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# Challenges and lessons learned for institutional review board procedures during the COVID-19 pandemic

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## Abstract

The COVID-19 pandemic changed the clinical research landscape in America. The most urgent challenge has been to rapidly review protocols submitted by investigators that were designed to learn more about or intervene in COVID-19. International Review Board (IRB) offices developed plans to rapidly review protocols related to the COVID-19 pandemic. An online survey was conducted with the IRB Directors at Clinical and Translational Science Awards (CTSA) institutions as well as two focus groups. Across the CTSA institutions, 66% reviewed COVID-19 protocols across all their IRB committees, 22% assigned protocols to just one committee, and 10% created a new committee for COVID-19 protocols. Fifty-two percent reported COVID-19 protocols were reviewed much faster, 41% somewhat faster, and 7% at the same speed as other protocols. Three percent reported that the COVID-19 protocols were reviewed with much better quality, 32% reported slightly better quality, and 65% reported the reviews were of the same quality as similar protocols before the COVID-19 pandemic. IRBs were able to respond to the emergent demand for reviewing COVID-19 protocols. Most of the increased review capacity was due to extra effort by IRB staff and members and not changes that will be easily implemented across all research going forward.

## Introduction and Challenges

Institutional Review Board (IRB) offices are generally the key component of larger Human Research Protection Programs. IRB offices are responsible for reviewing all human subject research protocols before the research is initiated. The IRB makes determinations that protocols follow all federal and local regulations before they can start. At most universities, IRB offices have also been transitioning to implement the new single IRB policy of the NIH with both commercial and other university-based IRBs.

The COVID-19 pandemic changed the clinical research landscape in America [1]. IRB leaders at academic health centers knew their offices would have to respond to several challenges associated with this pandemic [2]. The most urgent challenge was to rapidly review protocols submitted by investigators that were designed to learn more about COVID-19. The medical and public health communities had an urgent need for more evidence to make informed decisions about how to improve outcomes for patients with COVID-19. These protocols included treatment trials as well as protocols related to diagnostic testing, acquisition of biospecimens, patient-reported outcomes, and data-only protocols. Federally funded multicenter trials, pharma-sponsored multicenter trials, and investigator-initiated protocols were all being submitted and in need of urgent review. There is a general impression from IRB Directors that research teams submitting these proposals may not have been as experienced with clinical trials or had a history of working together compared to the usual multicenter clinical trial team. In light of this, research teams needed more assistance in submitting protocols than usual. In addition, many research teams needed guidance on how to work with the FDA related to INDs and IDEs. IRBs were also asked to make determinations of what activities could be classified as public health surveillance and which activities were better classified as human subjects research [3]. For many IRBs, this was a task for which they had little experience.

At the same time that demand for rapid review of COVID-19-related research was high, IRB offices had to address the risks and benefits of activities within non-COVID-19-related research protocols. There was limited data on the actual risks for COVID-19 transmission posed by continuing to participate in clinical research. However, many of the studies could not

continue because of the imposition of travel restrictions, limited business activities such as restriction of services in radiology and laboratory centers, and redeployment of research personnel to clinical care. IRBs had to supervise and support teams to substantially reduce the face-to-face interaction for research participants through approaches such as changing to e-consents, remote assessments, or mailing investigational medications to research participant's homes. Many institutions suspended their nonessential research and recruitment, and focused on safely continuing what was possible with research participants who had already enrolled in critical protocols. Many IRBs determined they had to identify a way to inform research participants that there may be some increased risk of contracting COVID-19 through participation in research. Other IRBs determined that this risk was not increased compared to otherwise normal interactions in the community.

As infection rates spread throughout the country, IRBs had to consider the impact on the overall portfolio of research protocols they were required to oversee. IRB committees recognized their first responsibility was to assure that each protocol had an acceptable risk/benefit ratio. The decisions IRBs made also needed to be consistent with the guidance the FDA was releasing about their interpretation of how research teams could balance the risks and benefits for ongoing studies. In many regions, university on-site activities were shut down requiring research support staff to work from home. This necessitated changes in IRB workflows, which were significantly greater in institutions that did not have mature electronic or web-based IRB submission systems.

