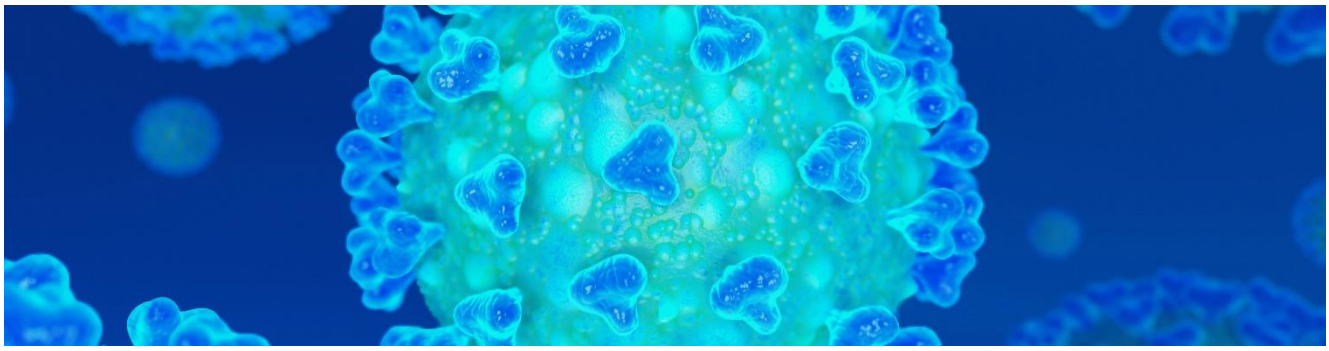
Impact of COVID-19 on Product Development: Information and Resource from Halloran



Halloran has formed a company-wide task force to curate information on the impact to the life science industry due to the current COVID-19 environment. We are leveraging our most experienced subject matter experts, using our deep life science experience to assess and address in real time the issues and new challenges facing your programs. The biotech industry was born with the belief that we would change the world, and collectively, we have many times over. We recognize that we can arm your business and our industry with regulatory, clinical, quality, compliance and technology to keep potential lifesaving programs moving forward. Our insights below are shared freely to support programs designed to treat patients with just about every conceivable medical condition as well as patients with COVID-19.

Our firm is committed to positively impacting human health by bringing unwavering commitment and firm resolve to patients, your programs, and your corporate goals. We understand that creativity and expertise will be required to make this happen and ensure business continuity. Your Halloran colleagues are committed to bringing our expertise and creativity to keep your programs and company on track.

Clinical Trial Impact and Risk Mitigation:

We've seen an immediate impact on clinical trials due to challenges coming from the COVID-19 travel bans, hospital/clinic visitation restrictions, and social distancing precautions, just to name a few. These factors have translated into the following issues challenging corporate milestones, budgets, and data integrity:

1. **Delays in patient enrollment or missed study visits resulting from the inability of patients to travel to on-site visits or limitations on non-essential in-office visits or testing.** We are recommending provisions of private car services for patients who have relied on public transportation to travel to sites. We are also recommending use of home health services for study drug administration (e.g., infusions) and/or study assessments, where feasible. IRB and Ethics Committees have been highly receptive to well-thought-out plans that ensure patients have access to care and to the clinical options that investigational agents represent.

2. **Delays in study initiation activities resulting from the inability to perform site selection/initiation visits and/or clinical vendor qualification visits, and subsequent downstream delays in patient enrollment.** We are encouraging a shift from on-site, in-person meetings for vendor audits, vendor/CRO bid defense meetings,

and site initiation/training visits to remote-based models using phone and video-conferencing software. This should include plans to allow for risk identification and future on-site visits as needed. While remote meetings and visits require more preparation on a sponsor side, we have optimistically observed our staff and our clients taking extra care to ensure key clinical points, from supporting safety data to procedures ensuring patient safety, are thoroughly communicated. We believe this extra care and attention may translate to better sponsor/site relations over time.

