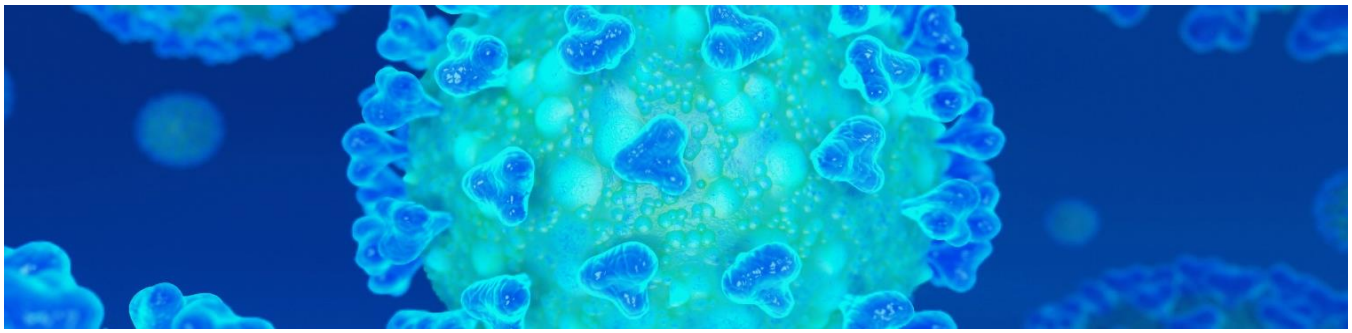
Clinical Study Risk Management During a Pandemic

Lessons Learned from a Virtual Town Hall held on March 27, 2020



As the impacts of COVID-19 continue to reveal themselves within the life science community, we continue to navigate through the appropriate measures to keep our clients and colleagues on track by focusing on the safety of our patients. Now more than ever, it is important to continue to share our collective experiences and best practices for identifying and managing clinical trial risks arising from the pandemic to address these critical issues with our extended peer network.

While COVID-19 has proven to be an extremely trying obstacle, it is crucial for organizations to not only focus on the short-term impacts of COVID-19 but on developing a long-term plan of action for how we return to business once the pandemic subsides.

On March 27th, 2020, as part of Halloran's Virtual Town Hall series, industry colleagues came together to discuss issues specifically related to identifying and managing clinical trial risk. The overwhelming influx of potential risks and new issues has continued to pour in daily, requiring clinical trial professionals to adapt quickly. As we begin to adjust to our new normal, it is extremely important to lean on each other and share ideas to help us move from a reactive to a proactive state of identifying and managing risks. In this newsletter, we have captured some key learnings and information shared during the virtual town hall:

1. Q: How should my organization determine if we should proceed with our clinical study?

A: Sponsor organizations must make an initial assessment of whether their studies are essential or non-essential. Johns Hopkins has a tiered breakdown that the institution uses to identify what studies and related activities are considered essential and can continue at various phases of emergency preparedness. Since Johns Hopkins has reached the highest level of emergency now, as a significant percentage of the country has, the limitations on clinical trial conduct are severe. Many organizations have already decided on whether they can proceed with an active trial or if a pause is necessary. For those that continue to stay active, numerous mitigations are now being put into place due to COVID-19. For those who have not yet decided what to do with an existing study, this needs to be done as quickly as possible.

Link to Johns Hopkins Risk Tier: https://hub.jhu.edu/novel-coronavirus-information/research-preparedness/research-preparedness-human-subjects/

2. Q: What are organizations struggling with the most when it comes to identifying risks?

A: Risk by definition is the potential for an event to occur that will cause a negative impact. Now that the negative event has occurred (in the form of COVID-19), sponsors are being called to evaluate their ability to identify, assess, mitigate, document and manage risk.

Organizations continue to feel overwhelmed and bombarded with information daily. As stated in the FDA guidance, sponsors are required to perform a risk assessment of the trial, the investigational sites **and the participants** so that measures can be taken to prioritize patient safety first while maintaining data integrity. Patient safety must be your overriding guide to navigate these uncharted waters. Upheavals to daily routines will continue so it will be crucial for organizations to systematically assess the impact and quickly tackle any potential areas of concern while documenting decision making continuously.

