

Considerations to Support Clinical Trial Monitoring Oversight During COVID-19

13 March 2020

The emerging coronavirus (COVID-19) situation is increasingly impacting clinical trial oversight, particularly on-site monitoring. The Association of Clinical Research Organizations (ACRO) recommends that sponsors, CROs and sites introduce emergency interim measures so that clinical trial monitoring is maintained during this period. These guidelines will ensure that data quality is unaffected, clinical trial sites are supported and that the patients enrolled in clinical trials are kept safe.

The use of centralized monitoring tools and technologies can supplement and support the recommendations outlined below. These practices and tools are already in place and do not require any additional sophisticated analytical tools or dashboards. Care should be taken that any remote monitoring activities implemented are proportionate to the risks identified. Further, they should not place any extra burden on clinical trial sites.

These recommendations should be considered in the following situations:

- When sites have suspended or restricted all visitors (including clinical research associates (CRAs)) from accessing medical facilities, but where patient visits are still occurring
- When local health officials have implemented regional quarantines
- When local CRAs are unable to travel to the sites (for personal health reasons or because of travel restrictions)

General Clinical Trial Oversight Considerations:

- Utilize regular site telephone contacts to monitor the situation and status of patient participation at the sites
- Increase the frequency of already programmed patient profiles or listing reviews
- Use existing key risk indicators (KRIs) and key performance indicators (KPIs) to assess the impact on early termination, Electronic Data Capture (EDC) data entry backlog, deviations, the volume of missed subject visits, adverse event (AE) reporting cadence, etc. KRIs and KPIs should be used to identify any trends that may require temporary interventions. Identified trends should be assessed for scale of impacts across sites which may require discussions across the project team/sponsor to mitigate risks to accommodate investigational product shortages, missed endpoints, alternative methods of monitoring subject safety, etc.
- In the event that on-site monitoring visits cannot be completed, consider implementing remote review of subject visit data via the EDC system with a focus on data most important to subject safety and data quality. While this will not cover the review of source documentation, this process can still alert the CRA to the following:
 - Eligibility violations visible in medical history, scales, ePROs, eDiaries, physical exam findings and concomitant medications
 - Protocol non-compliance with visit windows, gaps in investigational product administration, dose taper and dose titrations, SAE reporting, adherence to withdrawal criteria, etc.
 - Safety concerns through the assessment of labs, AEs and other assessments reported in the EDC system (or lack there-of)

- Document the results of these remote reviews. Subsequent site follow-up can be managed through remote interim monitoring visit (IMV) reports
- We do not recommend accessing electronic health records remotely (unless the process was already established with appropriate privacy and access controls)
- We do not recommend requesting that sites fax source documents for remote review

Documentation of Interim Measures:

If you choose to adopt any of these interim measures, we recommend following your company's procedures (e.g., planned deviation or Monitoring Plan addendum) to document the effective date of the interim measure. We also recommend that you document the date of when routine monitoring practices have resumed.

Resuming Routine Monitoring:

Before routine monitoring is resumed, strategies on how data is monitored in this interim period should be discussed with the sponsor and then documented. ACRO's position is that it will **not** be necessary to perform 100% source document review (SDR) and source data verification (SDV) of all subjects, visits and data. When routine monitoring resumes, a risk-based approach should be applied to subjects monitored using the interim measures noted above.

This may include strategies such as the following:

- 100% SDR/SDV of any screening and/or baseline visits during this time period to confirm consent and eligibility
- 100% SDR/SDV of a % of subjects or select critical subject visits (e.g., dose titrations, tapers, where SAEs reported, terminations, etc.)

In the Event of a Scheduled Database Lock:

If a database lock is scheduled to occur during this interim period, strategies should be discussed with the sponsor and then documented. ACRO's position is that it will **not** be necessary to ensure 100% SDR/SDV of all subjects, visits and data prior to locking. Emphasis should be placed on essential SDR as opposed to SDV. A risk-based approach should be taken when assessing whether the database lock can occur or if it should be delayed.

This may include strategies such as the following:

- If > x% of critical data (e.g., forms) are unmonitored, recommendation is to delay database lock
- If < x% of critical data (e.g., forms) are unmonitored, or only query responses require verification, and data quality is considered good, then consider proceeding without review of those final data points

ACRO and its members will continue to be vigilant as we manage the impacts of COVID-19 on clinical trial monitoring. We would like to share MHRA's [blogpost](#) from 12 March with advice on the management of clinical trials during this time. We may adjust or update these guidelines in the coming weeks as this situation evolves. For updates from ACRO, please visit www.acrohealth.org or follow [@ACROHealth](#) or [@CRO_Forum](#) on Twitter.