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The Real-Time IRB: A Collaborative Innovation to Decrease IRB Review Time

Dr. Ryan Spellecy,
Ursula Von der Ruhr Professor of Bioethics, Center for Bioethics and Medical Humanities, Medical College of Wisconsin

Ms. AnnMarie Eve,
IRB Operations Manager, Office of Research, Medical College of Wisconsin

Ms. Emily R. Connors,
Director of Evaluation, Clinical and Translational Science Institute of Southeastern Wisconsin, Medical College of Wisconsin

Dr. Reza Shaker, and
Joseph E. Geenan Professor Medicine and Director of the Clinical and Translational Science Institute of Southeastern Wisconsin, Medical College of Wisconsin

Dr. David C. Clark
Professor of Psychiatry and Behavioral Medicine, Office of Research, Medical College of Wisconsin

Abstract

Lengthy review times for Institutional Review Boards (IRBs) are a well-known barrier to research. In response to numerous calls to reduce review times, we devised “Real-Time IRB,” a process that drastically reduces IRB review time. In this, investigators and study staff attend the IRB meeting and make changes to the protocol while the IRB continues its meeting, so that final approval can be issued at the meeting. This achieved an overall reduction in time from submission to the IRB to final approval of 40%. While this process is time and resource intensive, and cannot address all delays in research, it shows great promise for increasing the pace by which research is translated to patient care.

Keywords

IRB Performance/Quality/Assessment/Evaluation; Research Ethics Committee/IRB; Clinical Trials; Collaboration; Evaluation Research

Correspondence should be addressed to Dr. Spellecy, Center for Bioethics and Medical Humanities, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226; rspellec@mcw.edu; (414) 955-8763.

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INTRODUCTION

The Clinical and Transitional Sciences Awards (CTSA) Consortium, led by the National Center for Advancing Translational Sciences (NCATS), is charged with accelerating and improving clinical and translational research. Many efforts have been made to document the factors limiting the translation of scientific discoveries such as insufficient resources for translational research, a shortage of qualified investigators, an academic culture that hinders collaboration, and an increasing regulatory burden (Heller & de Melo-Martin, 2009; Pober, Neuhauser, & Pober, 2001; Sung et al., 2003). Guided in part by NCATS, the 57 CTSA award institutions across the country employ a variety of strategies all aimed at accelerating the translation of research, and with the most recent rounds of CTSA awards, there has been a heightened focus and effort toward improving and streamlining methods and processes. To aid this process NCATS developed the Common Measure Initiative (CMI) as a tool for collaborative strategic management, where all 57 CTSAs report data and strategies using a common framework. One area of focus for the CMI has been in the area of regulatory compliance processes, specifically, institutional review boards (IRBs) and IRB turnaround time. While the IRB operation laudably fulfills the duty of protecting the rights and welfare of research subjects, an approach to make the process more efficient has not been systematically fulfilled. Although there are no firm figures on the number of abandoned research studies on the part of clinical investigators due to the regulatory burden involved, there is a widespread sense that worthwhile studies go unpursued due to the burden of regulatory requirements for compliance; this is especially true for translational research aimed at applying basic science discoveries to clinical practice and simultaneously generating hypotheses based on clinical observations (Pober et al., 2001). While investigators and sponsors understand the value and regulatory imperative of human research protection measures (Keith-Spiegel & Tabachnick, 2006; Whitney et al., 2008), they wish for faster IRB review/approval waiting times and note the need for novel regulatory mechanisms to adapt to novel research or sponsor requests such as NIH “just in time” review (Dyrbye et al., 2007; Hom, Podlogar, Stanley, & Joiner, 2016; Keith-Spiegel & Tabachnick, 2006; Mansbach, Acholonu, Clark, & Camargo, 2007; Varley et al., 2016; Vick, Finan, Kiefe, Neumayer, & Hawn, 2005; Whitney et al., 2008).

There are several categories of issues that result in delay in the IRB process. Incomplete applications or failure to respond promptly to IRB requests for additional information needed for review can delay approval, though regulatory support services have attempted to address these (Desai et al., 2017). At other times, the IRB review simply takes a long time due to the complex nature of research studies, experience and knowledge of IRB members, and competing time demands on IRB members and investigators. Other preparatory steps for human subject research – e.g., resource identification, budgeting and contract negotiation, scientific review – which will vary from institution to institution, may delay final approval.