Organizations are still operating in a reactive mindset but as this current state becomes our new normal, it is vital for organizations to begin to shift into a proactive state. To be clear, sponsors will need to be comfortable with their existing process of identifying risks in real-time as well as measures to mitigate those risks that have now become real issues.

Many organizations have leveraged their existing risk management processes while others have tried different techniques to ensure appropriate documentation. A few will be discussed in more detail below, but the overarching issue is that it is critical for organizations to review their protocol(s) to identify those critical data and processes that have been affected by COVID-19 through the lens of protecting patient safety and ensuring data integrity not only in the interim but for the long term.

For organizations with clinical risk management plans currently in place, COVID-19 should have triggered an immediate risk re-assessment. The key characteristic of a robust risk management plan is that serves as a framework that can be applied to unexpected situations. It is important to focus closely on the Likelihood, Impact, Detectability (LID) criteria in your reassessment.

For those organizations that are outsourcing clinical trial activities to a Contract Research Organization (CRO), it is essential to ensure close communication and partnership when approaching clinical study/site risks. There needs to be constant communication occurring on documentation of risks related to COVID-19 as well as appropriate mitigations that need to be put in place. Otherwise, CROs become extremely overwhelmed due to the industry-wide need for these activities to occur, so engagement early in this process may alleviate difficulties in the long run.

3. Q: What types of tools are organizations using to document risks pertaining to COVID-19?

A: As we are in the thick of handling the impacts of COVID-19, the method of documentation may seem like a low priority; however it has never been more important given the unprecedented interruptions that have occurred as a result of the pandemic. By using even a simple risk assessment tool, it allows sponsors to document real-time assessment and mitigation efforts as the sequence of events unfolds. The key to your clinical trials' future success will be the ability to recreate a clear narrative of your organization's actions and changes during COVID-19 so that there is little guesswork that needs to happen when things get back to normal.

Many organizations are using a modified version of the Transcelerate Risk Assessment Categorization Tool (RACT) when performing risk assessments. There are additional industry tools available outside of the Transcelerate RACT coming from organizations such as Metrics Champion Consortium (MCC) and AVOCA; however, access to these tools do require membership. As the Transcelerate RACT is a comprehensive tool, many smaller organizations are using a simple excel risk log to capture risks, actions, and mitigations.

Some organizations are creating chronological trackers to narrate study risks happening in real-time since there may be several trackers utilized to document risks in a heavily outsourced (e.g., vendors) clinical trial. This approach is similar to a storyboard describing events that are occurring on a daily or even hourly basis. Other organizations

are providing a weekly slide deck in a dashboard format per study that includes a site by site breakdown of emerging risks/issues that have been identified, assessed and mitigated.

Sponsors are using a mix of COVID-19 specific risk-assessment trackers as well as leveraging already existing study-specific risk assessment tools and adding on to what has already been identified (pre-COVID-19). The important thing to remember is that identifying, assessing and mitigating risks and documenting your actions in whatever way that works for your organization is the most important action you can take both now to ensure patient safety and for the future as your clinical trial resumes.

4. Q: Are organizations using a "point-person" to manage the documentation and transcendence of information to key stakeholders?

A: Some organizations are currently utilizing a COVID-19 project manager who is the central person for managing large amounts of information coming in daily. Others are using individual trackers managed by a representative from clinical operations. However, the majority of organizations are taking a collaborative approach to information gathering and dissemination across the organization as available centralized resources are limited.

5. Q: Once risks are identified, and mitigations are put in place what other tools can people use to continue to assess and monitor those risks and mitigations?

A: Organizations should already be using Key Risk Indicators (KRIs) and Quality Tolerance Limits (QTLs) to monitor risk thresholds and those critical key- to-quality factors during their studies. However, the documentation needs to include how your QTLs and KRIs are affected by COVID-19.

