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Review Article

Impact of COVID-19 pandemic on design and conduct of clinical trials: developing best practices based on lessons learned for risk and change management

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ABSTRACT

The coronavirus disease 2019 (COVID- 19) pandemic is disrupting clinical research in most of the world. We have seen an immediate impact on clinical trials due to challenges coming from the COVID-19 travel bans, hospitals/clinics' visitation restrictions, social distancing precautions and shifting operations to work remotely on a short notice. These factors have translated into the issues challenging clinical trials such as operations, milestones, budgets, data integrity, etc. Given the complex risk/benefit considerations associated with each specific clinical trial, there is no single solution to manage the risks in clinical trials conduct due to COVID-19. Each trial is unique with respect to patient population, study drug mechanism of action, concomitant medications, and geographic location needs. It is important to continue to engage the networks and communities to push forward with creative risk mitigation and develop solutions during this challenging time. Risk assessment should be a continuous and living process as the situation evolves over the coming weeks to months. Routine and ongoing cross checks with study teams are already proving to maintain alignment on key timelines, critical risk points and other study specific challenges as we are moving towards de-centralized settings in the conduct of clinical trials. We have analyzed lessons learned and attempted to develop best practices to mitigate risks and adjust clinical research operations during this unprecedented time.

Keywords: Impact of COVID-19 pandemic on clinical trials conduct, Change and risk management, Regulatory updates, Safety monitoring, Data integrity, Patient centricity

INTRODUCTION

Recently an outbreak of respiratory disease caused by a novel coronavirus affected most of the world. The virus has been named severe acute respiratory syndrome-2 (SARS-CoV-2), and the disease it causes has been named coronavirus disease 2019 (COVID-19). On January 31, 2020, the U.S. Department of Health and Human Services (HHS) issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS.[1] In addition, on March 13, 2020, the President of the United States (U.S.) declared a national emergency in response to COVID-19.[2]

On January 30th of 2020 World Health Organization (WHO) declared the 2019-nCoV outbreak a public health emergency of international concern, following a second meeting of the Emergency Committee convened under the International Health Regulations.[3] Subsequently, on March 11th of 2020, with more than 118,000 cases in 114 countries affected by this outbreak, the WHO characterized COVID-19 as a pandemic.[4] By mid-March, Europe became an epicenter of this pandemic. At the end of April, the WHO issued guidance on considerations in adjusting public health and social measures, such as large-scale movement restrictions. Challenges and circum-

stances vary from country to country, and there is no "one-size-fits-all" approach.

As of July 10th, there were 12,064.828 confirmed cases, 550,384 confirmed deaths with 216 countries and territories affected by COVID-19 pandemic.[5] The 155-country survey shows severe disruption to services for non-communicable diseases, which presents serious concern regarding how non-COVID patients with chronic diseases are managed. The WHO has released results of a survey, which was conducted in May of 2020, it charts the impact of COVID-19 on prevention and treatment services for non-communicable diseases (NCDs), since the pandemic began.[6] More than half (53%) of the countries surveyed have partially or completely disrupted services for hypertension treatment; 49% for treatment for diabetes and diabetes-related complications; 42% for cancer treatment, and 31% for cardiovascular emergencies. Rehabilitation services have been disrupted in almost two-thirds (63%) of countries, even though rehabilitation is key to a healthy recovery following severe illness from COVID-19. In the majority (94%) of countries responding, ministry of health staff working in the area of NCDs were partially or fully reassigned to support COVID-19. Among the countries reporting service disruptions, globally 58% of countries are now using telemedicine to replace in-person consultations.[6]

IMPACT OF COVID- 19 PANDEMIC ON CLINICAL TRIALS OPERATIONS, CHALLENGES AND REGULATORY RESPONSE

We have seen an immediate impact on clinical trials due to challenges coming from the COVID-19 pandemic with travel bans, hospitals/clinics visitation restrictions, social distancing precautions, shortage of supply chain and shifting operations to work remotely on a short notice, etc. These factors have translated into the issues challenging clinical trials' operations, enrollment, milestones, budgets, data integrity, etc. (Table 1).

Table 1: Potential risks and proposed new practices and mitigation strategies for clinical trials conduct during COVID-19 pandemic.

Issues	Potential risks	Proposed solutions and risk mitigation strategies
Delays in study initiation activities resulting from the inability to perform site selection/initiation visits and/or vendor qualification visits	• Delays in study activation and patient enrollment, resulting in subsequent delay of drug/device development programs that will affect getting new treatments to the market	• Encourage a shift from on-site, in-person meetings for site qualification/initiation/training visits, vendor audits, vendor/CRO qualification meetings to remote-based models using phone and online platforms; • Include plans to allow for risk identification and re-assess for future on-site visits as needed • Remote meetings and visits require more preparation upfront from all sides, however this additional efforts may translate to better sponsor/vendor/site relations in a long run
Delays in local IRB reviews and approvals due to limited or re-prioritized site staff	• Shifts in execution phase at individual sites due to delays at start up and downstream effects on study protocol amendments/procedural changes implementation due to delays with IRB approvals	• Utilize central IRBs, when feasible, to avoid the delays that are likely to continue with some local IRBs; • Discuss current IRB review turnaround time, new policies implementation, re-prioritization and workload with the sites and document decisions
Delays in study progress	• Significant effect on accrual rates and research subjects retention • Change of scope of the project and downstream resources availability, which need to support project, may change • Delayed care and/or ability to progress in clinical trials may result in missed therapeutic window to treat disease/condition, which may progress to more advanced stage with limited treatment options • Slower clinical trial timelines hinder drugs/devices approval process	• Discuss with IRBs/ Ethics Committees plans that ensure patients for their care have access to options with investigational agents; • Provide private transportation for patients who have relied on public transportation to travel to sites; • Utilize home health care services for study drug administration (e.g., infusions) and/or study assessments, if possible.

Continued.