It is important to recognize that there is often the misconception that IRB review is the only rate-limiting step to clinical trial activation. In truth, it is only one part of a bigger process that often includes other elements such as contracting, coverage analysis, budget negotiation, IND/IDE submission, scientific review, clinicaltrials.gov registration, and the creation of order sets in the electronic medical record. A holistic view of the ecosystem is important if the goal is rapid protocol activation to deal with emergent clinical trials during a pandemic. The management and prioritization of IRB resources are insufficient without similar efforts in the other critical study activation processes. Lastly, the IRB also needed to be involved in the assessment of novel approaches and technologies in the management of COVID-19 clinical trials, such as electronic consenting, video visits, mailing oral investigational drugs to homes, and other accommodations.

For the remainder of this manuscript, the focus will remain on the approach to reviewing and overseeing COVID-19-related research protocols by IRBs. The focus will not address how IRBs or institutions managed the reduction and resumption of activities in non-COVID-19 protocols. Some of those issues are discussed in other manuscripts from this series.

## Methods

To gather information on how IRB Directors managed COVID-19 research, an online survey was administered to CTSA PIs and IRB Directors in the 60 CTSA institutions. The survey covered many areas of clinical research operations including the IRB. The response rate to the online survey from CTSA institutions was over 95%. In addition, IRB Directors were invited to join two online synchronous focus groups for discussions about the questions outlined below. A total of about 12 IRB Directors were present on one of the focus groups.

## Results

### *How were Practices Altered/Redefined/Modified Streamlined to Address the Challenges and Exigencies of the COVID-19 Pandemic?*

IRB offices developed plans to rapidly review protocols related to the COVID-19 pandemic. IRBs were still required to thoroughly review each protocol and make all of the same determinations of whether the protocol should be approved. Informed consent forms still needed to cover all of the components required for individuals to make informed decisions about whether to participate.

IRB Directors established several approaches to meeting the demands for reviewing a relatively large volume of COVID-19-related protocols, particularly therapeutic randomized clinical trials. The survey of IRB Directors at CTSA institutions indicated that approximately 66% of institutions reported their processes included reviews of COVID-19 protocols distributed across all of their IRB committees, 22% assigned all COVID-19 protocols to one committee, and 10% reported creating a new COVID-19 only committee to review these protocols. COVID-19 protocols were thought to have been reviewed more quickly than other protocols. Fifty-two percent reported COVID-19 protocols were reviewed much faster, 41% somewhat faster, and 7% at the same speed as other protocols. IRB Directors were also asked to rate the quality of the review of the COVID-19 protocols. Three percent reported that the COVID-19 protocols were reviewed with much better quality, 32% reported slightly better quality, and 65% reported the reviews were of the same quality as similar protocols before the COVID-19 pandemic. Both in the focus groups and the survey, there were no situations identified where an IRB director indicated that the rapid review led to an unsafe research protocol for research participants.

### *What were the Key Lessons that were Learned? Which, if any, Extraordinary Practices Developed as a Response to COVID-19 Should Now Become Standard, and Which, if Any Raised Sufficient Concerns that They Should Not be Continued or Perhaps Even Considered in the Future in the Face of a Similar Public Health Challenge*

IRB Directors were able to develop review processes that increased the speed of the review. At this time, there is no evidence that the speed of review led to decreases in the quality of the review. However, there has been no rigorous evaluation of the quality of the review before and during the COVID-19 pandemic. Most focus group respondents agreed that since many of the protocols have not concluded, it is too early to definitely determine if there was any reduction in quality. There also was a consistent view that IRB approval did not equate to a protocol that is ready to be activated. In many ways, activation of the study was more dependent on other institutional processes.

