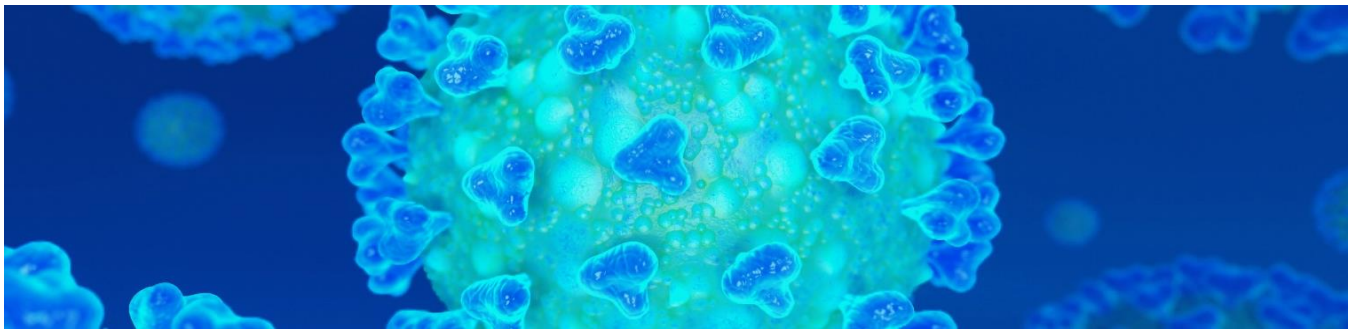
The Impact of COVID-19 on the Regulatory Landscape

Lessons Learned from a Virtual Town Hall held on April 10, 2020



The impact of COVID-19 on trial conduct and the regulatory landscape is rapidly changing, requiring continuous attention and adaptation. According to WCG's Knowledge Base™ Insights from 10 April 2020, 100+ non-COVID-19 trials had been put on official hold, and only 14% of sites are open for enrollment. Stats like this demand that we evaluate the regulatory impacts our industry faces in the wake of COVID-19 and what to expect in the months ahead.

On April 10, 2020, as part of Halloran's Virtual Town Hall series, Halloran convened a panel of experts to discuss what our network is seeing in terms of regulatory activity as some cases warranted and received expedited feedback, while others are seeing delays to reviews and receipt of commentary from the U.S. Food and Drug Administration (FDA). Specifically, there was discussion around the institutional review board (IRB) review prioritization rationale, regulatory CMC programs, ancillary functions, and more. Below are some key insights from the panel's experience conducting regulatory activities during the pandemic.

Impact to FDA meetings and reviews

- Having already faced resourcing issues before COVID-19 happening, the FDA's Center for Biological Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) is facing a further complicated workload. It appears that the **FDA is prioritizing COVID-19-related programs**, which naturally lengthens the timelines of other activities that have been deprioritized in the new environment. **Staff from review divisions across the FDA are being reallocated** into divisions directly related to the pandemic to strengthen resources.
- To date, **CDER and CBER have continued to meet their standard 30-day initial investigational new drug (IND) review cycles**. Though this could change over the next few months due to the influx of new therapies, including those for COVID-19, on top of the FDA's already record-breaking workload.
- Some formal sponsor-FDA meetings are being postponed. No face-to-face meetings are being granted, and **often teleconferences are being downgraded to Written Response Only (WRO)** as FDA adjusts

their resources for efficiency. While it's disappointing for sponsors to lose an opportunity to interact with the FDA in-person, in these cases, written feedback has been very thorough and helpful.

- **FDA has been very realistic and communicative** in their timeline appraisals and delay estimates. To keep up with the growing workload, they are working days, nights, and weekends to meet deadlines.
- To date, Halloran has not seen delays in the Center for Devices and Radiological Health (**CDRH) device trials**. To keep operations flowing, CDRH has been working via teleconference and written response to keep things moving to the best of their ability.
- In the European Union (EU), the European Medicines Agency (EMA) and Medicines and Healthcare Products Regulatory Agency (MHRA) have been very communicative. The regulatory agencies convened an emergency task force to manage all COVID-19-related activities and the guidance the EMA released detailing how to work under COVID-19 circumstances has been very helpful to sponsors.