Issues	Potential risks	Proposed solutions and risk mitigation strategies
Missed study visits, procedures/assessments	• Protocol adherence issues arising from an inability to comply with visit schedules, study procedures, drug administration, and monitoring procedures; • Potential safety and efficacy assessment issues due to inability to follow up with patients or perform assessments • Variability of new technology used can increase complexity and may require additional investment • Problems with interface of different electronic tools and lack of standardization can increase variability, leading to potential quality issues • Misalignment of processes between sponsor, vendors/CRO, sites for deviations and process change request review/approval	• Amend study protocol to decrease number of in-person study visits and supplement them with at-home visits or telemedicine • Develop partnership with remote labs or home health services for routine care and research related blood/specimen collection and non-invasive tests • Revamp monitoring plans to include more robust remote-based study progress and data monitoring strategies/tools • Evaluate third-party vendors to support this shift towards remote monitoring practices in the middle of execution phase for active studies • Document all changes in the protocol, manual of operations (MOP); formally amend monitoring plans and get approvals prior to implementation • Re-assess escalation process and establish new metrics/tools for prompt processing of change requests, evaluation of major deviations and safety information assessment *Note:* IRB and FDA are more prone to make accommodations for expedited reviews under these circumstances. In some very limited cases, under FDA's regulations, protocol changes may be implemented immediately if they are intended to eliminate an apparent immediate hazard to subjects, provided the sponsor subsequently notifies FDA and the IRB.
Delays in clinical supplies distribution and import/export delays due to limited manufacturing and operations staff, limited or reprioritized hospitals staff, and travel bans	• Disruption in dosing/treatment of research subjects • Lack of adequate drug/device forecasting due to shortage of personnel	• Determine if study drugs/supplies shipments can be sent directly to patient homes, with support from home healthcare services for drug administrations and accountability

The Food drug administration (FDA) recently issued a document entitled "FDA Guidance on Conduct of Clinical Trials of Medicinal Products during COVID-19 Pandemic", which reiterates the themes outlined above, emphasizing mitigation and precautionary strategies to be based on study specifics.[7] Guidance is also provided on management of procedural modifications, protocol amendments and deviations (e,g,: implementation, IRB approvals, FDA's consultations), as well as preparedness to describe the tactics and impact in the corresponding clinical study reports.[7] Some of these recommendations are also highlighted in the Association of clinical research organizations (ACRO's) from March 13th of 2020 "Recommendations to Support Clinical Trial Monitoring Oversight during COVID-19", and in Medicines and Healthcare Products Regulatory Agency (MHRA) March 12th of 2020 "Advice for Management of Clinical trials in relation to Coronavirus".[8,9] As well as recommendations highlighted by European medicines agency (EMA) in the document entitled "Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic" from March 17th of 2020 (revised on April 28th of 2020, current version 3).[10] The key changes in the version 3 include EMA addressing the distributor to trial participant Investigational medicinal product (IMP)

shipment, monitoring, remote source data verification and communication with authorities.[10]

Initially, we have seen suspension of all patient activities for trials, sites, or studies that do not have patients actively being treated. In these cases, we have seen follow-up visits being performed remotely, with third party vendors utilized for faster implementation of remote monitoring activities via digital tools. The immediate impact of the pandemic is felt in everything that requires in-person meetings (e.g.: site initiation and monitoring visits, regulatory inspections, audits, etc.). Once the peak of COVID-19 pandemic had passed, some local IRBs allowed to resume limited enrollment into clinical trials with therapeutic intent, where there were no viable routine clinical care options to treat patients; and investigational product had some potential to treat/alleviate the disease/condition.

Variability of local patterns of infection and different responses of local authorities contributed to misalignment of sponsors, investigators and CROs/vendors' team members on regional restrictions, updates and impact. We are recommending ongoing risk evaluations and assessment sessions with sponsors, investigators and CROs/vendors' teams to align on local restrictions, impact assessment, and create contingency plans to empower sites, vendors and develop study-specific risk mitigation strategies. Establishment and joint ongoing review of vendors'/sites' key performance and quality indicators will provide insights into their performance. Additionally, having clear and defined criteria when issues should be escalated to the sponsor will ensure effective monitoring of studies, especially as changes are made to these operational activities.

The pandemic has forced companies to challenge traditional study conduct and to implement some processes that have been deferred prior, such as remote monitoring, centralized risk-based monitoring, data analytics tools, electronic consent, electronic patient-reported outcomes (ePRO) tools, telemedicine, home visit options, and study protocol streamlining. Currently, many companies are taking this opportunity to innovate, adopt to new technologies, and to reflect on what is necessary to achieve the primary objectives of their studies.

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. The situation is somewhat worse in the European Union (EU), where General data protection requirements (GDPR) make remote monitoring very difficult to perform. In the U.S., sponsors are trying to transition to risk-based, centralized monitoring. Globally, all sponsors and investigators need to be aware of specific regulations and guidance in place at the national and institutional/organizational levels, which should be consulted before making any changes.

REGULATORY GUIDANCE FOR INSTITUTIONAL REVIEW BOARDS ON EXPANDED ACCESS DURING COVID-19 PANDEMIC

FDA plays a critical role in protecting the U.S. from threats such as emerging infectious diseases, including the coronavirus disease of 2019 (COVID-19) pandemic. During the public health emergency, the agency has received a substantially increased volume of individual patient expanded access requests for COVID-19 investigational drugs. Although FDA has issued guidance on expanded access requests, the agency is aware that Institutional Review Boards (IRBs) seek clarity regarding the key factors and procedures IRBs should consider when reviewing individual patient expanded access submissions, including for reviews conducted by a single member of the IRB, to fulfill its obligations under 21 CFR Part 56.[11] Therefore, FDA has issued guidance to provide recommendations regarding the key factors and procedures IRBs should consider when reviewing expanded access submissions for individual patient access to investigational drugs for treating COVID-19.[11]

TECHNOLOGY UTILIZATION DURING COVID-19 PANDEMIC

The COVID-19 pandemic has spurred tremendous innovation across biomedical products industry. We have been able to implement technology solutions that can facilitate continued progress in critical aspects of trials. Certainly, the utilization of telemedicine and virtual platforms is enabling us to meet our patients' needs, but most importantly it also allows to assess patient safety, study integrity, and data quality.

In terms of the digital technology landscape in clinical trials conduct before COVID -19, it has been used since the early 2000s. Home visits coordination, monitoring of at home procedures (infusions, blood draws, specimen's collection, etc.), self-report solutions, video visits, and digital endpoints were utilized previously. Prior to pandemic, the barriers to telemedicine utilization were related to regulatory obstacles around implementation, and perhaps, some resistance of the change management internally. Sponsors utilization of virtual technology historically was incremental, and successful launch required at least of 6-8 months of planning ahead. Even if solutions were implemented, patients may have been slow to adapt to it. According to an article published in Nature digital medicine, less than 0.4 percent of active trials listed on ClinicalTrials.gov used a digital solution such as telemedicine platforms, wearables, or smartphone data mining.[12] Clearly there is an opportunity to expand the use of these technologies.

