



Monitoring in Clinical Trial

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ABSTRACT

Clinical monitoring helps in understanding the data, protocols and the clinical evidence collected during a Clinical trial, this assures safety and effectiveness of the investigational product. The Effective monitoring of clinical trials is a critical method while assisting adequate studies and protecting human subjects. First of all, Clinical trials are a research study that determines the safety and efficacy of the pharmaceutical product. The Sponsor's Monitoring play an adequate role in performing an honest overseeing of the trials. This invigilation of trials takes place once in span of weeks, they check and review each and every aspect involved in the trial. According to FDA the monitoring should be done in an effective manner to ensure that the clinical trial has been performed in a clean and professional method. The recent days can deeply assist and explain the importance of centralized and remote monitoring and especially how important is to review the trial stage of Covid-19 as everything is quarantined. Every document should be reviewed and rechecked by the monitor. The significance of monitoring can be described in the following consequences to be appeared.

Keywords: Clinical trial, Monitoring, Monitoring visits, Centralized monitoring, Remote monitoring, Responsibilities.

INTRODUCTION

Clinical trials are a research study that determines the safety and efficacy of the pharmaceutical product, carried out in humans' volunteers either in healthy or sick volunteers, this depends on the pharmacological and pharmacokinetic reactions in human volunteers. These researches are mainly happened to be aimed at evaluating a medical, surgical, or behavioral intervention of an investigational product. The study helps in diagnosing, treating, preventing the ailments in humans. The scientists perform laboratory tests and studies in animals to test a potential therapy's safety and efficacy (pre-clinical trials) before the approval to begin a clinical trial by U.S. Food and Drug Administration (FDA). If these studies show favorable results, the FDA gives approval for the experiments to be tested in humans. These trials are important for our future growth.¹

What is Monitoring?

According to ICH-GCP it is defined as an act of inspecting the clinical trial, it is the responsibility of the sponsor assuring that trial is done according to protocol, GCP, SOP and regulatory requirements. The data that appears after performing a clinical trial which ensures the rights, safety and well-being of the subjects is credible and accurate. Monitor responsibility is to assure whether the trial is conducted in accordance with Schedule Y, ICH GCP guidelines, study protocol and any other guidelines / regulations. The main duty of a clinical research associate is to conduct the source data verification by analyzing the data filled in the case report form such as patient's hospital file, patient diary, previous prescriptions, etc. Monitoring also involves reviewing and submitting all the declaration

to the ethics committee for assuring all the safety updates, any protocol amendments, serious adverse events, etc. During the monitoring visit, monitor should check for serious adverse events occurred at the site and also which have not been reported to sponsor by site. After the completion of the monitoring, monitor should meet the principal investigator to discuss about the activities conducted during the trial and the things to be revised and improved. If they have done a good job monitor should not forget to appreciate them. The important things to be followed by the monitor are to develop good interpersonal relationships with site staff and should be supportive with the site. A monitoring visit report is written by the monitor about the activities conducted at the site and also any observations, protocol deviations and corrective action taken after the completion of monitoring. Regarding the activities conducted during monitoring visit and for any corrective actions required from site staff a letter will be sent to the principal investigator. In the study site the monitoring report must be filed that is available with the sponsor.²

Who is a CRA?

A Clinical Research Associate (CRA) is a sponsor representative conducts the clinical trial monitoring by visiting the clinical trial site at frequent intervals.³

Purpose of Monitoring

During monitoring, clinical monitors examine the trial. It is only the responsibility of the clinical monitor to review whether the site following the investigation protocols, keeping all the adequate and accurate records and documents, problems facing with informed consent form, reporting the adverse events, accounting for the



disposition of study drugs. Therefore, its main goal is to examine each trial site to assure that standard operating procedures are followed, reported, and managing the deviations from investigation plan. Monitoring is done to certify that rights and well-being of subjects are protected, and the data appeared after the trial is accurate, complete, and verified from the source documents. The trial which is conducted is in consent with recently approved amendments/protocol along with the GCP and the applicable regulatory requirements.³