Chances are, almost all of your current risks and KRIs will be impacted by COVID-19 since they are typically fueled by data collection methods that are now compromised by several factors (i.e., patients not coming in for visits, data entry staff either not at a site or prioritizing COVID-19 activities, monitors not allowed on-site, etc.). There will be common KRIs that you would expect to see exceed established thresholds such as protocol deviation rate, AE/SAE rates (underreporting), premature discontinuation and loss to follow up rates (higher). It will be important to continue to collect this information to ensure that you have ensured strong documentation (including dates) so you can appropriately evaluate and assess the long term COVID-19 impacts.

Subject safety needs to be the highest priority and a KRI for key safety visit completion should be added to your RACT/risk log and closely evaluated. QTLs will need to be re-assessed and watched closely since their main purpose is to assess endemic subject safety or trial result reliability, so most companies tend to have QTLs built around patient discontinuation and key efficacy parameter completion. Organizations should be discussing QTL assessments with their statisticians and medical stakeholders.

6. Q: How have risk categories been used to assess the appropriate impact? How do we leverage our site relationships to assess the site and patient risks?

A: Some organizations are trying to work with CROs to include the CROs assessment of site-level risks related to COVID-19 and included them into the algorithm with their centralized monitoring tools so that these risks may be assessed centrally. Sponsors are starting to see how complicated risk management can be when you have many vendors engaged and haven't had a coordinated approach to managing risks to date. It is important to align your CROs risk categorizations across your clinical trial to ensure a consistent approach. This goes back to keeping those lines of communication open with the CROs and being heavily engaged in this risk assessment process.

Also, it was shared that communication with Principal Investigators (PIs) has been crucial during this process. Some organizations have found that there are PIs whose caseload had significantly decreased due to COVID-19 so there is an opportunity for communication to happen more easily. The local reports on the ground (at sites) have been extremely helpful to understand the full picture of patient/site/study risk in real-time.

7. Q: What types of risks are organizations currently seeing at the subject level?

A: The approach to subject level risk will differ based on whether the study will continue during COVID-19 or if it is currently being put on hold. For those studies being put on hold, it is important to keep the subject engaged and ensure that information being disseminated from the sponsor to the CROs and sites is also trickling down to the subjects. For those studies that will continue it is important to assess subject access to the sites. If telehealth visits are occurring, it is important to understand the risks associated with home health with respect to COVID-19 exposure and protected health information (especially in Europe due to GDPR requirements). Subjects may also have limited access to public transportation depending on where they are located. Sponsors need to provide patients with information on how they are ensuring their safety during this pandemic. Keeping the lines of communication open with the site and subject and providing reassurance through Sponsor level efforts will go a long way for subjects.

8. Q: Does the approval of home healthcare professionals need to go through the IRB if not in the protocol?

A: Based on the FDA guidance you can implement the change immediately due to patient safety issues and inform IRB as soon as possible. Organizations are heavily leveraging urgent safety measures to implement clinical trial protocol/process changes quickly while ensuring subject consent. Therefore, it will be important to handle the use of home healthcare visits on a case by case basis.

9. Q: How are sites being affected by COVID-19? How can sponsors work with sites to alleviate some of these issues?

A: One of the risks that sponsor organizations are currently seeing at the site level is constrained resources as many site staff members have been pulled in to help with other COVID-19 efforts. In some instances, clinical research at sites have been "shut down" and limited only to treating patients. Institutional Review Boards (IRBs) have been stretched extremely thin as they have many submissions with the need to prioritize COVID-19 research. Some IRBs aren't able to reach quorum as physicians sitting on the IRB have been pulled to help with COVID-19 efforts. There has been limited site accessibility with staff working remotely. Depending on the institution there has been some confusion as to whether or not sites are considered essential. Sponsors must provide guidance to the sites on what and how to stay engaged with clinical trials and assist them in the key areas of priority for them to focus on during this time. The lines of communication need to remain open so that sites continue to see Sponsor support and guidance to work through issues. This is where your site relationships become important and if they have not before, they will be tested and can be strengthened.