The current situation is forcing us to innovate further since many clinical trial teams must either find a way to support virtual visits or cancel in person visits and put the study on hold. The technology is widely available and, for the most

part, familiar (i.e., video platforms, email, online shared spaces). Also, regulators have loosened restrictions on the use of virtual platforms, and patients expect options now. Recently conducted survey has shown that patients still want to participate in clinical trials during the pandemic.[13] It is remarkable that even under the current circumstances, more than half of surveyed patients indicated they would be willing to participate in a trial within the next month. Only 22% indicated discomfort participating amid the COVID-19 pandemic. The vast majority supported an increase in telehealth services and digital solutions.[13] In addition, the use of telemedicine helps conserve personal protective equipment (PPE), decrease personal potential exposure in ongoing pandemic and safeguards the integrity of our healthcare system, so we can serve more vulnerable populations and those in acute need for immediate medical care.

Sponsors, if planning to utilize telemedicine/ virtual visits, should consider developing a patient-centered solutions. In the context of a sites and patients' needs assessment, virtual visit technology solutions can be assessed according to the process illustrated in Figure 1. Considerations should be made for training home care personnel to assist patients with clinical trial assessment and data collection at home (e.g.: bringing phlebotomists, medical assistants and nurses into the patient's home to perform medical procedures/clinical trial specific assessments, collect specimens that would traditionally be executed in the clinic). Sponsors must remember that patients are also adjusting to the rapidly changing pandemic environment and develop a robust communications plan. Study teams transitioning to "at-home" or virtual visits should communicate upfront with the patients to address any of their concerns regarding safety, equipment availability, logistics, personal hygiene, patient's condition and any other anxieties related to COVID-19 still evolving pandemic. Operationally, decision-making is often a rate-limiting factor and it can take time to implement changes, as many organizations have policies and approval process in place according to which new technologies have to be reviewed and approved by the local authorities before they can be utilized. Addressing those organizational barriers upfront can help to move forward more efficiently with new technology utilization in the light of our new reality (Figure 2).

Also considerations described in Figure 3 should be taken into account by sponsors, while selecting a telemedicine/ virtual technology vendors or developing a methodology for remote digital solutions. The COVID-19 pandemic is devastating to the biomedical product industry in so many ways, but we have the tools, and an opportunity presented itself unexpectedly for further innovation of technologies we utilize in the design and conduct of clinical trials. We must work together to realize the potential that we have to create long lasting solutions that will better address the unmet needs of clinical trial participants.

INCORPORATING PATIENT CENTRICITY INTO STUDY DESIGN

Patient centricity has been discussed in industry circles for quite some time now, with sponsors connecting it to either reduced protocol assessments or increased use of technology in trials. The industry still has a lot to learn about patient-centric trials, but having patients' input will help to gain their perspective and better understand their concerns during and after COVID-19. So far patients' general concerns during this crisis include supply chain and drug shortages; stress around maintaining personal drug inventories, while navigating the logistics of coordinating shipments, sitting on hold on pharmacy phone lines, and adapting to a rapidly changing environment with little visibility into the rationale for those changes; blood shortages and donor matches; home health care providers entering patients' personal space with limited personal protective equipment (PPE); trial delays/de-prioritization, especially among rare disease patients; and fear that experimental treatments may become unavailable or that trials will be paused. In addition, some patients are reluctant to leave home because of restrictions on movement, lack of information or because of their fear of infection with the COVID-19 virus. In addition, many healthcare workers are unavailable because of restrictions on travel, shortage of PPE, or re-assigned to COVID-19 response duties.

To address these concerns, sponsors can adopt a various strategies (Table 1). Maintain a close connection with patient communities and with individual patients. These relationships are especially important during time of social distancing. Develop communication plan and engage with patients to keep them updated with the latest news on the status of their trial and any forthcoming changes of their study protocol and procedures. Finally, actively engage with sites to better understand any creative solutions they may have already implemented to mitigate patients' burdens and alleviate anxiety for their routine clinical care. These strategies can be useful for clinical trials as well.

According to recently conducted surveys, patients agreed that the introduction of virtual visits and remote capabilities is long overdue. Generally, they hope that these solutions will be integrated into post-COVID protocols. However, there are some concerns, including home healthcare workers' unregulated personal hygiene, lack of PPE and rapid introduction of digital tools/portals that are challenging for patients to use as a new emergent technology, navigate through varies platforms, which often have issues with interfacing with other systems utilized (e.g.: hospital electronic medical records, electronic data capture systems, centralized monitoring platforms, etc.).

Despite excitement about virtual and remote visit solutions, patients are increasingly eager to get back on-site and into their "normal" routines. The power of personal interaction cannot be underestimated, nor is the importance of predictability and consistency. For many

patients, regular therapy is a source of comfort, and relationships with physicians and research teams are deeply meaningful. Patients hope that technological innovation in our industry will not come at the expense of the personal bonds and emotional comforts of human interaction. From a practical standpoint, a physician will need to listen to a patient's lungs, heart or closely examine an allergic reaction.

While an option, telemedicine visits do not facilitate sample collection or diagnostic procedures requiring special equipment, application of biological products with short half- life such as wound care products, complex study assessments requiring qualified facility and specially trained personnel; which is ultimately necessitating documentation to justify 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.

It is important to ensure that regulatory authorities, institutional review boards (IRBs), 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 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 re-negotiated with the sites as illustrated in Figure 2. Close coordination is required across many different functional teams at the Sponsors, CROs/vendors and sites. An ongoing and close communications with project teams are required and cannot be underestimated to keep things moving forward in this unprecedented time (Figure 2).

Sponsors can address patients' concerns by continuously seeking patient feedback to identify anxieties that can be mitigated through knowledge sharing or planning, and not assuming a single solution as "one size does not fit all," and recognizing that telemedicine inevitably introduces mental health concerns by limiting human interaction. Flexibility and ability to choose different options will be critical in patient-centric trial design. Therefore, sponsors should build flexibility into new processes, and identify channels that will enable to communicate directly with patients about study impacts, process changes, modified timelines, etc. (e.g.: sending communications to sites for distribution to patients, leveraging the ClinicalTrials .gov help line as distribution channel, etc.).

The elements of employing patient-centric protocol design are described in Figure 4. We must find a way to use lessons learned in this devastating pandemic to set a new standard of patient-centricity and put patients' perspective at the forefront of clinical trials, which now is an expectation of regulatory authorities.