Selection and Qualification of Monitor

The sponsor should appoint the monitors who are known as CRA (Clinical Research Associate). They are selected based on their qualification, Training, Experience, and scientific knowledge on the clinical trial. The Qualification of monitor should be record and documented. Monitors should have keen knowledge on the investigational product to be trialed, the documents, investigational brochure, informed consents given by the subjects and other information been provided to the subjects, the GCP, SOPs and the regulatory requirements followed by the sponsor.³

Extent and Nature of Monitoring

Monitoring should be adequately conducted, this should be based on the understanding the accurate information such as purpose, objective, complexity, design, and endpoints of the trial. The truth is that there is need of monitoring before, during and after the trial. In the past days, on-site monitor had a good demand in the market, as the monitor invigilates all the protocols and documents in the trial site itself having more communication with investigator and the sponsor. However, there are some exceptional situations where the sponsor conduct a remote monitoring i.e., centralized monitoring of the trial, that can be done centralized in a reserved manner which are comparatively adequate and evidential, as all the protocols and written information, guidelines and the documents are recorded in an electronic documents with complete accuracy.

The sponsor should create a systematic and private environment of the clinical trial. The sponsor has right to opt for the type of monitoring to be conducted either on-site or centralized monitoring or the combination of on-site and centralized monitoring. The sponsor can document the logics and plans to be implemented in the monitoring.³

Roles and Responsibilities of Monitor

- The main responsibility of monitor is to observe the process of trial and to check the study is conducted and data is prepared in accordance with the protocol, good clinical practice, SOPs, ethical and regulatory requirements, look at the figure 1.
- Monitor is the communication link between the investigator and sponsor and is appointed by sponsor.

- Monitor should verify the investigator's curriculum vitae and his (or) her qualifications and the documents those which are related to the equipment and laboratories.
- Investigational products are verified whether storage conditions and supplies are sufficient throughout the trial, and also verifying that investigational products are supplied only to eligible subjects of specified doses mentioned in the protocol.
- Monitor verifies that the investigator follows approved protocol and amendments.
- The written informed consent which was collected from each subject before participation in trial is verified.
- Monitor should assure that investigator and staffs are continuously informed about the trial.
- Monitor should verify whether investigator is enrolling eligible subjects.
- Verifying that source documents and trial records are accurate, complete and are maintained up-to-date.
- Monitor should verify whether investigator is maintaining essential documents.⁴

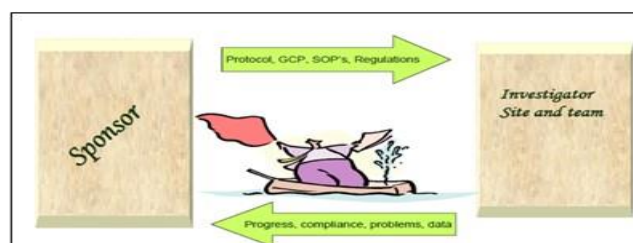


Figure 1: Role of Monitor ⁵

MONITORING PROCEDURES

There are some of the main procedures and protocols to be followed by the monitor:

Source documents/Data quality verification

Source Data Verification (SDV) is the most important activity performed during an on-site monitoring, see figure 5. The main objective of source Data Verification is to ensure the data accuracy of the final trial confirmations. This oversees the checking of data or case report forms against data collected from the database and source documents, respectively. The monitor should ask for the queries against any possible similarities in the local sites or the documents produced in the trial site. Many times, source data or documents may not be available after the patient gets discharged, or sufficient data may not be recorded. The team trial should maintain all the documents even after the discharge of the subject as they might be a use for an emergency purpose. All the data should be transcribed from original documents. There should be an adequate reservation of the SDV by the site staff at least for 5 years and make sure that the medical records and other originals are not erased.⁶

Informed consent

The informed consent forms (ICF) are the fundamental information collected from the subjects, ensures that the rights, safety, and wellbeing of the subjects are protected, and the data are acceptable. This process can be organized either by centrally or on-site. If the ICFs are monitored centrally, identifiable information should be transferred to the trail team first from the subjects.⁶

