Published in final edited form as:

J Empir Res Hum Res Ethics. 2018 April ; 13(2): 139–144. doi:10.1177/1556264617752725.

Regulatory Support Improves Subsequent IRB Approval Rates in Studies Initially Deemed Not Ready for Review: A CTSA Institution's Experience

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Abstract

We evaluated the impact of a regulatory support service (known as the Regulatory Knowledge and Support Program; RKS), part of the Medical University of South Carolina's Clinical and Translational Science Award, on the success of IRB applications that have previously been deemed by the IRB to be Not Ready for Review (NRR). At the time of this evaluation, 77 studies had been deemed NRR, 53 of which came from trainees and junior faculty. All of the applications that received regulatory support either received IRB approval or were deemed to not be research, and therefore did not require IRB review. 39.1% (n=18) of the research teams who did not accept regulatory support successfully received IRB approval. Providing regulatory support, particularly to trainees and junior faculty, may be associated with better success in obtaining IRB approval as well as preventing the unnecessary submission of projects that are not research and would therefore not require IRB review or approval.

Keywords

Institutional Review Boards; clinical research; translational research

INTRODUCTION

Institutional Review Boards (IRBs) are required by United States federal regulations (DHHS Protection of Human Subjects, 2009) to review and approve research involving human subjects before such research may be initiated at a given institution. Thus, one of the rate limiting steps for successful study implementation is the time it takes to obtain IRB approval. The IRB review process has at times been characterized as “slow and cumbersome” and IRBs have been accused of unduly delaying research (Silberman and Kahn, 2011). Silberman and Kahn (2011) analyzed data from 25 studies encompassing data from 631 IRBs and 336 protocols that reported IRB efficiency and time to IRB approval. IRB review times ranged from 13 to 116 days, with an average range of 220 days between shortest and longest time to approval for any given study. Most of the studies (18/25) were multisite protocols across multiple IRBs. However, it is unclear from where the sources of the delays lie. The efficiency with which an IRB is able to complete a review and approve a submitted research proposal is dependent upon multiple factors including the number of proposals reviewed, the complexity of the proposed research, the quality of the submitted application, as well as the size of the IRB staff completing the reviews. Although many studies report the overall time to IRB approval, there is no delineation of the time each party (e.g. investigative team, IRB staff) contribute to the overall time. There are no data on the quality of the applications, the time it takes the IRB staff to review or the time it takes the research team to respond to IRB queries or requests for changes. Even for multisite trials in which a coordinating center or lead investigative team has provided template documents for a local principal investigator (PI) to use, there is still significant variation in what the local PI ultimately submits for IRB review.

Submitted applications to an academic institution’s IRB can be prepared by a wide variety of investigative teams that are likely to have varying degrees of experience in preparing an IRB submission. It has been our experience that some research applications are so ill-prepared that they are not ready for IRB review in their initial form and require substantial editing in order to have an application that can be reviewed and potentially approved. Gross examples contributing to ill-prepared submissions include omission of essential documents, inadequate description of the proposed research procedures, or lack of background/justification for a study that is greater than minimal risk. Having IRB members or staff review applications in this condition increases the time for review and negatively affects overall IRB efficiency and work flow. Researchers submitting applications of this quality are often unfamiliar with the regulatory requirements and could benefit from guidance from experienced research staff.

To address this translational hurdle, we developed a novel approach for addressing proposals received in a state in which they would be deemed Not Ready for Review (NRR) and returned to the investigators with the recommendation for consultation by an experienced regulatory team who could assist in the development of the proposed research and the IRB application. Consultations are performed by the Regulatory Knowledge and Support (RKS) program supported by a Clinical and Translational Science Award (CTSA). MUSC’s RKS program is staffed by two Certified Clinical Research Professionals and a Certified Clinical Research Associate, all of whom have significant regulatory experience. These individuals handle most of the regulatory consults, including navigating the electronic IRB submission

system, responding to IRB reviewer comments, helping with lay language in consent documents, identifying documents needed for submission, providing feedback on documents for completeness/accuracy prior to submission, providing guidance on the proper type of IRB review, and helping with determinations of whether a project is research or not. The Associate Director of RKS is Chair of one of MUSC's IRBs and provides guidance on complicated regulatory issues and assistance with protocol writing. The Director of RKS is the Assistant Provost for Research Compliance and provides oversight of the program with monthly face-to-face meetings. Herein we describe how we implemented this change to our IRB processes and the impact the regulatory consultation service had on successful resubmissions to the IRB.