Studies addressing the COVID-19 pandemic may have been particularly ill-suited to benefit from single IRB processes. There were many local differences in the burden of the disease in the community, limited business operations impacting types of research that were allowable, availability of remote consent processes, and availability of clinical resources that required an in-depth review of the local context. Single IRB processes are less likely to improve the efficiency of study start-up and more likely to lead to gains in efficiency in the review of the conduct of the studies [4]. Therefore, it is possible that the single IRB process might be of benefit in the near future as many COVID-19 clinical trials

continue to recruit. It is important to note that the CDC and OHRP issued a letter to IRB Directors that they would strongly consider exceptions to the single IRB requirement for COVID-19 protocols (<https://www.hhs.gov/ohrp/determination-exception-single-irb-review-requirement.html>).

IRB offices did gain experience in incorporating additional reviews by complementary committees that might be of value going forward. Many institutions created committees to review COVID-19 protocols that focused more on feasibility, particularly as it relates to the plan for recruitment. These committees either directly or indirectly focused on competing trials and prioritization of trials. Historically, IRB committees focus on the single protocol they are reviewing and do not usually consider the protocol in relation to other protocols except through the review of alternatives to participation. Several institutions required prereview of COVID-19 protocols by a committee that focused on the prioritization of studies. One goal was to identify protocols that were unlikely to get prioritized for recruitment and therefore could be de-prioritized in review by the IRB. Questions about whether a patient could be enrolled in more than one protocol were carefully considered. Through this approach, it would be possible to conserve IRB resources and communicate to the research team that it probably was not worth the time and effort to get such a protocol activated. However, this required highly efficient institutional communication with both investigators and the IRBs to determine study prioritization and thus, the priority of IRB review. IRBs are not trained nor is it within their responsibility to prioritize studies. In addition, IRB committees and Human Research Protection Programs were concerned that patients with COVID-19 not be approached with too many research protocols in light of issues such as fatigue, anxiety, and isolation. Research administrators were looking to cancer centers that were more likely to have a protocol review committee that served some of these functions. In the future, this approach might be expanded to protocols beyond COVID-19 protocols.

One novel aspect of feasibility related to the COVID-19 pandemic was biospecimen collection, especially from an inpatient population. Key considerations included (1) the use of personal protective equipment for research staff; (2) the high frequency of specimen collection for most COVID-19 protocols, (3) challenges around pharmacokinetic-timed blood samples, and (4) the fact that many COVID-19 trials have similar competing high-intensity specimen collection regimens. Even when an external committee was responsible for the prioritization of COVID-19 clinical trials, IRBs had to consider the impact of the totality of sample collection in terms of risks posed to the clinical condition of very ill COVID-19 patients. Other related challenges included balancing the need for in person versus remote consenting of a hospitalized patient by the research team as well as ensuring proper use of witnesses, especially during periods when hospital policy did not allow for any visitors. Lastly, IRBs had to navigate variability in when and how studies decided to use a public health exception.

IRB Directors noted that as the pandemic progressed over several months, it was necessary to begin to prioritize for review based on the type of protocols. Not all COVID-19-related protocols needed to receive priority review. While all agreed that protocols of therapies for COVID-19 should be reviewed quickly, protocols of surveys of healthcare professionals related to the stress of COVID-19 or protocols using data to compare outcomes of patients with various chronic diseases with and without COVID might not need the additional IRB resources necessary for a very quick review. IRBs were also very busy reviewing biospecimen

collection protocols and developing new recruitment tools like COVID-19 volunteer research registries.

The IRB Directors were unanimous during the focus groups in the opinion that the shorter time of review of COVID-19 protocols could not be maintained without additional resources. Overall, the review process did not change for COVID-19-related protocols. These protocols were given permission to be reviewed ahead of other protocols. This was usually done at the expense of quick reviews for non-COVID-19-related protocols. One institution reported it was now taking several months for non-COVID-19-related protocols to be reviewed. Most institutions were not in a position to rapidly bring experienced IRB staff or reviewers into their system. They either asked their IRB staff and reviewers to do more or non-COVID-19 research review effort was reduced. All commented on the stress to their staff and that it would not be possible to continue at this level of activity. Direct and indirect costs for IRB reviews generally fall into three categories: IRB staff, IRB reviewers, and IT support. Research administrators should carefully consider if the increased resources required for rapid IRB review are a good use of funds. In most cases, one would have to assess if it was cost-effective to direct resources to IRB offices to reduce study start-up by a few weeks when most clinical trials take several years to be completed.