Pharmacy monitoring

There is a crucial role played by the pharmacy in monitoring site. This ensures that the investigational medicinal product is securely stored with proper suitable conditions. Areas to consider when monitoring the pharmacy are documents/ delegation log, protocol compliance/SOPs/ local regulations, investigational medicinal product (IMP) storage, labelling, expiry date randomization, accountability, breaking blind shipment. Documents ensure pharmacy file contains all the applicable standard operating procedures (SOP's) and also logs relating to IMP. Protocol compliance ensures that pharmacy procedures comply with trial protocol, SOPs, and local regulations. Back-up facilities should be available in case of issues with electricity supply and access to IMP should be secure. Expiry dates should be in range and noted in accountability logs. During shipment, chain of custody and information on temperature stability should be documented.⁶

Laboratory monitoring

The laboratory consisting many areas are examined with an at most care during the monitoring visits. Areas to consider when monitoring the laboratory are documents, agreements and contracts, logistics, facilities/ equipment/supply, sample storage. For sample collection, analysis, storage, shipment, and disposal documents such as protocol and laboratory specific standard operating procedures should be reviewed. If samples are to be shipped outside the country for analysis, then material transfer agreements should be in place. All details should be documented and checked such as sample tracking, processes for dealing with issues and identification of any samples that should not be stored. References ranges and laboratory accreditation certificates should be reviewed. Temperature of freezers and duration of storage should be checked. Sample labels should be reviewed to ensure that there are no patient identifiers and should comply with SOP requirements and there is no label deterioration.⁶

Adverse events

It is the first priority to monitor adverse events to check the safety of the subjects during the clinical trial. Central monitoring plays an accurate role in signal surveillance where the investigators take a quick response to any frequency of adverse reactions in the subjects. Even monitoring can also occur during the site visit while reviewing the source documents which ensures that all the

adverse events are resulted to the team, clinical ethics committee and regulatory authorities.⁶

Other documents

Most often errors are found in the Trial Master File (TMF) or other important valuable documents should be rechecked during the monitoring visits. Areas to consider for monitoring remaining trial documents are training log, delegation logs, screening logs, randomization logs, ethics and regulatory, contracts and agreements.⁶

MONITORING PRACTICED: THEN AND NOW

In 1988, The FDA appealed guidelines for monitoring of clinical investigation which has accepted monitoring approaches for clinical trial industry. Researchers stated that monitoring the clinical investigational trials should be conducted in most effective way. This led to rapid conduction of on-site monitoring visits with 100% data verification. These on-site visits are often fixed schedules for every 4-8 weeks of the clinical trial. Every visit had the similar kind of reviews of the investigation of the trial, but the communication with the investigator of the trial was done in a clinical method. In those days, the monitoring was not an advanced process as now that includes about centralized monitoring.¹²

Types of Monitoring

1. On-Site Monitoring
2. Centralized Monitoring
3. Risk based Monitoring
4. Remote Monitoring

On-site monitoring

On site monitoring is done by the designated monitor visiting periodically (often the contracted independent monitors depending on the type of trial, or the trial manager for non-commercial trials, or contracting local monitors may be beneficial, as they have experience in the local language, culture and practices) as explained in the figure 3. Early phase trials, for example firstly in human studies, which usually take 100% approach and also carry an inherently higher risk, assuring that all the data is accurate and verifiable against source data. Later phase trials, or trials which include less risk, certain percentage of participants data may be verified at site.⁸

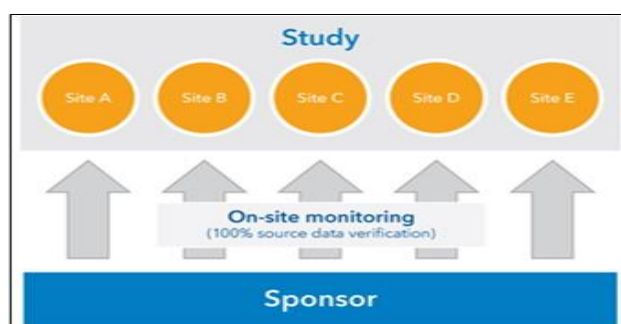


Figure 2: On-site monitoring ⁷

Centralized Monitoring

The trial may be centrally monitored in addition to trial oversight committees. For example, data can be identified and reviewed by central coordinating study team as per specified time points. Eligibility criteria can be reviewed monthly or frequently before the initiation of trial; adverse events may be reviewed by the members of the trial management group frequently; consent forms can be reviewed centrally to ensure trial team of the timing of consent and the forms have been completed correctly and also reviews drug accountability logs centrally to ensure whether the site has sufficient stock, dosing, and enrolment data. Safety reports are submitted at specified time points to the DMC/DSMB.⁸