DATA INTEGRITY AND QUALITY ASSURANCE

Currently trials that have continued in the midst of the pandemic are producing data, and sponsors need to adapt statistical analysis and reporting strategies to fit into the circumstances. Data integrity is important now more than ever, and it's imperative to develop a plan to ensure it.

Performing an impact assessment is important for focusing future efforts on most problematic areas of study conduct. At the beginning of the pandemic, some companies performed large impact assessments, with the goal of identifying studies and sites that could stop trials with the least disruption. Initially, the impact assessment was an enrollment issue, heavily focused on recruitment obstacles at the study level. As the pandemic progresses, impact assessments are becoming more detailed and focusing on number of "affected patients" (regardless of whether the study was or was not paused). The next round of impact assessments should focus on data, specifically reconciliations, management, and analysis. These efforts can ensure that mitigations strategies will be proactive in nature and well informed by real data (Figure 2, Step 4).

Assessing the impact of data will be protocol-specific and will be a balance between how much treatment a patient received and the endpoints of the study. The assessment will need to evaluate: how many patients do not have enough data to assess efficacy due to missed visits or other factors; and determine if the duration of a patient's treatment meets the protocol specific requirements to be deemed evaluable. If there was a necessary interruption or delay in their treatment due to COVID-19, would the patient be allowed to restart treatment or need to be replaced to ensure adequate data for analysis?

Mitigation strategies should be focused on: mitigating the risk of patients not getting treatment and/or being unable to assess the patient. Extending visit windows or having additional visits should be considered as part of mitigation strategy. Sites should explore the possibility of infusions to be done locally or mailing oral investigational product to patients. Study drugs administration for biologics with complex preparations and short half –life may not be possible to be done in patients' home settings. It is important to utilize all available options to keep the patients on study treatments, always prioritizing patients safety and preserving data integrity.

RISKS RE-ASSESSMENT DURING COVID-19 PANDEMIC

All decisions to adjust clinical trials conduct should be based on risks assessment by the sponsor, with the input of site investigators as they are closest to the study participants and aware of their needs/concerns. The sponsor must implement measures that prioritize patient

safety and the integrity of the trial data. The patient safety should always prevail above all. The 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, establishing a record of the full story of the changes and the rationale behind them.

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 impact of risks associated with COVID-19 on the studies (Figure 1).

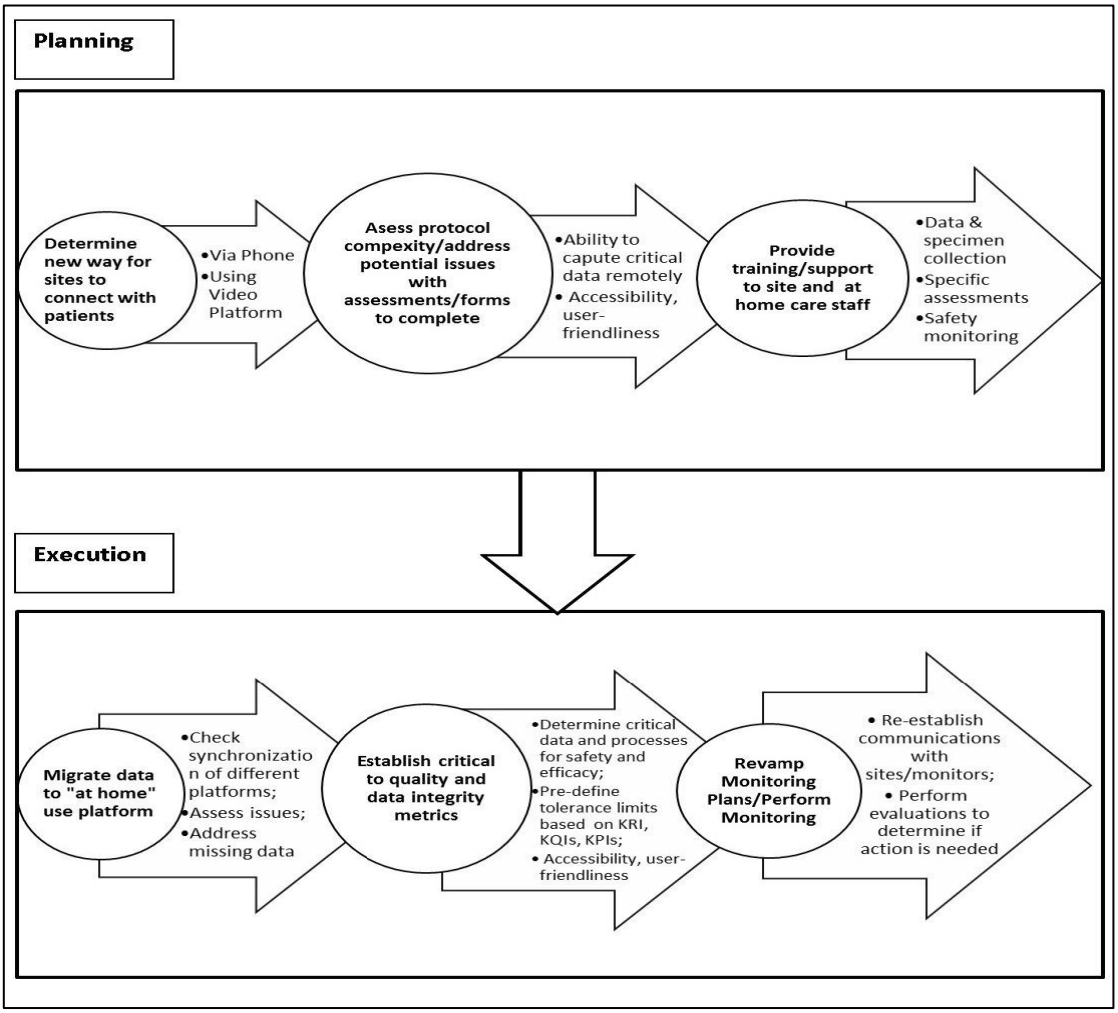

Figure 1: Establishing process for technology utilization during COVID-19 pandemic and revamping monitoring activities.

Abbreviations: KRIs- key risk indicators, KQIs- key quality indicators, KPIs- key performance indicators.

While most sponsors have employed some type of risk assessment in their studies, many are still relying on their vendors for risk assessments, which is proving to be challenging as CROs/vendors 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. Assess how well each vendor's risk management infrastructure handles such drastic changes in their operations. This must be an ongoing and iterative process as new risks are identified. As the entire healthcare system adjusts to this crisis, each adaptive measure taken must be documented and justified.