Many IRB Directors and institutional leadership took their responsibility for social justice seriously. The challenges of enrolling COVID-19 patients who were more likely to be from underrepresented groups were substantial. Research teams were asked to create materials for including non-English speakers particularly those who speak Spanish. As remote consent procedures were utilized more frequently, there were concerns that those without computers/smartphones not be left out of the opportunity to enroll in studies. In addition, many institutions had to develop new and acceptable procedures for reaching out to these communities so they had the same opportunities to participate in COVID-19 related as other groups. In general, the consensus among IRB Directors was that there was a lack of resources and training for investigators to address these barriers to access to research.

## Conclusion

### *If a Similar Public Health Challenge Occurred in the Future, What Would be the Sequence of Actions You Would Take in Response*

The committee agreed that it might be too early to develop specific recommendations at this time because we are still in the midst of the pandemic and there have not been rigorous evaluations of the research oversight component. However, while the experience is still very real to the IRB community, we offer the following recommendations:

## Recommendations

1. Designating a single national IRB for responding to pandemics will not likely be useful. IRB professionals think that single IRBs have the promise for greater efficiency not in the start-up of multicenter protocols, but in the continued review of the conduct of these studies. As described earlier, both the CDC and OHRP issued a statement that they recommend that COVID-19 studies be given an exception to single IRB requirements if appropriate. Both CDC and the NIH did give an

- exception to the single IRB requirement for COVID-19 trials. The need for prioritization of COVID-19 studies, substantial integration with local health system operations, and assuring the community about the ethical oversight of each protocol all highlight the greater importance of local context in trials to address pandemics. We recommend that the process for gaining an exception to single IRB requirements be clarified and enhanced for quick decisions so there remains flexibility to determining the best IRB approach for studies initiated in response to a pandemic.
2. IRB Directors and staff report that the reduced time to review for COVID-19-related protocols was done primarily because IRB staff and IRB committee members dedicated additional time to the review process. It was not thought this effort was sustainable into the future. In addition, several IRB Directors reported that non-COVID-19 research was delayed in the review process to accommodate the COVID-19-related research.
  3. All experiences at this point relate to the process of study start-up. There is little experience with oversight of the conduct and closeout of the study. Oversight of the entire research process is important so any changes to IRB review should be done with caution. Adding rigorous evaluation to the understanding of how to improve IRB oversight during pandemics is recommended.
  4. Attempts to enhance the speed of study start-up need to focus both on IRB approval and the broader requirements for study start-up and activation. Fast-tracking IRB review may not ultimately decrease the time to study activation. Future efforts should measure if quicker IRB review times lead to increases in amendments early in the study activation phase.
  5. At this time, IRB Directors are not able to identify one specific approach to increase IRB review capacity. It might be useful to rigorously evaluate the benefits of extra review committees, new disease-specific committees, or spreading the burden of review across multiple IRB committees.
  6. IRB committees cannot take full responsibility for the prioritization of studies. Institutions will need to create separate committees for this task. It is recommended that there be close interaction between these committees and the IRBs. Examples include having IRB members on the prioritization committees or ensuring the IRB has some visibility into the status and outcome of the feasibility and prioritization process, perhaps even as a precursor to IRB review to ensure proper IRB resource allocation.
  7. IRBs should encourage the use of innovative remote approaches to recruitment, consent, study/subject management, and monitoring that have been pressure tested during the pandemic as a bridge to potential strategies toward a more efficient and patient-centric approach toward clinical research post-pandemic.
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