Risk-based Monitoring

It is the process of assuring the quality of clinical trials by identifying, assessing, monitoring, and reducing the risks which could affect the safety of a study, sees the figure 4. US Food and Drug Administration (FDA) describes three steps for guidance.

- a. Identify critical data and processes – Quality of a study and the safety of its participants are accurately monitored, sponsor should be aware of these elements that are important for each particular study – from the informed consent to eligibility screening and tracking of adverse events.
- b. Perform a risk assessment - A risk assessment determines specific sources of risk and the effect of study errors on those risks.
- c. Develop a monitoring plan – According to guidance of FDA’s, monitoring plan should describe methods, responsibilities, and requirements of trial. Monitoring plan is for everyone involved in monitoring trial for communicating risks and monitoring procedures.⁷

Remote monitoring

Remote monitoring a subgroup of clinical trials where the monitor or clinical research associate (CRA) reviews the data without visiting the research site through secure online workspaces or other platforms.⁹ Protocol is executed in normal manner by the monitor and any other additional data is entered in the electronic case report forms (eCRF’s). All the trial related documents such as documents including informed consent forms, source documents, and medical lab histories, are uploaded to secure online workstation. So, that the data can be accessed immediately by the CRA whenever required. Once the data has been uploaded CRA compares the data included in eCRF with the source document data and this becomes monitoring visit. As the source data verification is conducted remotely, this is termed as remote-based monitoring.¹⁰



Figure 3: Risk Based monitoring¹¹

Difference Between Centralized and On-Site Monitoring

Centralized Monitoring	On-site Monitoring
<p>1. Informed Consent: Copies of signed informed consent documents are reviewed sent from site.</p>	<p>Source documents are reviewed to confirm the patient’s signature, whether the patient was consented before the study procedures, and that proper consent processes were followed by site.</p>
<p>2. Eligibility criteria: Verified as per source sent from site</p>	<p>Verified as per source and review all available medical records (paper / electronic).</p>
<p>3. Protocol procedures: Review of CRF/ source to ensure the site is following the protocol sent by the site.</p>	<p>Verification of CRFs with source, obtaining outstanding data, ability to assist site etc.</p>
<p>4. Regulatory documents: Retain “shadow file” of site regulatory file documents sent from the sites.</p>	<p>All regulatory documents are reviewed to ensure maintenance of accurate, current, and complete records. Any deficiencies or missing documents are addressed to site and confirming that sponsor has a copy of documents.</p>
<p>5. Investigator involvement: Discussions to follow up on study progress or to answer questions via telephone or e-mail.</p>	<p>Allows the monitor to verify important sites/ staff’s issues that may not be clear at the site.</p>
<p>6. Product accountability: Verifying the product log against shipping records and product labels of patient source</p>	<p>Product log against the sponsor shipping records are verified and also products in stock, device labels in patient source documents and also location of product storage are verified.</p>

documents sent from site.	
7. Adverse Event: Remote reviewing of adverse events submitted by site	For additional unreported AEs, all available medical records (paper/electronic) are reviewed. Regarding the reporting of AEs to the IRB are discussed with the site.
8. Protocol Deviations: Remote reviewing of protocol deviations submitted by site.	For additional unreported protocol deviations are reviewed. Discussion regarding the reporting of deviations to IRB with the site and estimating whether additional training required or not.
9. Relationship with site staff: When communication is via telephone or e-mail the relationship is limited.	In person visits at the site is more comfortable in working relationship will be formed. ¹²

Advantages of Centralized Monitoring over On-site Monitoring –

Use of centralized monitoring techniques is the primary feature of risk-based monitoring and opposed to on-site monitoring based on 100% source data verification. Centralized monitoring has many benefits:

Fewer errors – Any manual effort is limited in scope and prone to error during on-site monitoring, whereas automated reviews are used in risk-based, centralized monitoring to determine the need for manual intervention and mostly uncover errors.