At our institution, all protocols already undergo a rigorous pre-review screening by IRB staff to correct issues that may lead to delays in approval, discussed below. Based on the data presented in Table 1, our team [redacted] identified two specific delays related to IRB processes that we sought to improve; first and foremost delays due to what we call “post-approval communications” for studies that are approved with minor modifications (or

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contingently approved) and second, delays due to “tabling,” both of which arise as a result of issues that arise during deliberations at the IRB meeting. In short, having taken steps to proactively decrease turn-around time *prior* to IRB meetings, we sought to further reduce turn-around time by addressing issues that arise *during* the meeting. At [redacted] studies are tabled if they fail to address one of the eight regulatory criteria or have major ethical concerns. While modification request letters are typically sent out in 1–3 days, additional delays in responding by the study team can more than double this time. As can be seen in Table 1, while tabled protocols accounted for approximately 20% of studies (and 19% in the previous year), studies approved with modifications accounted for 64% of studies. Since the mean difference in total turn-around time between tabled protocols and those approved with modifications was only seventeen days, yet studies approved with modification accounted for 64% of studies, we saw the primary benefit to studies that are approved with modifications, though it is possible that some studies that might have otherwise been tabled due to issues raised in committee discussion were addressed. As noted below, we have enacted other steps to reduce tabling of studies. The challenge then became what can be done to minimize the IRB review duration without compromising the integrity of the review? We previously employed several strategies to reduce turn-around time, including enhanced pre-review of protocols by the IRB office, process mapping the internal IRB processes to identify redundancies, waste, encouraging and training IRB members to resolve issues in advance of the meeting with the study team whenever possible, etc. Here we present our novel approach, entitled Real-Time IRB, and data regarding how this portion of the process can be modified by using a face-to-face approach in real time between the IRB committee and investigators, as well as the resulting decrease in overall time to approval for those studies.

METHOD

This project did not meet the criteria to be considered Human Subjects Research according to the [redacted] IRB Definition of Human Subjects. In the pilot phase of our Real-Time IRB review process, we limited eligibility to investigators who have submitted at least three clinical trial (as defined by NIH) IRB applications in the last two years that were approved by the IRB at the first convened full committee review meeting. The rationale for this was to initially focus on investigators who have put in the effort to learn the institutional IRB policies, become modestly proficient using the electronic IRB application system, and have presented approvable studies (in their original application) in the recent past. The approach is designed for the experienced investigator who can designate a subset of trials that would benefit from faster than usual IRB review, which we acknowledge may have skewed the results for faster turnaround time. This process applies only to full-board IRB reviews, as that is the category of IRB reviews that can be affected by the challenges listed above. At our institution, we have implemented other steps to facilitate faster review for expedited and exempt reviews, which are not discussed here. Eligible investigators, after they volunteered and identified a study that might benefit from Real-Time IRB review, were asked to contact the IRB office and provide the date (within a day or two) of their planned IRB submission. This allowed the IRB time to allocate staff resources for prompt review, so primary/

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secondary IRB reviewer members can be alerted and an IRB meeting date can be selected on or before the day of submission.

As noted above, the [redacted] IRB utilizes an IRB staff pre-review process for all studies that entails a review of the entire IRB application, consent form and attached documents. This pre-review process is the same for all submission regardless of the review process (Real-time or standard convened meeting review). A checklist guides this review and assists in identifying information that needs to be changed, modified or corrected. This review is effective at identifying failure to meet the criteria for approval under the federal regulations and compliance with state law and institutional policies, thus correcting obvious problems that could lead to tabling, though not the nuanced issues or misunderstanding of medical science, disease process or routine care for a specific disease that tend to arise in committee deliberation and may result in tabling or approval with modifications. Through the Real-time IRB review process, we have found that face to face discussion allows for easy identification and resolution of these issues. At our institution, the IRB reviews Real-Time applications within 14–20 days of submission, while non-Real-Time studies averaged 30–45 days, partially accounting for some of the savings, though we do consider those savings as part of the Real-time process. Also, each of four IRB committees routinely convene twice per month on a fixed schedule. While reviewers of the Real-Time protocols were notified that the study would proceed under Real-Time to prepare for the presence of the study team at the meeting (this is not usually the case at our institution), this did not appear to affect completion of reviews or the nature of the review.

The key to this approach is that the investigator and at least one other key research team member, hereafter referred to as the investigative team, must be available to attend in-person the duration of the scheduled IRB meeting. After convened full committee review of the application, the IRB Chair invites the investigative team into the meeting for an explanation and discussion of any/all approval criteria (i.e., 45 CFR 46.111; 21 CFR 56.111; and any special protections requirements) that were not satisfied. Then, the investigative team is given time to address these specific deficiencies at a designated computer station in a different room while the convened full committee continues reviewing other applications. After the investigator has made all the indicated changes in the electronic IRB application system, he/she is invited back into the convened full committee meeting to summarize and demonstrate the changes where a projector displays the altered IRB application for committee members, who can also view the original application on their individual laptops. The committee, if it feels that all their concerns have been appropriately addressed in writing and that all the approval criteria have been satisfied, can at this point vote to approve the application as is or contingent upon minor changes (not bearing on the approval criteria); minor changes may be submitted directly to the IRB chair following the meeting for final approval. In general, the investigative team is given one chance to absorb the committee's concerns, make IRB application modifications, and present those modifications to the convened full committee.