3. **Protocol adherence issues arising from an inability to comply with visit schedules, study procedures, drug administration, and monitoring procedures.** We recommend modifying the number of protocol-mandated in-person study visits and supplementing them with at-home visits or telemedicine and using remote labs or home health services for routine or standard-with-blood and non-invasive tests. We also recommend revamping monitoring plans to include more robust remote-based data review strategies and tools. There are several third-party options available to support this shift midstream in your studies. Of course, these must be documented in the protocol and plans, and we have seen some 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.

4. **Delays in clinical material distribution and import/export delays due to limited manufacturing and operations staff, limited or reprioritized hospitals staff, and travel bans.** We recommend that considerations should be made to determine if study drug shipments may be sent directly to patient homes with support from home health services for drug administrations and accountability. Recent statements have been released from several health authorities on the supply and distribution challenges: EMA on 10 March 2020 on the Impact on Medicines Supply in EU, the Medicines for Europe on 13 March 2020 on COVID-19, and FDA's statement from March 10, 2020 on Foreign product importation inspections.

5. **Some delays in local IRB reviews and approvals due to limited or reprioritized site staff.** We recommend prioritizing the use of central IRBs, when feasible, to alleviate the delays that are likely to continue with some local IRBs. Of course, this would have to be discussed with the site and documented.

6. **In some cases, we have seen suspension of all patient activities for trials, sites, or studies that do not have active patients being treated.** In these cases, we have seen follow-up visits being performed remotely and the use of third parties are being utilized for faster ramp-up of remote monitoring activities and tools.

7. **Misalignment with sponsors, investigators and CRO/vendor team members on regional restrictions, updates and impact.** We are recommending ongoing risk evaluations and assessment sessions with sponsors, investigators and CRO/vendor team members to align on local restrictions, impact assessment, and create contingency plans to bolster already existing site, vendor, and study-specific risk mitigation strategies. Establishment and joint standing review of vendor key performance and quality indicators will provide insight into their performance. Additionally, having clear and defined criteria on what events should be escalated to the sponsor will ensure that, as a sponsor, you are effectively monitoring your studies, especially as changes are made to these operational activities. This should be a continuous and living process as the situation evolves over the coming weeks to months. Routine and standing touchpoints for study teams are already proving to maintain alignment on key timelines, critical risk points and other study specific challenges.

8. **We are also seeing major scientific and professional conferences and meetings; and KOL, investigator, and scientific advisory board meetings being cancelled or postponed (indefinitely in some cases).** We recognize so much of the education and collaboration across our industry comes from these venues. We are recommending virtual meetings wherever possible. Several industry groups are looking at holding simulated virtual events so we can continue to move forward and share our insights.

The FDA recently issued a guideline (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 be based on study specific circumstances. Guidance is also provided on management of procedural modifications, protocol amendments and deviations (e.g., implementation, IRB approvals, FDA consultation) as well as preparedness to describe the tactics and impact in the corresponding clinical study reports. Some of these

recommendations are also highlighted in the Association of Clinical Research Organizations (ACRO's) 13 March 2020's Recommendations to Support Clinical Trial Monitoring Oversight During COVID-19 and in MHRA March 12, 2020 Advice for Management of Clinical trials in relation to Coronavirus.

Given the complex risk/benefit considerations associated with each specific clinical trial, there is no single solution to manage the risks facing clinical activities due to COVID-19. Each clinical trial is unique with respect to patient population, study drug mechanism of action, concomitant medications, and geographic needs. It is important to continue to engage the network and community to push forward with creative risk mitigation and issue resolution plans during this challenging time.