10. Q: How are organizations handling the protocol amendments and other study-specific documentation?

A: We must take the lessons learned during this period and apply them as we make updates to applicable study-specific documents such as protocols. It is not only crucial for our current state but what if we have a second wave of COVID-19? It is important that we begin to evaluate our timeline and goals based on the issues we have seen and ensure flexibility is built into future protocols.

An issue that was also brought up was the update to the informed consents and the potential impact on the liability clauses should a subject be exposed to COVID-19 during the study or with home health nurses adding a new level of risk for COVID-19 exposure. These are new issues that are being brought up and should be consulted with the legal department.

Each organization must reference the regulatory guidance from the various regulatory authorities to address any protocol changes. Each country has nuances that are important to be followed, so sponsors need to be aware of the specific guidance that is in effect for their study and their sites. There are several useful references below as it pertains to COVID-19 clinical trial impacts.

11. Q: What will happen when we go back to a "normal" state?

A: EMA has released a guidance document that discusses the need to look at how organizations will view data and perform analyses of affected/non-affected populations. It is important to start thinking about how you are going

to perform an analysis of the efficacy of your study as well as an analysis of how COVID-19 impacted your study design.

It was suggested that engaging or using a **Data Monitoring Committee (DMC)** to assure the safety of trial participants and assist in performing an analysis from a risk-based perspective on the impact COVID-19 may be having on your trial participants directly. They can also assess the impact of protocol and oversight modifications and how clinical study conduct may be compromised. If your study already has a DMC in place, it can be utilized to perform these analyses. If your study does not have a DMC in place, you should consider putting one in place.

It will be necessary to track COVID related deviations so that information can be easily highlighted within the CSR. As discussed, missed visits and protocol deviations will happen but the documentation should chronologically make sense. It is important to begin having discussions around how many consecutive missed visits could impact patients' evaluability in the analysis and whether the sample size may need to be amended. The impact at a subject level is discussed within the FDA guidance documents related to COVID-19 and will need to be documented within the CSR. This is also an opportunity to leverage a DMC to help in making and documenting decisions on subject disposition and data analysis based on the impact COVID-19 has had on the study.

12. Q: Do we go back to "normal" or has COVID-19 provided the industry with hope for a "new normal"?

A: From an industry perspective, we must think about how we move forward from this in a broader sense and the potential for future improvements in clinical trial conduct to get our products to market. We are proving now that we can do what we always thought was unachievable.

Who would have thought we could change course in a matter of weeks (not months) in the way we conduct clinical trials? We have altered how we monitor our study data, have quickly processed protocol amendments, have changed the way we perform subject study visits and have assessed how critical only certain data is in our studies. It is the perfect time to start thinking about the changes and technology we are implementing and how we conduct our studies and prioritize our resources once we get past this pandemic and look to the future.

It may also be time to re-evaluate your risk management methodologies, your risk management tools as well as how you are collecting key data points so that in the future you can easily see by looking at Key Risk Indicators (KRIs) and/or Quality Tolerance Limits (QTLs) to make rapid changes in your approach.

13. Q: Are sites beginning to test for COVID-19 before any procedures are happening in studies?

A: Major institutions have implemented testing before procedures happen in studies. Lack of access to tests has prevented many sites from performing testing before participation but sites are beginning to think about it.

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We have offered some valuable links to additional key Guidance Document links are listed below. However, we recommend visiting these health authority websites often as they have been updated frequently as new information becomes available.

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic Last updated March 27, 2020

EMA Guidance on Points to consider on implications of Coronavirus disease COVID-19) on methodological aspects of ongoing clinical trials

MHRA's Guidance on Managing Clinical Trials During Coronavirus (COVID-19)

UK's NHS COVID-19: Guidance for sponsors, sites, and researchers (v2.2 26 March 2020)

U.S. Department of Health & Human Services Notification of Enforcement Discretion for Telehealth Remote Communications During the COVID-19 Nationwide Public Health Emergency

Please also reference our previous newsletters here for more information and be on the lookout for our future virtual town halls as we continue to learn more to share.

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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