Published in final edited form as:
Clin Trials. 2013 October ; 10(5): 761–766. doi:10.1177/1740774513500080.

How Good Does the Science Have to Be in Proposals Submitted to IRBs?: An Interview Study of IRB personnel

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Abstract

Background—IRBs have been increasingly criticized for how they review protocols, but how IRBs perceive, and make decisions about, the quality of the science of protocols has not been examined.

Purpose—To explore how and when IRBs view and make decisions about the quality of the science of studies they review.

Methods—I contacted the leadership of 60 IRBs (every fourth one in the list of the top 240 institutions by NIH funding), and interviewed IRB chairs, co-chairs, administrators and a director from 34 (response rate=55%), and an additional 7 members.

Results—Interviewees faced several ambiguities and questions concerning the quality of the science of protocols. IRBs are often not sure how, and to what extent to evaluate the science of protocols; whether the science should be "good enough" (and if so, what that means) *vs.* as good as possible. Federal regulations state that IRBs should ensure that risks are minimized, and commensurate with benefits. Thus, at times IRBs feel that changing the science is ethically necessary. But IRBs also then struggle with whether to adopt a higher threshold; 1) that social, and thus scientific *benefits be maximized*; and 2) that scientific efforts and resources should not be wasted. Committees face dilemmas – e.g., if a "perfect" study is not feasible. For protocols already approved elsewhere (e.g., by the National Institutes of Health [NIH]), IRB's vary in how much they feel they can request alterations; and sometimes make changes nonetheless. Larger institutional contexts and biases can shape these issues, and IRBs differ in how much they are "pro-research", and have sufficient expertise. IRBs at times also approve studies despite reservations about the science.

Limitations—This study includes interviews with IRBs, but not observations of IRB meetings.

Conclusions—IRBs often face ambiguities and conflicting goals in assessing scientific quality. Many IRBs try to improve the science beyond what the regulations mandate. These data have important implications for improving practice, education, research, and policy.

Keywords

research ethics; research integrity; conflicts of interest; risk/benefit assessment; qualitative research

Background

IRBs have been criticized for how they review the scientific quality of protocols, yet how IRBs themselves view and approach this issue remains unclear. Regulations mandate that IRBs minimize risks and ensure that these are reasonable in relation to anticipated benefits and to the importance of the knowledge that may be produced.[1] IRBs must also "be

sufficiently qualified through the experience and expertise of its members" to evaluate studies.[1]

IRBs recommend changes in protocols,[2] but they vary widely in lengths of time to approval, types of review (e.g., exempt, *vs.* full review), number and types of changes,[3,4,5,6,7,8,9,10,11] requests for information,[12] changes to consents,[10] reading levels of consent forms[13] and responses to hypothetical questions.[14] IRB changes can decrease response rates, and thereby reduce generalizability.[15] Past published studies have examined logistical aspects of IRBs, particularly sociodemographics of chairs and members,[3-9,16] but not *how*, *why* and *to what extent* IRBs make decisions concerning the quality of science in protocols they have reviewed. Extensive literature searches on Medline and Google Scholar revealed no published studies exploring what challenges and questions IRBs see themselves as facing in making these evaluations, and what factors are involved – e.g., how IRBs define "sufficient expertise."

Thorough Medline and Google Scholar literature searches suggest that while several scales have been used to assess the quality of clinical trials, these instruments vary widely. Most have not been adequately developed or tested for validity and reliability,[17] and no "gold standard" exists,[18] causing problems, and affecting the outcomes of meta-analytic studies.[19] Research quality may be reflected indirectly in the number of articles that result and the impact factors of journals publishing these,[20] but these assessments are *post-hoc*. Broad general principles have been suggested (e.g., studies should be "well designed",[21] and better benchmarks are needed (e.g., for funding decisions),[22,23] yet no clear consensus or measure has emerged.[18,19,24] In 2011, the Advanced Notice of Proposed Rule Making (ANPRM),[25] recommended changing U.S. IRB regulations, but didn't mention IRB roles in evaluating science.

I recently interviewed IRB chairs, members, and administrators, concerning their views and approaches concerning research integrity (RI), broadly defined, as part of which many other related issues arose – e.g., concerning IRBs' conflicts of interest (COI) and inter-IRB variations.[26,27,28,29] Many interviewees also discussed issues concerning the quality of science – e.g., how IRBs view the quality of science across a wide range of protocols, what standards they use, how they ensure and balance the quality of science against other goals, and view their role in these regards. It was felt that the attitudes and dilemmas of IRB personnel as expressed in these interviews could provide directions for future systematic research in this domain.