Lower cost – Activities like on-site audits can be limited to study sites where problems are occurring, which can reduce the cost of monitoring during centralized monitoring.

Better analysis – Statistical and graphical checks can be easily used to determine the presence of unusual patterns or outliers in the data.

Cross-site comparison – Comparing data between sites to assess performance, identify potentially fraudulent data, or locate mis-calibrated or faulty equipment is achievable in centralized monitoring.

More time results – During the ongoing trial, a dashboard can make it possible to identify and resolve issues.

Targeted on-site investigation – In-person investigation is needed at a particular site during dashboard monitoring and further analysis. In such cases, depending on the nature of study it may be appropriate to visit and perform a more traditional source data verification activity.⁷

Monitoring Visits

Monitoring visit is an oversight visit to review the process of the study and assure protocol adherence, data accuracy,

subject safety and consent with regulatory requirements and good clinical practice guidelines of a clinical trial at the trial site.¹³

Monitoring Process During Site Visits

The monitor conducts various activities during the site visit to ensure the proper conduct of the clinical study. Monitor serves an important role in the sponsor responsibility to ensure the site is following the regulations and also serves as “eyes and ears” of sponsor on-site. Main function of the monitor is to verify site data with the study and source documentation, which consumes more time during on-site monitoring. To verify study data, monitor performs some additional tasks.

- Informed consent documentation review.
- Reviewing of subject enrollment information, including subject recruitment and eligibility criteria.
- Verifying that the site is familiar with the protocol and required procedures.
- Review of essential regulatory documents and assessing the site familiarity with the required IRB policies, study agreements, and applicable FDA regulations.
- Assessing the involvement of investigator with the study.
- Overseeing of the investigational product accountability.
- Reviewing of protocol deviations and adverse events.
- Building working relationships with the site staff and principal investigator.

Depending on the research site, complexity of patient enrollment or clinical investigation, monitor could make many trips which become very costly for a clinical trial to perform source data verification over the course of the study at the site. Frequent monitoring visits to the site are considered to be disruptive and time consuming to the research study personnel.¹²

TYPES OF MONITORING VISITS

Monitoring is a continuous process conducted before, during and after the trial. Hence, it is classified into four types of visits (see the figure 2):

- a. Site Evaluation/ Qualification visit
- b. Site Initiation visit
- c. Site Monitoring visit/ Interim monitoring visit
- d. Site Close-out visit

Site evaluation visit (SEV) (Site Feasibility)-

It is also known as site selection or site qualification visit. This type of visit is conducted by the sponsor or CRO to determine the capability of the investigator and the clinical site for conducting the study. During this visit, investigator



and the study coordinator should be present. This visit takes three to four hours to complete. SEV reviews much of the information regarding basic data of the site such as investigator qualifications, adequate site resources and facilities, and protocol review/discussion.^{13,14}

Site Initiation Visit (SIV)-

It is a monitoring visit which is done after the site evaluation visit. It takes place after the study sponsor has selected the site for conducting a clinical trial. This visit is performed by the sponsor to ensure that the investigator and the study staff are well trained and have understood the study protocol. This visit takes four to eight hours.^{13,14}

Interim Monitoring Visit (IMV)-

After the site initiation visit it is Interim or routine monitoring visit which continues till the site is closed out. It starts with the most important processes and data point identification. The main aspect of this visit is to determine the process of trial by the means of accuracy, completeness, and verification of reported trial data. IMV

reviews information about storage conditions, allocation and accountability of investigational drugs, study conduct to confirm the safety and welfare of the subjects protected at the site and also informed consent documents, source documents, regulatory binders, occurrence and reporting of adverse events and protocol deviations.^{13,14}

Site Close out visit-

Close out visit occurs when the subjects are no longer dosed and all the data have been collected without any adverse or serious adverse events and it is ready for statistical analysis, and the study conduct has ended. After completion of the study conduct, monitor visits again to shut down the site. This visit is done to ensure that site is neat and tidy, and the documentation is well organized, intact, and accessible when needed for regulatory reasons and for the final review of regulatory binder and verifying that all the biological samples have been submitted. The investigator submits a final report stating that the site is closed to IRB.^{13,14}

