces like Interlinks VIA and other similar platforms. Uploading all of the source documents, laboratory reports, medical histories, consent forms, and other such documents to the secured virtual workstation which can then become available to the CRA instantaneously. Once the documents for a specific visit are within the virtual workspace, the CRA can conduct their "monitoring visit" by comparing the source documents to the knowledge that was entered within the eCRF. Because the monitor completes the source data verification remotely, this monitoring strategy is usually mentioned as "remote monitoring". [1]

Because of the recent advance in virtual workspaces to the clinical research industry, sites and their CRAs and Sponsor, can collaborate more effectively on finalizing these documents — essentially reducing the time for the research site to start screening of study participants significantly. The site initiation process has always been conducted remotely in past, but now we have tools like Intralinks VIA that greatly speed up the method.[1]



Definition of Monitoring in ICH GCP E6 (R2)

"The act of overseeing the progress of a clinical trial, and of ensuring that its conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)." Section 5.18.3 of Guideline E6 states: "The sponsor should ensure that trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The 2016 ICH E6 GCP guidance suggested the use of technology in clinical trials.[2]

Remote monitoring should focus on the activities which can be reviewed and monitored remotely, such as consistency checking, data completeness, identification of high error rates or protocol violations. Where source data are within the CRF or electronic records are added to an

electronic trial master file (eTMF), these can be accessed and therefore, checked remotely.

Centralized monitoring provides monitoring that can complement and decrease the extent and frequency of on-site monitoring and help to differentiate between reliable data and unreliable data.[3]

- Examination of data trends like the range, consistency, and variability of data within and across sites.
- Evaluation of errors in data collection and reporting at a site or across sites, or potential data manipulation or data integrity problems. [23]
- Analyzing site characteristics and performance metrics.
- Selecting sites and processes for targeted on-site monitoring.

Challenges to Remote Monitoring

1. Need to create own policies and procedures.[4]
2. Less accountability than on location.
3. Audit implications.

Inside the Centralized Monitoring Toolbox

The tools for centralized monitoring include centralized statistical monitoring, key risk indicators, quality tolerance limits, and informative data visualization.[5]

Site Identification and Selection Remotely

Site identification is important for any clinical trial as it drives the fate of the drug. Improper site selection, inefficient clinical investigators lead to failure in patient recruitment and generation of quality data. Various platforms have been developed to help sponsor or CRO to identify potential sites and qualified clinical investigators.[6]

Many web-based platforms, where the trial manager or sponsor can conduct feasibility with clinical investigators and sites all around the world for any therapeutic areas are been developed.

Smarter ways to clinical trial feasibility

The feasibility can be done by following ways:[7]

- Access ready database of investigator and sites
- Utilize ready professionally designed clinical trial feasibility questionnaires
- Perform web-based clinical trial feasibility

Remote Site Initiation Visits

The Clinical Trials Monitor, or designee, will discuss the necessary items over the telephone (or via another remote communication method) with the study team, provide training with respect to the sponsor's SOPs and discuss GCP and the study protocol as required. Remote SIVs must document all items that have been verified. Evidence should be provided by the site where required. The Monitor, or designee, who conducted the remote SIV will complete the SIV Report using the information provided by the study team.[8]

Remote Close-Out Visits

Sites may be selected to be closed by the Clinical Trials Monitor, or designee, remotely. Reasons that a remote COV is considered appropriate will be clearly documented in the COV Report and/or monitoring plan. In a remote COV the Clinical Trials Monitor, or designee, ensure that the PI can confirm that all close out activities, has been completed as per COV Report. Where required the PI will be asked to sign a statement to confirm that all close out activities have been completed prior to study materials being archived. Where remote closure cannot be successfully completed, an on-site COV will be performed.[9]

Common Methods for Remote Monitoring

Fax, Email, and File Sharing

Faxing and emailing source documents increases the e-mail load on already fully allocated staff. Sites struggle to find extra time to find, send, retrieve, scan, and attach documents to emails. Similarly, monitors must allocate efforts away from areas where sites need support to organize and track documents received.[10]

Direct Access to the Electronic Medical Record

Providing monitors direct access to an EMR can work, provided the proper consents and agreements in place. Research institutions should implement well thought out policies when providing direct EMR access to monitors, as many EMR systems don't have controls in place to restrict views for study monitors.[11]