Methods

In brief, as described elsewhere,[26-29] I contacted the 60 IRBs (every fourth one in the list of the top 240 institutions by NIH funding), and conducted 46 interviews from 34 institutions (response rate = 34/60 = 55%): 28 chairs and co-chairs, one director, 7 IRB members, and 10 administrators.

Appendix A presents portions of the semi-structured interview guide. I used grounded theory[30] to identify and highlight key themes that emerged multiple times strongly and clearly across interviewees. The Columbia University Department of Psychiatry IRB approved the study. All interviewees gave informed consent.

Results

What is the IRBs' role in evaluating the science of a proposal?

IRBs wrestle with what their role is, and how to decide – whether their task is to alter the quality of the science, and if so, when, how and to what degree.

> Is it the committee's role to get involved or not? If the study is poorly designed, does that increase the risk for subjects, and should the study not occur? The other argument is: our job is just making sure they're applying the regulations and treating subjects ethically. Who are we to criticize someone's design? Should it matter if it's been more or less invasive? **IRB23 (Administrator)**

IRBs thus confront several questions regarding their roles: whether their job is to ensure that the quality is adequate; or to alter or stop inadequate studies; and whether these roles should increase for riskier studies.

IRBs are aware that PIs are wary of the IRB widening its scope.

> Researchers feel that the IRB often oversteps its bounds...going beyond just looking at risks and benefits, and actually dipping in – trying to dictate researchers' protocols. It's a fine line. **IRB35 (Community Member)**

What scientific standard to use?

IRBs face quandaries about whether protocols should be "*good enough*" to justify the risks *vs.* as good as possible. IRBs confront questions of whether simply to follow the federal regulations, narrowly defined (i.e., minimizing risks, and ensuring that the risks are commensurate with benefits), or "go beyond the regulations", and maximize protocols' potential social benefits by enhancing the quality of the science. Generally, almost all IRBs felt justified in altering protocol design if they felt the study may not justify the risks. Yet studies' eventual benefits are unclear because the outcomes and longer-term impact are unknown.

A moderate number of interviewees felt that their IRBs were "pro-research" and at times used somewhat less strict standards (e.g., the science doesn't "have to be great."). These IRBs' leniency, often reflected the chair's or IRB members' attitudes, and/or the institution's mission and ethos.

> A study would have to have something really substandard or really bad for *us* not to approve it. *It doesn't always have to be great science*. Sometimes, studying a little spin on conventional therapy is fine. We think, "This is not a great comparison," so it's not great science; but it's what the investigator wants to do – as long as it's not *egregious* or really increasing the risk, or giving other potential subjects inferior care. In general, we don't give investigators that much of a hard time. **IRB14 (Chair)**

A few interviews said that studies may not harm subjects, but that aspects were unnecessary, and should thus be eliminated or altered.

> We were able to convince an investigator to drop observations of students in a school...it wasn't going to generate the type of information he wanted, and was just poorly thought out. We were able to convince him, because the *two scientists* on our board were in agreement. It wouldn't really have harmed subjects. It was just unnecessary. **IRB26 (Administrator)**

Other interviewees felt they had a larger role in advancing science, and should compel researchers to avoid studies that investigate easy questions, are not the most promising, and "waste" scientific resources.

> We're just trying to prevent investigators from slipping through the easiest, least sought out ideas, and wasting a tremendous amount of effort on something that other researchers think is really just not the direction we should be going. **IRB43 (Member)**

IRBs then face questions of whether to permit imperfect protocols, if these may lead to later, better-designed studies. But whether these later studies are performed is unknown and not monitored.

> If you're going to need 1,000 patients for this study to be effective, and you have fewer, but the risk is negligible, should it be approved? I want to encourage research, but know you're just going to get indeterminate results. I wrestle with that a lot, and decide *case-by-case*. I'd like to say, "Don't bother: it's not going to be level one data." But then I think: success builds success. If you let someone do a study, maybe they'll do the definitive study next. So, if the risk is negligible, I usually lean to saying, "Just do it." But that's probably my bias, being a clinician. Others say, "Why bother...it's going to be an indeterminate study," or, "It's not perfect science." So, studies get squashed. But sometimes the perfect study isn't going to get done. It's too laborious or not feasible. Each study can't be perfect. Theoretically, there's some happy medium. **IRB42 (Member)**

Should studies pursue goals other than science?