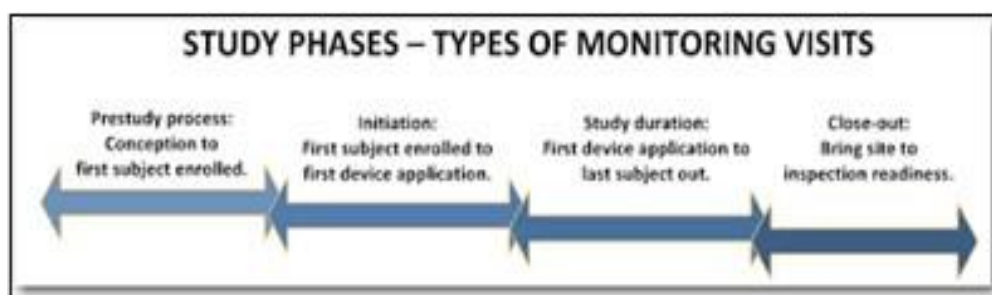


Figure 4: Types of monitoring visits¹⁵

Source Data Verification in centralized monitoring

The ways through which remote monitoring or Centralized monitoring are conducted by:

- Uploading the copies of the trial related source documents by using online communications, scanning and sending of the valid documents to the Centralized monitoring team.
- Observing the videos shared by the trial site using computer screen to the monitor. And the site team should make sure that the online or offline videos should be safe using a secured video conference application.
- Restricting the remote access (read only) to the trail subjects and the healthcare members using electronic medical records (EMR)¹⁸

HOW MONITORING CAN AVOID AUDIT FINDINGS¹⁸⁻²⁰

Audit findings can be explained as:

1. Common deficits in RBQM-related SOPs & their implementation

The FDA says that RBQM, i.e., Risk Based Quality Management is the next level of Risk based monitoring. According to the audit findings, SOPs are produced only after the RBQM regulatory documents are created but not

all the risk management or centralized aspects are involved in the advanced theories of SOPs. Mostly the following SOPs must be updated with quality management SOPs, risk management SOPs, writing monitoring plans and procedures of SOPs, monitoring SOPs, source data verification SOPs, clinical trial adverse events reporting SOPs, Protocol deviation SOPs.¹⁶

2. Failures in risk assessments and its connection with the actions

Risk assessment is the first activity and one of the most important aspects of monitoring. It starts with the identification of the most important processes and data points. Some CRO Organizations observe disconnecting the risk assessment from the data quality evaluation or key risk indicators (KRIs) or mitigation action. This is a common mistake. The key-word is 'probability'. The risk assessment should decrease the severity of reactions which satisfy reducing the risk event happening.¹⁶

3. Technology & IT Issues

This section repairs and verifies all the mismatch, incorrect tools or excel sheet, in additional if a company fails to produce validation process of an accurate documents and some more malfunctions in the software validation of the clinical documents.¹⁶

4. Patient safety issues

There would be a drastic fall if there are no proper corresponding changes in the process of monitoring and other actions. This unsuspected danger leads to disconnected strategies of Source Data Verification (SDV) reduction from the risk evaluation and risk control and, as a result, insufficient quality assurance in a trial. There would be no wonder auditors react allergically and this results in many critical findings.¹⁶

MONITORING REPORT

It is an essential part of documenting the clinical trial after monitoring. After each trial site visit or trial-related communication a written report is submitted to the sponsor

by monitor, Look at figure 5. Report should contain date, site, name of the monitor, name of the investigator or other individuals. Summary of what the monitor has reviewed during clinical trial monitoring and also the monitor's statements regarding the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken and actions recommended to secure consent should be included in the monitoring report. After the visit, the report should be immediately written and reported. The sponsor's designated representative should document the review and check out of the monitoring report with the sponsor. A signed copy of report and responses should be kept for reference in the sponsor file and also in the trial master file/ investigator site file.⁶