Impact to Regulatory Interactions, Inspections, and Audits:

While we have not seen any significant delays in the approval of products to date, the impact of COVID-19 on global health authorities will continue to evolve. We expect a variety of potential delays in regulatory communication and meetings that will continue for months, if not years. Current travel restrictions and the remote working environment have brought the following considerations:

1. **Face-to-face interactions with the FDA that were previously scheduled for March and April of this year have been or will be converted to teleconferences.** While most in the industry appreciates the benefits of a face-to-face meeting with FDA or any regulatory body, there are advantages to a phone conversation compared to an in-person meeting. Teleconferences allow the sponsor/applicant team (as well as the regulators) to go on mute to discuss important topics, gain team consensus, and then return to the dialogue and quickly progress the conversation. A teleconference or video conference also allows a sponsor to use chat and instant messaging capability to coordinate and focus responses for maximum effect. Halloran has held many teleconferences with health authorities and can identify additional tactics that work effectively in tele and video conferencing.

2. **Review cycles and timelines for meetings to be granted may be delayed.** This, of course, will depend on how much the virus impacts the health authority review teams. Should they become short-staffed due to illness or are re-assigned, we should expect delays, similar to what happened in the U.S. government shutdown in 2019.

3. **We are seeing global health authorities working in close partnership with industry and academia to quickly progress therapies, vaccines, and diagnostics for COVID-19.** While the relationship between industry and the regulators is variable, this is a time for us to partner closely with health authorities to accelerate emergency use treatments and quick startups to ensure that these potential products are of top priority. See FDA's statement on March 16, 2020 on the latest Diagnostic Emergency use Authorization. Halloran has several clients who have received incredibly prompt and engaged responses from FDA on investigational agents for COVID-19 treatment. Worldwide regulators have proven time and again that they will find ways to work with industry in the face of previous health emergencies – Ebola, Zika, SARs, H1N1, etc.

4. **We can expect to see delays of onsite pre-approval manufacturing site inspections.** While FDA has announced suspensions of inspection activities in China and Europe, the extensive international travel restrictions and border closures that have been announced this week will severely limit, if not entirely halt pre-approval and many other routine facility inspections. Regulatory bodies are likely to defer any inspection that can be reasonably deferred and to employ a few virtual or correspondence-based inspections where possible. It is unclear if regulatory bodies will delay action dates or extend review periods when inspections are not possible or practical.

5. **The limitations of on-site pre-approval facility inspections extend to clinical and sponsor inspections.** We expect FDA and other regulatory agencies to rely upon several forms of virtual inspections and audits to ensure that the rights, safety, and welfare of subjects are protected, to verify the accuracy and reliability of clinical study data, and to assess study compliance with regulations. We can likely expect regulatory agencies to request sponsors to provide information electronically that would normally be evaluated during an on-site inspection. Additionally, agencies may request access to the electronic Trial Master File (TMF) and other

systems in order to assess the conduct of the trials without an in-person visit. Interviews with subject matter experts may be conducted using either teleconferencing or video conferencing technology. It is important that you prepare for a virtual inspection with the same rigor and structure that you would an on-site inspection. Conducting a virtual mock inspection is a great way to test your organization's capabilities and preparedness during this time. FDA released a statement on March 10, 2020 on COVID-19 foreign inspections and we may see additional guidances released in the coming weeks.

6. **With social distancing and travel bans, on-site GxP audits and vendor selection visits have already been impacted.** Performance of investigator sites and vendors that would normally be evaluated during an on-site audit will now need to be evaluated using alternative methods. While qualification visits and audits of vendors and sites may have to be done virtually, the requirement for maintaining documentation of sponsor oversight is as important as ever, in addition to identification of the potential risks, mitigations, and process for continuous assessment.