METHODS

Rationale and Definition of Not Ready for Review

The Office of Research Integrity (ORI) at the Medical University of South Carolina established a policy for determining a submitted IRB proposal to be Not Ready for Review (NRR) as part of its quality improvement program. This policy was initiated by IRB staff due to the number of protocols that were submitted without essential details required for review and approval. Rather than committing IRB staff time to enumerating the corrections required to the application, the application is deemed NRR and is referred back to the investigator with a recommendation for consultation with RKS staff. MUSC leadership, including the Vice President for Research has been fully supportive of this policy. Applications determined to be NRR are those that are prepared in such a way that the proposed research procedures are unclear or large components of the application are missing (examples of scenarios are shown in Table 1).

Process for Handling of Proposals Deemed NRR

All IRB applications are routed electronically and receive a preliminary review by an IRB administrator prior to being forwarded to an IRB Chair or other IRB reviewer. When an IRB application is deemed NRR by an IRB administrator, it is returned to the PI with a general description of the deficiencies identified (e.g. inconsistent or unclear description of procedures such that the reviewers are uncertain of what is being proposed). The PI is also given a recommendation to seek consultation from the free on-campus research support services. A simultaneous email notification is sent to RKS staff apprising them that an application has been deemed NRR. Subsequently, the RKS staff reaches out within one business day of email receipt to offer assistance. There is no requirement for the PI to get assistance prior to re-submitting the application to the IRB. During consultations, RKS staff spend a great deal of time educating research staff on US federal regulations as well as institutional policy. For the NRR consultations, RKS staff spend an average of 3.3 hours (*SD* 1.8) per application. The first hour is typically a face-to-face consultation, with subsequent consultations occurring either via phone or providing comments on corrected documents via email. RKS staff show research staff how to access MUSC protocol templates and standard wording for consent documents. They may provide general edits or suggest phrasing for clarity, but they do not write the documents for the PI. The RKS staff works very closely with the IRB, and if there is an overtly challenging regulatory question, RKS staff will

consult the IRB and/or the Associate Director of RKS (who is also an IRB Chair) before providing guidance to the investigator. If needed, the RKS staff may consult with other experts on campus for issues regarding intellectual property rights or investigational drug services. For applications submitted by trainee PIs, the IRB advises the PI to talk with the PI's mentor to receive guidance on how to provide a complete application. There is also an offer to arrange a meeting with the IRB Administrator and/or Chair as part of the NRR notification to the PI. Additionally, when RKS staff meet with a trainee, they request that the PI's mentor attends the consultation as well, to ensure that the mentor understands the regulatory concerns and can appropriately support the trainee in resolving them.

Metrics

The RKS staff tracks all IRB applications deemed to be NRR to ensure that they have reached out to offer support and guidance as well as to track the effectiveness of the RKS program. Relevant attributes of the submitted proposals are recorded including the type of submission (e.g. exempt, expedited, full board review), and the investigative team (e.g. department, academic rank, whether there is a mentor). Key metrics include whether a regulatory consultation is requested, the eventual outcome (e.g. resubmitted and approved, never resubmitted, or withdrawn), and the time to approval.

Statistical Analyses

Two-sample *t* tests were used to compare IRB turnaround times between those who did and did not utilize RKS services.