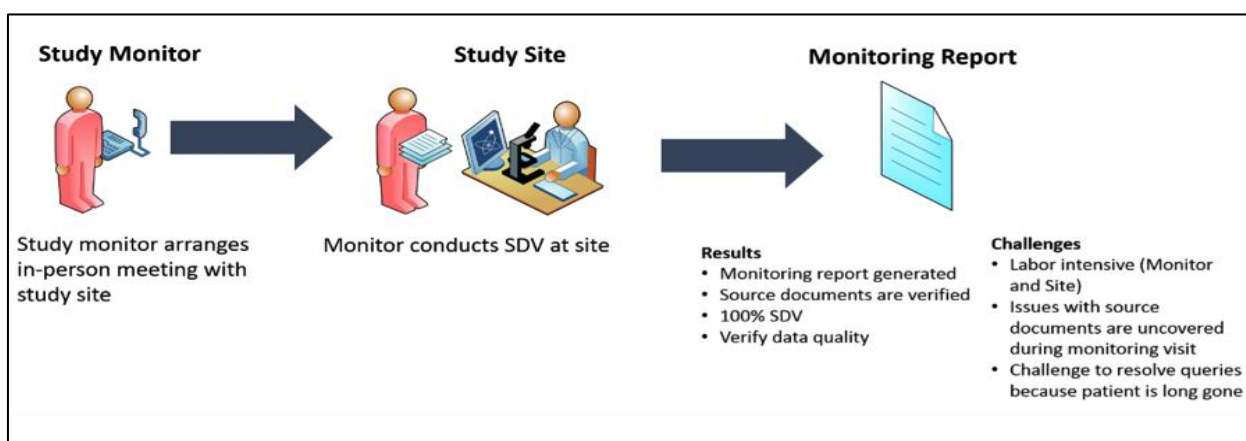


Figure 2: Monitoring Process¹⁷

THE PRESENT SCENARIO – COVID-19

The life-threatening breakthrough faced by the world is the coronavirus (2019-2020) an ongoing public health emergency. This has become a great challenge for the doctors or investigators and the clinical scientists to discover a vaccine for the treatment. They are trying to fight with the invisible enemy, damaging the countries. Since the SAR CoV2 has become very severe in the recent days, the investigators are finding difficult to discover a vaccine, needs maximum intervals to have success in the clinical trials. As per the survey and the latest updates, already the clinical trial has been initiated in many countries. The WHO (World Health Organization) has appealed companies and regulatory organizations to perform the investigation on the clinical trial subjects. Many trial subjects are involved for the ongoing treatment. Most of the affected patients are getting cured with their true immunity to fight against the deadly Corona. Though the drug surname differs, the patients are treated by isolating them and with the common type of vaccines where drugs are treated for various kinds of diseases. The pharma industries and companies are trying to update the existing vaccines hoping to be useful for the virus treatment. The disease has increased rapidly, and everyday thousands of people are losing their lives. So as per the epidemic is concerned, no individual is allowed to move out of their houses, the world is quarantined in their premises and hometowns. Currently the situation is against on-site monitoring as the people

cannot move frequently in overseeing of the trial. Therefore, Centralized and Remote monitoring can play a vital role in solving all the monitoring issues that the sponsor has to face. As mentioned above, centralized monitoring helps the clinical trial to invigilate in a remote centralized site where the CRAs assist to oversee progress of the trial and assure that the study is conducted and data recorded is in compliance with the protocol, Good Clinical Practice, and applicable ethical and regulatory requirements. The CRAs act as a media role to have a clean and adequate report. This process takes several months to have a good successful.

CONCLUSION

The Profession of monitor in clinical trials plays a very huge responsible role in performing his or her tasks as per the situations. The purpose of monitoring should not be underestimated, it's a pack of trial design and conduct and process and result. The challenge to conduct a clinical trial in source-limited settings can be a prominent wonder. But planning the trial carefully and well-conducted monitoring can be achieved with accurate scientific results with the respect to the international guidelines and patient's safety as concerned. A gentile suggestion to prefer Centralized monitoring as per the present situations, as the world is enveloped with COVID-19. Since the situations are getting worse day by day, it is better not to move out of our residence.⁶

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