COVID-19 Programs

- **FDA is re-allocating reviewers into divisions dealing directly with novel coronavirus program reviews.**
- **CDER requires that information on COVID-19 programs be submitted in a combined format** which includes the pre-IND Meeting Request *and* Briefing Document together in a single package (rather than the Meeting Request and then the Briefing Document separately) to streamline the review process.
    - Halloran has seen a WRO returned in as little as 14 days rather than the typical 60 days.
- CBER is providing the following advice to sponsors planning to submit an ID+ND for a COVID-19 program:
    - If a sponsor feels that their investigational product may be ready to proceed to clinical use *within a matter of weeks*, it is recommended to submit an IND rather than a pre-IND Meeting Request. CBER will do its best to work interactively with the sponsor during the review process.
    - If a sponsor does not intend to submit an IND for *several months*, then a pre-IND Meeting Request may be the best mechanism to receive input and feedback.
    - For concise pre-IND Meeting Packages (i.e. fewer than 100 pages), CBER may be able to provide WRO back within 21 days.
    - The requirements and expectations for pre-IND Meeting Package and IND application content has not changed.
- FDA **has issued guidance around plasma products and blood products in general**, which includes pathways for use, donor qualifications, patient eligibility, labeling, and recordkeeping.
- FDA is willing to work with sponsors to expedite the review process as much as possible within reason. While the Agency has expedited its regulatory timelines in response to the COVID-19 pandemic, **sponsors should not assume decreased scrutiny** around thoughtful approaches, data-driven dosing justifications, etc.

Impact to ancillary functions that support clinical trials

- **Access to nonhuman primates (NHPs)** has become an issue likely to cause a significant impact to IND-enabling preclinical activities. Additionally, the cost per monkey has risen from ~$4.5K to now $8K.
- **Contract Research Organizations (CROs) are limiting their activity and production to** promote a safe working environment for their staff. These facilities are working at decreased capacity by:
    - **Limiting access to experts such as biostatisticians** due to resource reallocations that prioritize COVID-19 activities.
    - Allowing some CROs to let staff perform husbandry on animals, but not initiate new studies.
    - Limiting the number of staff allowed on the floor thus decreasing their efficiency to manufacture drug products.

Impact to Regulatory CMC programs

- Cell therapy companies are considering **risk assessments to assess the possibility that the SARS-CoV-2 virus is present** in their cell-based products.
- **Sponsors should proactively amend their stability protocols** to ensure coverage for longer durations of clinical usage.

General regulatory considerations

- **Changes and updates to existing INDs** may be delayed due to academic medical center IRBs continuing to prioritize COVID-19 programs first and life-threatening diseases second. INDs that fall outside these two categories may see impacts on their timelines. This prioritization may continue to be a rate-limiting factor into the fall as a result of the significant backlog the prioritization is creating.
    - Johns Hopkins Institute for Translational and Clinical Research has detailed their **prioritization rationale** on their website linked here.
- Unsurprisingly, we have seen Pre-Approval Inspections (PAIs) postponed. **At this point, all routine inspection activity (domestic and foreign) is suspended**, and there has not been any indication of when these inspections will pick back up. Unless a virtual solution surfaces to keep inspections moving, this will become the rate-limiting step ahead of NDA and biologics license application (BLA) approvals.
    - The panel has seen utilization of virtual audits, which could mean that virtual inspections could be a reality soon. To prepare, sponsors should prep their trial master files (TMFs) and examine their video capabilities.
    - **The panel recommends that sponsors pause inspection activity and transition to preparing a plan to manage the activity backlog when study activity comes back online**. This includes, but is not limited to:
        - Internal communication plan
        - Vendor/partner communication plan
        - Documentation plan
        - Data integrity reviews
- In terms of regions outside the US and EU, the panelists have seen delays in Australia due to observed conservative CROs.
- **Most US sponsors are choosing to postpone clinical studies** potentially due to internal budget/resource considerations, expected recruitment and enrollment difficulties, and/or limited site activity and IRB timelines.
    - **Sponsors pursuing life-threatening indications are continuing their clinical trials.**
- From the panelists' perspective**, long term changes to the regulatory landscape** due to adjustments made during COVID-19 might include:
    - Regulations around telemedicine, virtual visits, and remote monitoring
    - Availability of post-licensing patient materials online
    - Remote access to EMRs
    - Changes to FDA structure to support pooling reserve resources for future crises

Conclusion

When considering the regulatory obstacles around starting/conducting clinical trials during a pandemic, sponsors should think beyond the IND – is it feasible to conduct a clinical trial at this time? Is it possible to wait until health authorities aren't so heavily burdened and sites are running at normal capacity? Resource shortages, remote monitoring, and protocol amendments are some of the many factors complicating the regulatory landscape right now. We can expect an activity backlog to build over the next few months, which is another reason to limit submissions as much is feasible for non-life-threatening conditions. Thoughtful delays for some noncritical programs could significantly lighten the load for our reviewers, and hopefully, make the return to normalcy easier when the time comes.

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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