ADJUSTING MONITORING PLANS AND AUDITS, INSPECTION PREPARATION STRATEGIES IN COVID-19 PANDEMIC

A flexible monitoring strategy is key to mitigating study-level impact of COVID-19 and ensuring data integrity. Remote monitoring should be considered, if sites are not allowing external personnel to visit their organization in person, or if restrictions are still in place and qualified site personnel is still working at least part-time remotely. Especially with smaller sites that have less infrastructure,

employing interview-based techniques can be helpful in checking on site activities during COVID-19. Sponsors/CROs should treat each site on individual basis since regional situation for sites as well as organizational policies and procedures can vary. Ask study coordinators/study nurses to provide patient status and safety updates. Leverage your relationship with sites now more than ever and support them as much as possible as we are all in it together.

There has been a decrease in reported adverse events (AEs) during the pandemic, likely due to patients' inability or reluctance to visit sites in person. So, qualified site personnel should be communicating regularly with the patients to maintain an understanding if any AEs occurred and need to be reported. FDA updated COVID-19 clinical trials guidance to address serious adverse events reporting during pandemic.[7, 14]

Flexibility in timing for remote monitoring visits is critical. Organizational policies and procedures can vary at individual sites for external virtual technology utilization or external personnel access to their internal systems (e.g.: electronic medical records, virtual access to facilities, etc.), but in general they are becoming very familiar with and accepting of remote monitoring methodology as we move forward (Figure 2, Step 3).

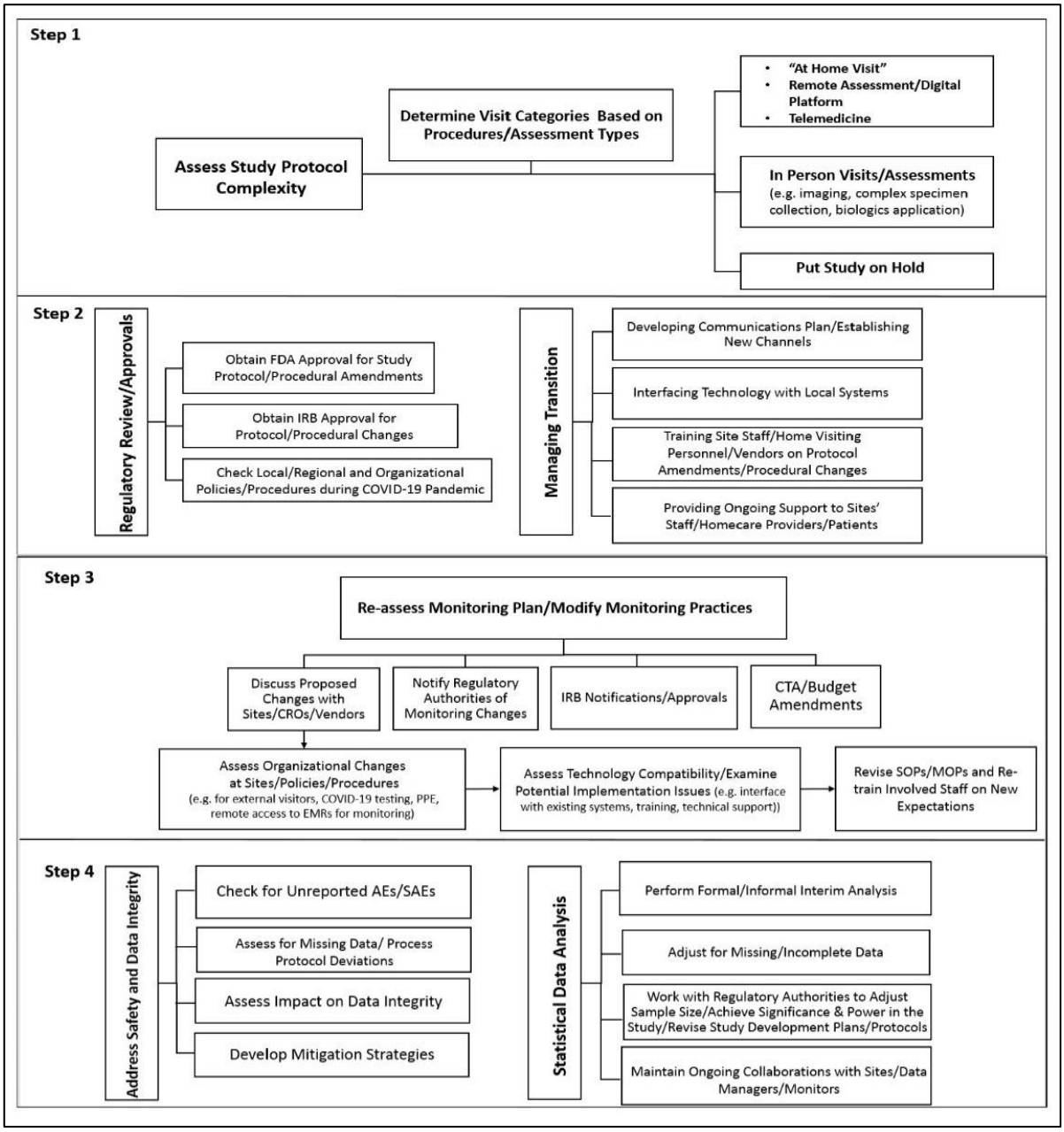

Figure 2: Adaptive approach to establishing new process workflow for clinical trials during COVID-19 pandemic.
Abbreviations: FDA- Food and Drug Administration, IRB- Institutional Review Board, CRO – Contract Research Organization, CTA – Clinical Trial Agreement, AE - adverse event, SAE - serious adverse event, SOP - standard operating procedures, MOP- manual of operations, PPE- personal protective equipment.