Impact to Technology and Mitigations:

With all of the above priorities coming our way, technology may be one area that you may consider not directly impacted by COVID-19. With many of our clients' clinical and informatics platforms being cloud-based, most business continuity plans are not prepared for a near complete switch from in-office presence to remote users. For any plans that did, it was unlikely expected to occur nearly overnight as we are currently experiencing. As our clients transition to an entirely distributed (home-based) user environment, the following are worth highlighting:

1. **The architecture of many remote and/or virtual working environments is to facilitate some remote staff or to allow multiple company locations to communicate with ease.** It is important to ensure that the following are available to all employees or on a much larger scale than just a few weeks ago is a critical path activity:

    a. hardware (laptops, monitors, & peripherals)
    b. access points (licenses, seats & VPN connections)
    c. support (user guides, FAQ, & troubleshooting guides)

    Virtual video conferencing capabilities should be available for all employees supporting continued team connection and business continuity. We are seeing an increase in clients relying upon interactive tools such as document sharing, instant messaging apps (like Slack), whiteboarding apps, and meeting platforms to provide employees with the more real-time interactive communication tools to aid in the remote work transition.

2. **We do not anticipate any network outages due directly to COVID-19; however, some are companies are experiencing a slowdown in their networks, particularly those relying upon VPN connections to physical or virtual servers versus cloud-based applications.** Now, more than ever, companies are thinking about moving to cloud-based systems and applications, but we know this is a longer-term investment and will not solve the immediate challenges some clients are facing. With some slowdowns, we have seen companies employ very intense network monitoring programs and testing procedures to try to improve connectivity issues.

3. **With a heavy reliance upon remote access and a distributed work force, information security practices and protocols are now being tested more than ever.** It will be surprisingly easy for staff, especially those new to remote working, to download and store sensitive information on relatively unsecure home networks and devices. Many U.S. households have Alexa enabled networks, rely on cloud-based backup programs (such as iCloud), or have other highly connected technology. Therefore, it is very important to continue to stress information security policies and procedures for employees during this time.

4. **Business Continuity plans must be put in place (if not already) on how to operate as a business when systems are down.** Disaster recovery plans should be tested and redundant systems and testing of such to ensure these backups are working properly should also be prioritized at this time. Continuity and contingency plans may soon be tested as different countries, states and cities enact quarantines or other restrictions on free movement of people. Those restrictions could severely impact the personnel who maintain the networks & technology platforms your business is relying upon.

5. **As noted above, the industry is pivoting away from on-site operational aspects of a clinical trial to a more decentralized clinical trial technology to enabling home virtual visits, telemedicine, and remote monitoring capabilities.** An immediate assessment of the options available and impact of using these tools is highly encouraged. In addition, we are recommending each client take a critical look at employing accelerated and abbreviated validation practices to get these tools in-use faster than may be typical while recognizing these streamlined approaches must align to the regulations and be supported with appropriate documentation. If a third-party tool can be deployed and is already validated, that option is worth considering to further shorten deployment and ramp up timelines. These options should be discussed with your IT department to prevent further unnecessary delays in managing clinical trial activities and ensuring critical treatments to patients who need them.

Business Matters

We are actively monitoring the business and social impact that COVID-19 is having to our community in real-time. We recognize that most of the global workforce will be juggling a host of personal matters during regular working hours including childcare, distance learning curricula, and care for our extended families and communities. We also recognize that many of you are also implementing new processes and procedures to protect your employees from exposure to COVID-19 while requiring careful and clear communication in addition to the logistics of setting up remote working environments. What is clear is that all of us must plan for potential program delays and disruptions to our normal course of business for at least the next several weeks and perhaps months. While the Halloran team will be managing these same challenges at home, we are committed to being as flexible as possible to ensure that project plans stay their course with minimum delays and that we are keeping you informed of any issues and mitigations that may help as we navigate these uncertain times together.

Halloran will be hosting several virtual town hall meetings to engage our life science community to share experiences and solve for some of the common issues and challenges real-time. The first Virtual Town Hall: Impact of COVID-19 on Clinical Trials will be held on Friday, March 20, 2020 at 11:00am – Noon EST. Click here to learn more or RSVP. We are all in the business of getting lifesaving products to patients safely while doing what we can to prevent avoidable delays through creative solutions.

Halloran is available to help you develop and assess your own business continuity or response plans, including timely and targeted communications to your workforce, customers, and communities-at-large, so please reach out with any questions you may have.

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