For Real-Time IRB applications that require the sponsor's input or agreement, the IRB office asks the investigative team to contact the sponsor to ask if the sponsor would be able to make a representative available during the meeting – i.e., a representative with authority

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to approve changes to the research. Otherwise, the investigative team may report that IRB-requested changes necessary to satisfy the approval criteria will have to await sponsor ratification at a later date, undoing the convened full committee's ability to reach an approval vote on the same day. Our experience shows that most sponsors are willing to provide this kind of support for the Real-Time IRB review process, and that most recommended changes[1] fall within a sponsor representative's scope of authority. Industry sponsors have just as much stake in achieving a faster, high-quality review/approval process as do academic investigators. Sponsors who are not willing to facilitate this interaction are simply not eligible for the Real-Time IRB process.

RESULTS

The Real-Time IRB review process has been in place since June 2016. To-date 16 studies and 14 investigators have met the criteria to participate. Initial results are summarized in table 2 below.

Mean turnaround time for full committee applications from all IRB committees not reviewed using the Real-Time IRB review process during this time frame was 63 calendar days from submission to receipt of the final approval letter. Mean turnaround time for applications reviewed using the Real-Time IRB interview process is 27.8 calendar days from submission to receipt of the final approval letter, and was 18.76 days when delays external to the IRB process were excluded. Institutional policy requires that letters are sent within 5 days of the committee meeting, though are usually sent within 3.

DISCUSSION

The types of studies reviewed under the Real-Time IRB review process were all greater-than-minimal-risk clinical trials ranging from single-site Investigator initiated studies to multi-site Industry sponsored clinical trials and included both behavioral and medical interventions. The Real-time IRB review process has been found to be suitable for any type of research that requires review by a convened IRB Committee, though it would particularly helpful when funders such as NIH require a "just in time" review.

Conducting a Real-Time IRB review presents several challenges. First, it is difficult to schedule applications for a Real-Time IRB review meeting date that will accommodate the investigators busy clinical schedule. Second, these reviews are disruptive to the usual convened full committee review process due to the impact on the meeting agenda. The initial review, discussion with the study team, and then review of changes requires additional time and flexibility in setting the agenda. This process requires the IRB coordinator to set the meeting agenda differently when a Real-Time IRB review is scheduled since the entire review process for the Real-Time IRB review of one application takes an average of 20 minutes, whereas a non-Real-Time study takes approximately 15 minutes. Additionally, at [redacted], convened full committee meetings are always capped at 2 hour hours in length, so the IRB coordinator must assign the number and type of submissions that are likely to be

[1]Days are calculated in calendar days

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able to be reviewed within the meeting timeframe. This process requires the IRB chair to be experienced in meeting management and directing focused review and discussion of agenda items to accommodate the review of the entire agenda. Note that the Real-Time IRB process requires full, lucid documentation of the investigator's changes (clarifications, explications, changes, and answers) in the IRB application (a secure electronic management system) before the IRB will entertain re-consideration and a second vote. While the investigator summarizes the responses he/she has made to the IRB's initial review after returning to the same meeting, full committee review of the written responses is a necessary step, as we have defined the process. This reflects our belief that the investigator's verbal responses during the meeting (whether recorded or not) and IRB minutes capturing those responses are not sufficient documentation to alter an IRB vote from table or approve with modifications to outright approval.

Feedback regarding the Real-Time IRB review process from the IRB primary and secondary assigned reviewers is that they feel pressure to complete their reviews sooner in an attempt to seek clarifications and modifications for administrative changes from the investigator in advance of the meeting to narrow the scope of questions and modifications that require discussion during the convened full committee meeting. Feedback from the IRB chairs is that the review of an application through the Real-Time IRB review process does add time to an individual meeting and complexity to meeting management; however, the IRB chairs and IRB committee members alike have provided overall positive feedback regarding the Real-Time IRB review process. IRB committee chairs and members have identified that at least half of the submissions reviewed through this process to date would have received a table decision had the investigative team not been present to explain procedure and clarify misconceptions.

Lastly, there are other ancillary safety and compliance reviews required by the institution that occur either serially or subsequent to IRB review and these reviews are often yoked to final IRB approval. The Real-Time IRB review process puts additional burden and pressure on these departments and compliance offices to re-arrange their review process to accommodate a faster turn-around time for these projects. While departmental and ancillary safety committee reviews are performed prior to the application being routed to the IRB office in the electronic system, and investigative teams begin contacting the safety committees to request an expedited review because they were scheduled for the Real-Time IRB review process, the IRB office began to receive calls from the safety committees wondering what this review process was and then began trying to accommodate the investigative team requests. To avoid this confusion, the IRB office now notifies the safety and compliance committees of each application scheduled for Real-Time IRB review in advance of the review. However, external issues such as finalizing contracts and state radiation variance approval were not and cannot be addressed by Real-Time review. These are captured by the third row in table 2, which shows these five studies had longer, widely ranging approval times. Also, different institutions may have different requirements for ancillary reviews, though we view this process of discovery as positive as we can now identify delays in final approval that our outside the IRB process and the institution can direct efforts at decreasing those barriers.