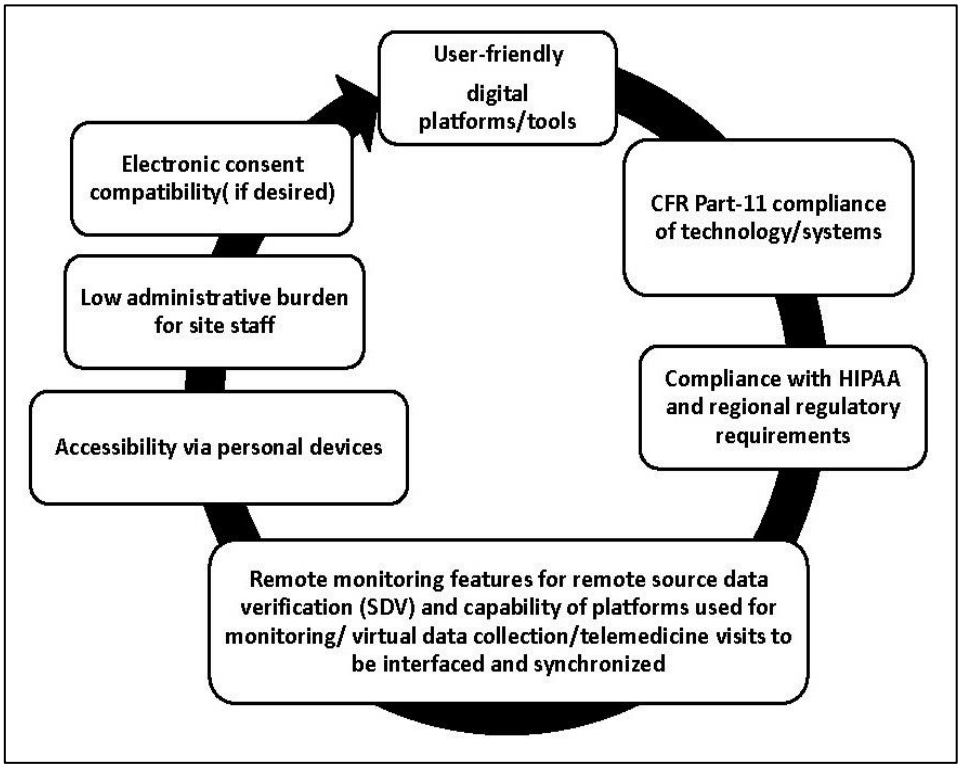

Figure 3: Considerations for development and utilization of patient-centric digital solutions/tools in clinical trials. The complexity of the study protocol and procedures: biometrics, functional studies, imaging, etc. should be taken into account when choosing a digital technology that will be most effective for the study specifics (e.g.: biopsies, imaging, and blood draws are some of the most challenging procedures to execute virtually). Assessments should be made on how data collected during telemedicine visits via digital platforms will be monitored for critical to study protocol variables and data integrity will be maintained.

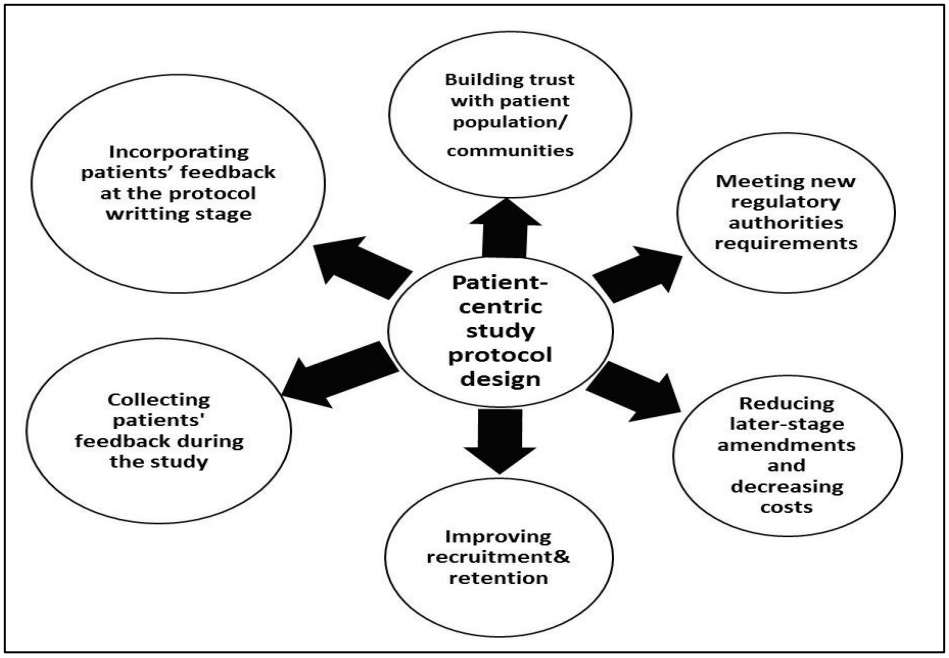

Figure 4: Elements of employing patient-centric study protocol design. Incorporating patient perspectives early will allow sponsors to focus on endpoints that are scientifically meaningful and also important to the patients, which will lead to achieving the right balance between compliance with the regulatory requirements and study protocol. It will be more appealing to the patients, as well as lead to the reduction of number of later-stage protocol amendments and decrease costs.

Also, consider employing or expanding centralized, risk-based monitoring to identify additional data integrity issues and focus on critical data and processes. The use and analysis of data to trigger monitoring visits and identify potential signals early is becoming a more widely used method across industry due to this pandemic. This approach, however, requires almost real-time access to the data, understanding the appropriate key risk indicators (KRIs) and key quality indicators (KQIs), thresholds and triggers, which will most likely require re-assessment and adjustments during COVID-19 pandemic. In addition, transition to centralized, risk-based monitoring requires access to technology to build a platform/develop dashboard, dedicated internal team with appropriate knowledge/skills or outsourcing to a qualified vendor to establish a process and train involved personnel at sponsor and site levels on centralized monitoring techniques/ expectations in accordance with their roles/responsibilities. Centralized monitoring offers a more comprehensive view at the data, focused on proactive rather than reactive approach in finding trends, including trends across an entire portfolio. Insights gained from centralized monitoring allow sponsors to determine areas of focus for monitoring and follow-up, identify training opportunities, and may even trigger protocol amendments, if needed.

Sponsors/CROs should consider performing a gap analysis to determine if processes implemented during the pandemic have been and continue to be effective moving into post-pandemic stage. Frequently reassess key performance indicators (KPIs), thresholds, and quality tolerance limits (QTLs) as triggers for possible adjustments based on review of collected data and evolving trends. Utilization of risk-based approach, while analyzing the remote and centralized monitoring findings, will help to modify the monitoring processes and strategies accordingly. Also, sponsors/CROs should establish and maintain open channels of communications with monitors and sites. It can be challenging since most people still work remotely. Ask how their monitoring visits went and if there was any feedback from coordinators, other qualified site personnel, study subjects or investigators. When on-site patient visits resume, compare protocol deviations that occurred during COVID-19 with the deviations that occur afterward. These newly revealed in pandemic patterns should drive the on-site monitoring visits and influence future monitoring strategies.