RESULTS

Since the launch of the NRR policy in June 2015, there have been 1420 applications submitted to the IRB of which 77 (5.4%) were deemed NRR. If only investigator-initiated proposals are included (i.e. excluding industry-sponsored applications) those deemed NRR represent 5.2% of submitted proposals. Of the 77 submitted proposals, most were submitted for either expedited review (66.2%; *n*=51) or full board review (18.2%; *n*=14). The remaining applications were submitted as either exempt (10.4%; *n*=8) or not human research (5.2%; *n*=4). It is important to note that at MUSC, it is an institutional requirement for an IRB member to review and approve exempt research. As a teaching institution, individuals new to research may not have sufficient understanding of the regulations to submit an application at the appropriate level of review. There have been applications submitted as exempt that were actually deemed greater than minimal risk, requiring full IRB review. An IRB member also reviews and acknowledges Not Human Subjects Research for the same reason. MUSC is accredited by the Association of the Accreditation of Human Research Protection Programs (AAHRPP).

Only 40.2% (*n*=31) of investigators requested regulatory assistance through RKS. The eventual outcomes clearly favored those who sought consultation (Figure 1) with 100% achieving either approval or recognition that the proposal was better suited to a quality improvement project and did not represent human research. None received a second NRR determination. This compares to a success rate of only 39.1% (*n*=18) for those applications

in which a regulatory consultation was not pursued. For the remaining proposals in which consultation was not requested, 6.5% (n=3) were resubmitted and again deemed to be NRR, 13.0% (n=6) remain unresolved, and 39.1% (n=18) were ultimately withdrawn.

Academic rank of those submitting NRR applications is listed in Table 2. Full Professors were most likely to refuse help (83.3%; n=10), however, they were also the group most likely to be successful without consultation from RKS (83.3%; n=10). On the other hand, 66.7% (n=18) of Assistant Professors refused RKS support, and only 22.2% (n=4) of those successfully obtained IRB approval on their own. Over half of this group (n=13) either withdrew their studies (n=9) or have not yet resubmitted their NRR application (n=4). Of the trainee projects, 30.4% (n=7) did not seek guidance from RKS, and of those, 42.8% (n=3) were successful without RKS guidance. Many investigators are a bit surprised when their application is deemed NRR. When they take the time to read what was submitted, many are able to identify the inconsistencies or lack of clarity and are able to address the issues and ultimately get approval. However, other investigators, often those who are primarily clinicians, do not understand the regulatory differences between research and clinical practice. These individuals often get frustrated with the IRB approval process and may be more likely to withdraw their IRB application. There have only been a few investigators who have gotten upset or defensive about receiving a NRR. When this happens, these individuals are referred to either the ORI director or the Assistant Provost for Research Compliance.

Since the majority of studies submitted were for expedited review, we evaluated the time from first submission to the IRB to approval for this group of studies (n=51). The average total number of days to approval was 73.4 days (*SD* 32.6) for those who received RKS support, compared to an average of 178.6 days (*SD* 176.0) for those who did not receive RKS guidance ($p=0.036$). The majority of the time for both groups was the time the application spent with the research team, which was an average of 31.5 days (*SD* 25.2) for those who received help from RKS staff, and an average of 121.6 days (*SD* 158.4) for those who did not get RKS help ($p=0.041$). In comparison, during the same time frame an additional 593 expedited studies were approved; the average total time to approval was 57.0 days (*SD* 50.0), and the time the application was with the research team was an average of 21.9 days (*SD* 34.1).

DISCUSSION

The review of a research proposal by IRB staff often results in questions regarding clarifications or alterations before deemed appropriate for approval, but some submitted proposals require major revisions. As the mission of the IRB is to provide oversight to the conduct of human research, the work required to repair such applications is a poor use of IRB staff time. When it is evident that investigators need guidance in the further development of an IRB application, this activity is better provided by an institutional resource dedicated to that purpose. At our institution that service is provided by our RKS program, which is supported by our CTSA. The service is provided free to investigators but it is not a required consultation; rather it is voluntary and why we chose to recommend consultation when an application is deemed NRR.

