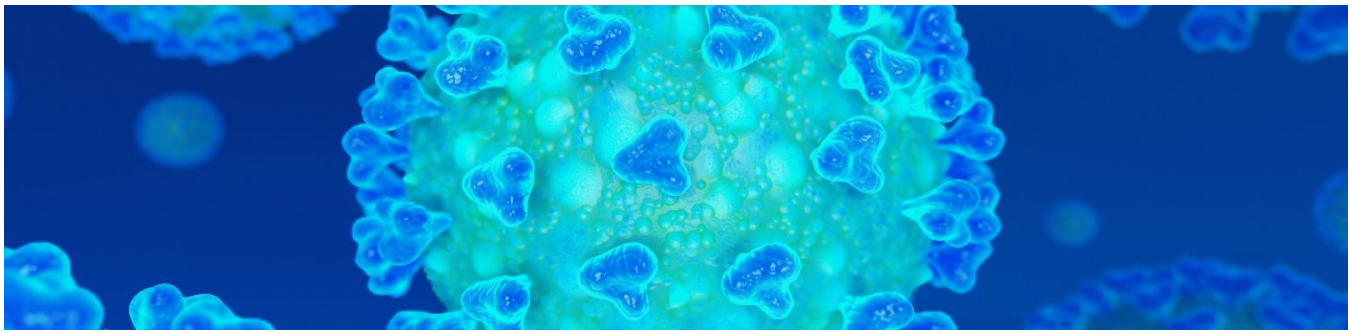
Clinical Study Conduct During a Pandemic

Lessons Learned from Virtual Town Hall held March 20, 2020



Life science companies are all scrambling to mitigate the impacts of COVID-19 on their clinical studies and business operations across the world and there are no clear-cut answers at this time, nor a one-size-fits-all solution. But what we do know is that we are all in this together and that this is another challenge that the biotech industry was built for – to take an unknown medical problem with no clear path forward and try to find the best one. We want to share the knowledge we gather to help ensure that patients who are most in need have a contingency plan in place to continue receiving therapies, while patients who are enrolled, stay safe.

We are all faced with addressing a myriad of issues, such as patients' inability to attend site visits to receive treatments and/or for follow-up visits, delayed investigational product shipments, questions about study drug stability due to delayed shipments, site inspectors and clinical study representatives not being allowed to visit sites, patients declining to attend study visits, and sites suspending research activities altogether.

On March 20, 2020, as a follow-up to our recent newsletter, Halloran held the first in a series of Virtual Town Halls to openly discuss some of these COVID-19-challenges. It is clear that everyone is looking for answers and turning to their industry colleagues for advice and knowledge sharing. As promised, we are sharing some of the insights that have been gathered to date.

The immediate impact of the pandemic is felt in everything that requires in-person meetings (e.g., site initiation visits, monitoring visits, regulatory inspection, audits, etc.). Yet, additional significant risk lies in the reliance of the transportation industry to deliver study drug and biological samples to their destination. Also, many companies are looking to immediately implement remote monitoring procedures, but because such procedures have been unevenly employed in the U.S. to date, sponsors lack the infrastructure and established processes to transition quickly to remote monitoring. The situation is worse in the EU where GDPR requirements make remote monitoring nearly impossible. In the U.S., sponsors are trying to transition to risk-based, centralized monitoring. Globally, all sponsors and investigators need to take into account that there may be specific regulations and guidance in place at the national and institutional level which they should consult before making any clinical trial changes.

Data, once entered into electronic systems, allow sponsors the opportunity to clean and analyze it in real-time through review of listings and blinded patient profiles generated from the EDC system. Remote monitoring is a little more difficult if a sponsor does not have prior remote experience but **taking a risk-based approach and focusing on the critical safety data from the sites and subjects is a good first step**. Conducting source document verification remotely is a challenge, but some sponsors have found success by setting up secure email feeds to receive data. Any changes to monitoring strategy must be documented, ideally in the Monitoring Plan.

Audits of sites and vendors are also impacted by the lack of accessibility to investigational and vendor sites. Again, a risk-based approach should be employed. Alternative methods such as questionnaires, remote/virtual audits have been successful and could also leverage web-based file share platforms such as Box for review of documentation and SOPs for which read-only access can be provisioned to the necessary people for finite periods.

Since patients have been unable to get to investigational sites, some sponsors have been able to replace **site visits with telemedicine visits**. Telemedicine visits, while an option, do not facilitate sample collection or diagnostic procedures requiring special equipment, have fewer laboratory-based and diagnostic procedures required, ultimately necessitating documentation to justify the protocol deviations due to the pandemic. Additionally, sponsors are experiencing long lead times in getting telemedicine visits implemented as site resources are constrained. Home health visits are also an option that has been discussed, however, many patients are uncomfortable with the potential exposure that would come with outsiders visiting their homes. Additionally, the growing demand on home health services may limit capacity as the number of studies utilizing their resources expand exponentially.

We recommend that you ensure that the regulatory authorities, IRB, and study participants are aware of any changes to study protocol and procedures. **Participants must also be informed of the changes and re-consented.** Many sites are conducting virtual video consent or using e-consent procedures so that the patient does not have to come to the site. Depending on the changes to the study protocol and/or procedures, sites and patients may need to be trained on these new protocol procedures or study tools. **The impact of these changes on study site budgets will need to be calculated, and budgets may need to be renegotiated with the sites.**

All decisions to adjust clinical trial conduct should be based on a risk assessment by the sponsor of each individual trial and in collaboration with the investigators as it pertains to each participant. **The sponsor must implement measures that prioritize patient safety and the integrity of the trial data.** In the case of a conflict, patient safety should always prevail. This risk assessment should be documented on an ongoing basis and should be reassessed as the situation develops. Each reassessment should also be documented for future inspection readiness so there is a record of the full story of the changes and the rationale behind them.