The most prevalent data integrity challenge during COVID-19 has been missing data due to missed visits. As we continue to modified study visits, coordinators are dealing with the increased workload by contacting patients, collecting as much data as possible despite missed visits, and entering data as complete as possible into the electronic data capture (EDC) systems. Sponsors need to ensure that collected data will provide useful, meaningful information in the future.

As it was expected the protocol deviations have increased during COVID-19, but the industry lacks consensus on how to document them. Some sponsors think that differentiating COVID-related deviations from non-COVID related deviations is not necessary. Instead, monitors specifically state in visit reports that the patient visit was conducted during COVID-19. If there is a clear and direct attribution of deviations to COVID-19, it should be written up as such. Sponsors should seek FDA's guidance on how to handle study protocol deviations and adjust their monitoring plans during pandemic. In these unprecedented circumstances, sponsors may deviate from the original monitoring plan and/or study protocol but the deviations should be reviewed by the sponsor to ensure research subjects' safety. All changes to monitoring plan and process, as compared to original monitoring plan, must be reviewed and approved by regulatory authorities prior to implementation. Each individual deviation should still be captured in monitoring visit reports and electronic data capture systems. Consider using a standard data collection method to capture information related to COVID-19 in one central place, such as adding uniform COVID-19-specific data fields to case report forms to ensure consistency across studies and standardize processes for data capture between different sites.

Accurately collecting and reporting data affected by COVID-19 means defining "before," "during," and "after" time points. Identifying what timeline constitutes before, during, or after is challenging due to the virus' regional, local spreading patters and site-related variations. Recently, the FDA issued a guidance to industry entitled: "Statistical considerations for clinical trials during the COVID-19 public health emergency."[15] The recommended approach is to put the pandemic in the context of the trial. Consider setting dates at appropriate inflection points such as the earliest date of COVID-19's trial impact, the date when study subjects' assessments could resume, etc. Attention will also need to be paid to what exactly was affected at these time points. Sponsors should work with each site to confirm their impact dates (i.e. enrollment hold, visit conversion to telemedicine or at home visits, etc.) as each site may have implemented precautions before regional impact was known. Sponsors should use these timelines to document the parameters around the data and to inform the coding needs in preparation for data analysis.[15]

Regulatory authorities will need to see detailed data on a site level, including activity pause/resume dates once they resume on-site inspections. Despite pausing on-site surveillance in in March of 2020, FDA investigators have conducted other critical activities to ensure FDA-regulated industries are meeting applicable requirements.[16,17] Currently, FDA is using a number of tools as part of the agency's risk-based approach to ensuring quality, including remote assessments and import alerts as well as other compliance requirements. As the COVID-19 pandemic continued, they adjusted processes and guidance as necessary to maintain the appropriate level of review to

ensure the safety of consumer products, including hand sanitizers, diagnostic tests, etc.[16] At the same time, FDA has been closely monitoring re-opening criteria established at the federal, state or county levels and planning to identify when and where to resume domestic and foreign inspections, prioritizing them based on risks and other factors.[16,17]

To arm their investigators with most reliable and accurate information, the FDA has developed a rating system to assist them in determining when and where it is safest to conduct prioritized domestic inspections. The COVID-19 Advisory Rating system (COVID-19 Advisory Level) uses real-time data to qualitatively assess the number of COVID-19 cases in a local area based on state and national data.[16] Resuming prioritized domestic inspections will depend on the data about the virus' trajectory in a given state/locality and the rules/ guidelines that are put in place by state and local governments. The FDA has also determined that, for the foreseeable future, prioritized inspections will be pre-announced to FDA-regulated businesses. This will help assure the safety of the FDA's investigator and the firm's employees, providing the safest possible environment to accomplish their regulatory activities, while also ensuring the appropriate staff are on-site to assist FDA staff with inspection activities.[16,17]

In preparation for possible audits and inspections, sponsors must understand the effect of COVID-19 on a patient level, specifically concerning protocol deviations, identifying which deviations were due to COVID-19 and which were true site deviations, if possible. Sponsors should still report protocol deviations via their normal process but should also be building and planning a strategy together with their statisticians for how this information will be reported out at the end of the trial. This will ensure they are capturing and collecting the right level of data to ensure data integrity.

Sponsors should perform assessment detailing how many patients they have lost, protocol deviations that could have impacted the evaluable population, any gaps in the data, etc. If the study is still ongoing, sponsors should preferably perform this assessment before the trial stops recruiting, just in case additional patients will need to be enrolled to address any discrepancies and lack of statistical power in the study (Figure 2, Step 4).[15] Performing blinded reviews now will help sponsors to decide if additional enrollment is needed to reach endpoints of the study, and/or if an early interim analysis needs to be performed, if recruitment is paused and/or extremely delayed due to COVID-19.[15]

Although many countries around the world are still in the midst of COVID-19, it's time for sponsors to begin looking beyond the pandemic, focusing attention on strategies for assessing the pandemic's impact on data integrity, develop mitigation strategies, and methods to ensure overall data integrity. Flexibility, careful consideration for meaningful data to be collected, answering questions of what be necessary/important in the future should be the key factors as we conduct studies both during and after the pandemic.

DISCUSSION

Around the globe, organizations are implementing strategies to manage the COVID-19 pandemic. Most industries have already recognized the benefits of digital technology, but biomedical companies have traditionally been slower to embrace new technologies and process changes. For the past 20 years biomedical industry utilized inefficient monitoring and trial management approach, which was reactive rather than pro-active. The fear of relying on digital technology and/or doing something wrong by getting away from 100% source verification had slowed down the innovation. COVID-19 pandemic has made it even more obvious, and it also has left no choice for sponsors/CROs but to embrace remote, centralized data monitoring. The FDA and EMA guidance for managing clinical trials during the COVID-19 pandemic payed special attention to the need to apply this approach whenever feasible.[7,10]

In 2016 the ICH Good Clinical Practice Guidelines were revised by introduction of ICH GCP E6 (R2) Addendum, which was meant to address advances in modern technology, complexity and globalization in design and conduct of clinical trials.[18] These revised guidelines required sponsors and CROs to implement a more robust and formalized risk-management process in clinical trial conduct with focus been placed on patient safety and data integrity.[18]

Site staff need to analyze how they are tracking and communicating updates to monitors regarding critical to quality risk indicators. For data integrity points to consider include examining how issues related to data integrity will be escalated from the site to the sponsor and from the monitor to the site. Also, site personnel should understand how trends in high risk categories are being escalated to the sites and CRAs will need to provide key study updates and clarifications to site personnel. Communication regarding these risks and time in the new paradigm are the most essential elements. Potential safety issues and critical to quality trends will need to be escalated as quickly as possible to CRAs and sites.