A Solution to Improve Monitoring for Both Sites and Monitors

Supporting communication between sites and monitors

Tracking the detailed, back and forth communications between a site and monitor when reviewing source documents is critical when supporting source data

verification (SDV) and source data review (SDR). Without a purpose-built system, these detailed communications get lost in a web of emails and attachments, adding time and confusion to the review process. [12]

Organize and prioritize work

The increasing complexity of today's research environment makes it difficult for even the most seasoned researchers to stay on top of their to-do lists. A system can alleviate this burden by flagging documents and actions that may require immediate attention. With better visibility, sites and monitors can quickly focus their efforts and plan their day-to-day work more easily.[13]

For example: Documents associated with protocol deviation are often automatically flagged to assist sites and monitors expedite the review process. [22]

Centralized monitoring and central review of data collected

Centralized monitoring of data acquired by electronic data capture systems (e.g. eCRFs, central laboratory or ECG / imaging data, ePROs etc.) that are in place or could be put in place provides additional monitoring capabilities that can supplement and temporarily replace on-site monitoring through a remote evaluation of ongoing and/or cumulative data collected from trial sites, in a timely manner.[14]

Off-site monitoring

Additional off-site monitoring activities could include phone calls, video visits, e-mails or other online tools in order to discuss the trial with the investigator and site staff.[21] These activities could be used to get information on the clinical trial progress, to exchange information on the resolution of problems, review of procedures, trial participant status as well as to facilitate remote site selection and investigator training for critical trials.[15]

Remote source data verification

Remote source data verification (SDV) will currently only be considered necessary for few trials when in line with national law (or temporary national emergency measures) . Remote SDV may be considered only during the public health crisis for trials involving COVID-19 treatment or prevention or in the final data cleaning steps before database lock in pivotal trials investigating serious or life-threatening conditions with no satisfactory treatment option. It should focus on the quality control of critical data such as primary efficacy data and important safety data. Important secondary efficacy data may be monitored simultaneously, provided this does not result in a need to access additional documents and therefore in an increased burden on site staff.[16,17]

Health officials are providing further guidance to support remote monitoring solutions to maintain oversight of clinical sites and ensure participant safety:

> *"If planned on-site monitoring visits are no longer possible, sponsors should consider optimizing use of central and remote monitoring programs to maintain oversight of clinical sites." — FDA*[18]
>
> *"Remote monitoring can be considered; however, this should not place an extra burden on trial sites, and subjects must consent to any sharing of their personal information outside the trial site." — MHRA*[19,20]

CONCLUSION

More source data verification ensures the better quality data. The majority of the finding which can be identified by onsite monitoring can also be identified during remote monitoring too. It also helps sponsor for cost effectiveness and time saving. The remote monitoring might affect the HIPAA, so it might be challenging in the field.

The remote monitoring might be cost effective but may have long term consequences. Instead of making frequent onsite monitoring it can done based on the risk levels and site performance.

Measures regarding on-site monitoring may include limited, targeted on-site monitoring identifying higher risk clinical sites, if not already applicable for the trials of concern. The on-site monitoring plan will need to be adapted and alternative measures. Centralized monitoring of data acquired by electronic data capture systems that are in place or could be put in place provides additional monitoring capabilities that can supplement and temporarily replace on-site monitoring through a remote evaluation of ongoing data collected from trial sites, in a timely manner. Remote SDV may be considered only during the public health crisis for trials involving COVID-19 treatment or prevention or in the final data cleaning steps before database lock in pivotal trials investigating serious or life-threatening conditions with no satisfactory treatment option. It should focus on the quality control of critical data such as primary efficacy data and important safety data. Important secondary efficacy data may be monitored simultaneously, provided this does not result in a need to access additional documents and therefore in an increased burden for trial site staff. The sponsor should determine the extent and nature of remote SDV that they consider needed for each trial under this exceptional situation and should carefully weigh it against the extra burden that introduction of any alternative measures would put on site staff and facilities.

When remote SDV is foreseen, it should be described in the initial protocol application (and informed consent form). In case of ongoing trials introduction of remote source data verification should be submitted, in line with national law or temporary national emergency measures, via a substantial amendment. These provisions should be in line with the principles of necessity and proportionality and in a way that protects trial participants' rights and should not

place any disproportionate burden on site staff as determined by the investigator and trial site staff.

Hence, remote monitoring and onsite monitoring can be combined together will result in quality data and securing compliance. The balanced combination approach can give confidence that patients enrolled in trials are been protected and their data is accurate.

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