It is also important to realize that there will likely be events related to COVID-19 infection or exposure that could have serious effects on the overall benefit-risk of the trial. Immediate action by the sponsor and investigator may need to be taken to protect subjects against immediate hazard. These **urgent safety measures may be taken without prior notification**, but they need to be reported as soon as feasible to regulatory authorities and IRBs/ECs and documented as part of the study conduct.

For some sites, investigator's and other study staff may be reprioritized to where the investigator has been conscripted to provide healthcare to patients infected by COVID-19 and therefore unable to fulfill clinical trial duties. **Some of our Town Hall participants suggested qualifying new Sub-Investigators to see patients for their study visits**. While we have received isolated reports of US based sites suspending all clinical study activities, some countries have imposed more broad restrictions towards continued clinical trial activity (e.g., Poland).

As the various constraints in patient visits and procedures extend over a longer period, new Case Report Forms may likely **need to be created or revised** to collect COVID-19 related data. Other potential issues arise for longer term considerations. For example, slowed or suspended enrollment of new study patients will prolong the study, driving budget increases and timeline delays. Inability to conduct critical procedures supporting primary endpoints or key secondary endpoints will impact data analysis. Early discontinuation of patients may require replacement of patients to preserve underlying statistical assumptions.

The clinical study report will need a separate section to address any impact of COVID-19 on the study procedures and analysis as well as what actions were taken in response. **The statistical analysis will likely need to be revised** to allow for analysis of the impact of COVID-19 on the endpoints of the study. It is important to keep an open dialogue about these protocol changes with regulatory agencies as well as the Ethics committees and IRBs to ensure there are no issues when the sites are ready to resume enrollment. It is important to keep an open dialogue about these protocol changes with regulatory agencies as well as the Ethics committees and IRBs to ensure there are no issues when the sites are ready to resume enrollment.

We are **looking to companies running clinical studies in Asia for answers** about how long we will need to rely on adaptive measures in response to COVID-19. A few sponsors running studies in China had input, and our Town Hall participants reported that they are now seeing sites being reopened in some cases to allow clinical trial subjects to be seen. Monitors have been allowed back on-site to conduct monitoring visits. The disruption to clinical trials in China began in early January 2020 and a resumption in some clinical trials in mid-March suggests we may expect a similar timeframe here in the U.S. of approximately two months before study subjects can be seen freely for hospital visits.

COVID-19 is forcing sponsors to appropriately assess and document the impact of the pandemic on their operations, safety, and data integrity, as well as the measures being taken to address these risks and issues. In some cases, this **risk assessment is being done at the program level and even down to the subject level** versus just at the study level, since the risks and issues are similar across the board. Quality Tolerance Limits (QTLs) and Key Risk Indicators (KRIs) are being newly established or adjusted to appropriately assess the risk COVID-19 will have on studies.

While most sponsors have employed some type of risk assessment in their studies as a matter of routine, many are relying on their vendors' risk assessments, which is proving challenging as CROs are also overwhelmed in their efforts to mitigate the crisis. Regardless of who initiates a risk assessment, it is important to include vendors in this process. It is critical to **assess how well each vendor's risk management infrastructure handles such dramatic shifts in their operations**. This must be an ongoing and iterative process as new issues become known and new risks are identified. As the entire health system adjusts to this crisis, each adaptive measure taken must be documented and justified.

The current effects of the COVID-19 pandemic will likely leave a larger set of long-lasting challenges. As we move out of this phase, we need to have strong and thorough documented evidence of every action taken to mitigate the risk to subjects and the integrity of data. These changes have implications not only on protocols and informed consents, but also on oversight plans, monitoring plans, statistical analysis plans, data management plans, and many other study related documents that will need to be prepared for future inspections. One recommendation from our Town Hall was to begin **documenting these clinical study changes in a storyboard for when inspections resume**, or as preparation for remote inspections.

With the environment continuously changing, close coordination is required across many different functions. Several companies brought up the importance of staying connected with their project teams regularly. **Some have initiated 30-minute video team huddles each day** to review changes, new risks, and effects. We cannot underestimate the importance of our teams, and the constant and close communication with the project teams required to keep things moving forward and maintain morale. This is certainly a topic that deserves its own focused discussion!

Although regulatory agencies have suspended on-site regulatory inspections, remote inspections are a real possibility. A successful remote inspection requires the agency to have access to all the clinical study data and trial master file (TMF). In this case, sponsors must establish procedures to allow inspectors to train on necessary tools and receive access to the data and documents in real-time.

The pandemic has forced companies to challenge the traditional ways of study conduct and to make ways to implement some of the concepts which have been deferred over time such as remote-based monitoring, centralized risk-based monitoring, data analytics tools, e-consent, ePRO tools, telehealth and home visit optionality, and

protocol simplification/streamlining. Fortunately, many companies are taking this opportunity to innovate, adopt new technology, and to reflect on what is necessary to achieve the primary objectives of their studies.

We have only scratched the surface of this conversation and will be diving deeper into these topics at future Town Halls. Things are evolving rapidly, and there is much more to learn from those on the front lines. Stay tuned!

There are a few COVID-19 clinical trial guidance documents that have been released and updated by the regulators and should be referred to as we navigate these mitigations:

- FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic
- EMA 20 March 2020 Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic
- MHRA guidance on Coronavirus (COVID-19)

Please reach out to us if we can help in any way or would like to be included in any of our upcoming town halls.

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