Cancellation or postponement of major scientific and professional conferences, investigator meetings, and scientific advisory boards put us all in siloes initially. Given that much of the education and collaboration across our industry comes from these venues, it was helpful to see that clinical research community resumed conversations on virtual platforms. So, we can continue to move forward and share our insights and share different perspectives regarding current situation. We have analyzed lessons learned during COVID-19 pandemic in attempt to share some suggestions and develop best practices to mitigate risks and adjust clinical research operations during this unprecedented time (Table 1). Now it's time to take

advantage of the fact that industry stakeholders and regulators are equally motivated to move quickly and adapt. There is an acute need to develop collaborations across different stakeholders as without cooperation between sites, patients, healthcare providers, sponsors, regulators, and CRO/vendors, there will be no progress in innovation spurred by COVID-19 into the future. We need to incorporate what we have learned into our organizational processes, include patient-centered virtual capabilities into future designs of the trials from the start of study planning, come out with creative solutions to ensure data integrity and patient safety, and enable effective scaling up of adapting processes and solutions.

CONCLUSION

Given the complex risk/benefit considerations associated with each specific clinical trial, there is no single solution to manage the risks related to clinical research conduct due to COVID-19 pandemic. Each clinical trial is unique with respect to patient population, investigational products' mechanism of action, concomitant medications, and needs based on geographic location. It is important to continue to engage the professional networks and communities to push forward with developing a creative risk mitigation strategy and plans to resolve issues during this challenging time. Risk assessment should be a continuous and ongoing process as the situation evolves over the coming weeks to months. Routine and standing cross checks for study teams are already proving to maintain alignment on key timelines, critical risk points and other study specific challenges as we are moving towards de-centralized settings in the conduct of clinical trials.

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REFERENCES

1. Secretary of Health and Human Services Alex M. Azar II. Determination that a public health emergency exists. 2020 (renewed April 21, 2020). Available at: https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx. Accessed on 03 August, 2020.
2. Proclamation on declaring a national emergency concerning the novel coronavirus disease (COVID-19) outbreak. 2020. Available at: https://www.whitehouse.gov/presidential-actions/proclamation-declaring-nationalemergency-concerning-novel-coronavirus-disease-covid-19-outbreak/. Accessed on 03 August, 2020.
3. WHO Director-General's statement on IHR emergency committee on novel coronavirus (2019-nCoV). Public health emergency of international concern declared by WHO. 2020. Available at: https://www.who.int/dg/speeches/detail/who-director-general-s-statement-on-ihr-emergency-committee-on-novel-coronavirus-(2019-ncov). Accessed on 03 August, 2020.
4. WHO Director-General's opening remarks at the media briefing on COVID-19. 2020. Available at: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Accessed on 03 August, 2020.
5. Weekly update on COVID-19th. 2020. Available at: https://www.who.int/publications/m/item. Accessed on 03 August, 2020.
6. Timeline of WHO's response to COVID-19. 2020. https://www.who.int/news-room/detail/29-06-2020-covidtimeline. Accessed on 03 August, 2020.
7. FDA Guidance for industry, investigators, and Institutional Review Boards on conduct of clinical trials of medical products during COVID-19 public health emergency. 2020. (revised on July, 2nd of 2020)
8. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency. Accessed on 03 August, 2020.
9. Considerations to support clinical trial monitoring oversight during COVID-19 by Association of Clinical Research Organizations. 2020. Available at: https://www.acrohealth.org/wp-content/uploads/2020/03/ACRO-Statement-on-Monitoring-Oversight-FINAL-3.13.20.pdf. Accessed on 03 August, 2020.
10. Francis G. and Wydenbach K. MHRA advice for management of clinical trials in relation to coronavirus. 2020. Available at: https://mhrainspectorate.blog.gov.uk/2020/03/12/advice-for-management-of-clinical-trials-in-relation-to-coronavirus/. Accessed on 03 August, 2020.
11. EMA Guidance on the management of clinical trials during the COVID-19 (Coronavirus) pandemic. Version 3. 2020. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf. Accessed on 03 August, 2020.
12. FDA Guidance for IRBs and clinical investigators: Institutional Review Board (IRB) review of individual patient expanded access requests for investigational drugs and biological products during the COVID-19 public health emergency. 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/institutional-review-board-irb-review-individual-patient-expanded-access-requests-investigational. Accessed on 03 August, 2020.
13. Marra C, Chen JL, Coravos A et al. Quantifying the use of connected digital products in clinical research. npj Digit. Med. 2020;3(5).
14. Clarke I. Data shows a majority of patients remain interested in clinical trials during the coronavirus pandemic. 2020. Available at: https://www.subjectwell.com/news/data-shows-a-majority-of-patients-

remain-interested-in-clinical-trials-during-the-coronavirus-pandemic/. Accessed on 03 August, 2020.
15. FDA updates COVID-19 clinical trials guidance to address serious adverse events. Available at: https://www.raps.org/news-and-articles/news-articles/2020/5/fda-updates-covid-19-clinical-trials-guidance-to-a. Accessed on 03 August, 2020.
16. FDA Guidance to industry: statistical considerations for clinical trials during the COVID-19 public health emergency guidance for industry. 2020. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/statistical-considerations-clinical-trials-during-covid-19-public-health-emergency-guidance-industry. Accessed on 03 August, 2020.
17. Commissioner of Food and Drug Administration Stephen M. Hahn. FDA Statement.
18. Coronavirus (COVID-19) Update: FDA prepares for resumption of domestic inspections with new risk assessment system. 2020. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-prepares-resumption-domestic-inspections-new-risk-assessment-system. Accessed on 03 August, 2020.
19. Commissioner of Food and Drug Administration Stephen M. Hahn. FDA Statement. Coronavirus disease 2019 (COVID-19) update: Foreign inspections. 2020. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-disease-2019-covid-19-update-foreign-inspections. Accessed on 03 August, 2020.
20. Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2). Available at: https://www.ich.org/fileadmin/Public_Web.../E6/E6_R2__Step_4_2016_1109.pdf. Accessed on 03 August, 2020.

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