The outcomes, in terms of IRB approval, clearly favor those investigators who seek regulatory consultation from RKS. Of those who sought support, all have either received IRB approval or were deemed to not be research and were withdrawn. The great majority of NRR applications have not been approved when the investigators elect to go without regulatory assistance. It could be argued that many of those protocols would never come to completion; indeed, approximately one-third were withdrawn, suggesting the enthusiasm of the investigator for that proposal was rather low. Nearly one-quarter remain unaddressed (i.e. neither resubmitted nor withdrawn) and it may be that many would also have gone uncompleted. Consequently, if a large fraction of these studies would never be completed, this could also be seen as a poor use of IRB effort, to devote time to studies that will never result in meaningful findings. Although the IRB turnaround time was long for both groups, it is important to remember that these studies were originally not ready for review, and required significant revision before they could be resubmitted. IRB turnaround for studies that were ready for review was similar to others (Desai et al, 2017), however, MUSC investigators kept the applications longer prior to resubmitting to the IRB.

The majority (68.8%) of the NRRs came from trainees and junior faculty (instructors and assistant professors). Although both IRB staff and RKS staff provide educational presentations on how to complete a successful IRB application, they are not always done at a time the trainees are actively working on an application. Without appropriate context, the information tends to get lost. Training modules are imbedded within the IRB application system, explaining the intent of each question, however it is unclear how many investigators avail themselves of these materials. Additionally, trainees and junior faculty are less likely to have study coordinators to help them with their applications and consent documents.

Other institutions have also reported poor quality of research applications submitted by trainees (Klitzman, 2013, Cleaton-Jones, 2010). Although trainee investigators must have faculty mentors to oversee the research at our institution, some mentors are more knowledgeable in the conduct of research than others. In requesting that the mentor accompany a trainee to the consultation with RKS staff, it is hoped that the RKS staff are able to provide guidance on regulatory requirements to the mentor as well.

Although the number of applications deemed NRR represent a minority of the overall new applications to the IRB, the IRB staff has precious little time to devote to the correction of severely deficient applications. It is also possible that many more applications could have been deemed NRR but the IRB staff was sensitive to using that distinction for only the most severely deficient applications. Establishing the threshold criteria for an NRR distinction could be tweaked as we get a better appreciation for the types of protocols (or investigators) that consume larger amounts of IRB effort, perhaps by looking at those applications that have the greater number of requests for corrections before final approval. This can be determined through continued evaluation of the metrics available within our electronic IRB management system (Obeid et al, 2016) which tracks key performance indicators and provides detailed data extracts for each application.

In conclusion, our institution has established a policy of defining those IRB applications which are clearly not ready for review and would result in a poor use of IRB effort in order

to repair the application to be considered approvable. We have provided opportunity for regulatory guidance to improve those applications. When utilized, it is associated with a high rate of success, much greater than when the investigators elect to address the problems themselves. This practice may very well help to improve the efficiency of the IRB and is translatable to other academic centers.

Acknowledgments

The project described was supported by the NIH National Center for Advancing Translational Sciences (NCATS) through Grant Number UL1 TR001450.

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BEST PRACTICES

Having a mechanism to “triage” IRB applications as being not ready for review may be an effective way to decrease IRB workload. Providing regulatory support, particularly to trainees and junior faculty, may be associated with better success in obtaining IRB approval.

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RESEARCH AGENDA

Additional research is needed on the IRB approval process and how regulatory support services may aid in that process.

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EDUCATIONAL IMPLICATIONS

Our data demonstrated that trainees and junior faculty are in the greatest need for regulatory guidance. Providing hands-on training at the time trainees/junior faculty are starting to devise research projects may circumvent some of the regulatory hurdles, and allow those individuals a more positive experience with the IRB submission process.

Figure 1:
Disposition of Studies Initially Deemed Not Ready for Review

Table 1:

Scenarios in which the IRB may determine that an application is not ready for review

<ul style="list-style-type: none">• Missing or inadequately prepared essential documents, including:<ul style="list-style-type: none">– protocol– consent form/s• Inconsistent or unclear description of procedures such that the reviewers are uncertain of what is being proposed• Project described does not seem to constitute research as written• Recurrent errors throughout the application and attachments to the extent that a detailed review and revision of the entire application is needed• Conflicting information provided across the protocol, informed consent form, and/or other supporting documents
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Table 2:

Academic Rank of PI for NRR Applications

Investigator Rank	Number	Number who requested RKS Consult
Trainee	23	16
Instructor	3	1
Assistant Professor	27	9
Associate Professor	12	3
Professor	12	2