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While there are challenges to implementing this approach, preliminary data suggest this approach can help contribute to more efficient IRB review, specifically working to reduce delays due to “tabling” a study and delays due to post-approval communications for those conditionally approved with minor modifications. Specifically, as shown in Table 2 above, the average time from initial submission to final approval letter for all Real-time studies was 27.8 days, and for those studies that did not have additional barriers outside of the IRB process (i.e. contractual issues with the sponsor), that time decreased to 18.76 days, compared to 63 days for studies not reviewed via Real-time and 62.4 days for studies reviewed via Real-time, but still had external issues that delayed the final approval letter.

The Real-Time IRB review process has been most effective not based upon the type of research study being presented, i.e. investigator initiated or industry sponsored, but on the investigator and their team. The reviews that have been most successful, i.e. shortest time to final approval letter, were the ones submitted by an investigator and research team who understand the research study being submitted for review, know the institutional IRB process and is responsive to and communicates regularly with the IRB office in advance of the review, regardless of the category of study (phase I, II, or III clinical trial) or department. The discussions between the study teams and the IRB committees have been fruitful, at times resolving misconceptions on the part of the IRB or the study team, and all were resolved in the meeting. This indicates that while an IRB can create a process that reduces time to final approval letter by 70% (excluding those studies with external, non-IRB delays), in our limited experience thus far, barriers remain and it is essential to provide guidance to investigators and their teams to take full advantage of such a process. An additional limitation is that this is a pilot study, and thus the overall impact on total IRB turnaround times is limited due to the fact that Real-time reviews comprise a small percentage of total reviews. This process has demonstrated a significant impact on IRB turnaround time, though given the limitations in implementation due to IRB cost in time and money, there is a limited class researchers and study teams for which this is realistic.

In order for this process to be successful it requires an equal amount of time investment between the IRB office and committees, investigator and their team, the sponsor of the research, and other institutional safety and compliance offices. If one of these stakeholders is not willing to work quickly and in coordination with the others, this process only slightly decreased approval time. However, when all stakeholders are willing to work quickly and collaboratively, the results are dramatic, lowering final approval from 63 days to 18.76 days on average, a decrease of 70% in total time from IRB submission to final review, which results in studies being implemented one and a half months sooner, answering NCATS call to accelerate the pace of translational research.

BEST PRACTICE

Given the resources required for a Real-Time review, both financial and time, it is important to carefully consider which studies are reviewed via this mechanism. Experienced study teams who can submit complete applications and work quickly to make changes as essential, but it is also important to consider what categories of studies might benefit most from Real-

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Time review, such as NIH funded studies that require Just In Time review as this process is not without cost to the institution in time spent by IRB staff, membership, and study staff.

RESEARCH AGENDA

As this is a pilot project, more work needs to be done in this area, particularly at other institutions. As we were able to learn discover that contract finalization through grants and contracts was a delay beyond IRB control, other IRBs may identify other delays. By replicating this process at other institutions, IRBs can share best practices to decrease delays.

EDUCATIONAL IMPLICATIONS

This pilot study demonstrated the ability to radically decrease the turnaround time for IRB reviews. It is necessary to educate PIs and study teams (i.e. attend department meetings, posters, announcements at research meetings, etc.) about key delays identified and, in our experience, educate PIs about the availability of this process so that they can utilize it.

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Table 1

All Full Committee Reviews June 1, 2016-June

IRB review outcome	Time from submit to final approval range - days	Time from submit to final approval median - days	Time from submit to final approval mean - days	Time from IRB receipt to final approval range - days	Time from IRB receipt to final approval median - days	Time from IRB receipt to final approval mean - days	% of PROs
Tabled	46–295	104	111	45–289	85.5	102	20.7%
Approved with mods	27–300	74	91	20–300	65	85	64%
Outright Approval	8–212	41	58	7–212	37	49	15.3%

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Table 2

Review Times

This table illustrates the review times for Real-time and non-Real-time reviews. Time to initial review and time to final approval letter are noted.

Review	From submission to full committee review (days)	TOTAL DAYS from submission to final approval letter
Non-Real-Time	37 (mean)	63 (mean)
Real-time (n=18)	17.2 (mean) 17.5 (median)	27.8 (mean) 21.5 (median)
Real-time with external issues (n=5)		62.4 (mean) 41 (median)