IRBs face particular problems with studies primarily aimed at goals other than scientific value, such as helping industry sponsors or students' education. With certain industry-sponsored studies (e.g., "me too" drug and post-marketing protocols), IRBs struggle with weighing relatively low perceived scientific and social benefit. Some members wondered if academic medical centers should even participate in studies aimed mostly at marketing products:

> The purpose of the study is to give the drug to clinicians free, so they can enter five or ten subjects from their practice...But the true purpose...is to assist with the marketing. **IRB12 (Chair)**

Sometimes low quality research was submitted by students, but permitted because of institutional pressures:

> We have had some intense screaming matches with certain departments. I am heartsick that somebody is earning a Ph.D. for a particular study because the science is atrocious...It's not my charge as chair, but when I see substandard...rigor and depth [for] a Ph.D....I have enormous problems. I have rattled cages – all the way up to the President – with little avail, because there's pressure to have high enrollment. **IRB21 (Chair)**

> We used to review proposals for a local college...Many of their studies were inane. Their methodology was fine, but the studies were just silly...Most of it had to do with early childhood education. They'd study if kids roll on balls and prove their balance...We would roll our eyes, but approve it, because it was to get a Master's. **IRB20 (Chair)**

Separate scientific review?

Many institutions have separate scientific reviews, but these vary widely in quality and scope, and at times IRBs thus nevertheless also review the science:

> Cancer investigators first get questions from the Scientific Review Committee, and then proceed to the IRB...PIs complain: “I had to answer all those questions for the Scientific Review Committee, and now the IRB is also asking me scientific questions. What's the deal?” I say, “Part of the IRB's charge is to make sure that subjects are putting themselves at risk for studies that are going to have a scientifically valid outcome.” **IRB14 (Chair)**

IRBs varied in whether they required academic departmental pre-review prior to IRB submission, and if so, who performed them. The quality and thoroughness of such assessments varied from substantive to mere formality. Departmental reviews can be perfunctory, vouching for researchers’ logistical support (space and time), rather than scientific quality.

> Department chairs are supposed to review protocols scientifically, but most have never even *looked* at it. They say, “Oh, it's fine.” So the *biggest frustration* is the issue of scientific value. We end up spending a lot of time *fighting* about it: is the study design adequate, is the sample size going to be meaningful? If there's no personal benefit, there should be no tolerable risk. But I don’t think those should be IRB issues. It should be vetted already. The IRB issue should be: given that this is scientifically valid, does the consent form explain it. **IRB3 (Chair)**

Some departments may simply approve protocols pro forma, “signing off” on protocols without fully reading them. (“A few chairs actually do look at it...I don’t know when they come up with the time.” [**IRB9 (Director)**])

What if studies were approved elsewhere?

IRBs vary in how much they feel they can alter protocols already approved by federal or other institutions. Some IRBs readily accept such studies:

> Some IRBs won’t believe that a study funded by NIH or NSF is scientifically sound, so they’ll take it upon themselves to evaluate the science. We try not to do that. **IRB28 (Chair)**

IRBs sometimes refrain from asking for changes in NIH-approved or multi-site studies because of the logistical burden of such requests, or the belief that such changes might be impossible. When unsure, some IRBs consider how important the changes they want are.

> We won’t like parts of an industry-sponsored multi-centered study. But if we want to change the design in any way, we couldn’t, because it's already at 50 or 100 centers. Then, we have to decide either that our objectives are *so strong* that we’re not going to let the investigator be part of it, or that we can live with the study the way it is. Most of the time, we can’t change an industry-sponsored protocol unless it's just at a few centers. A big multi-centered trial isn't going to change the protocol a few times a year for each committee. **IRB17 (Chair)**

In a few instances, IRBs felt justified in requesting changes in multi-site studies approved elsewhere (e.g., by the NIH). One IRB was the only one to complain about a multi-site study requiring patients to agree to enroll in a registry before entering a study.

> We were the only IRB that found issue with that – which amazes me. They thought it was not an IRB issue, because it was a registry – not a research study. But isn’t

this an invasion of a parent's right to choice and confidentiality? The researchers then rescinded it. A lot of institutions would have OK'd it. **IRB13 (Administrator)**

Conclusions

IRBs face dilemmas and ambiguities in assessing the quality of science – determining what roles and standards to use. Some IRBs see needs to alter the science – to ensure that risks are minimized, and commensurate with benefits[1] – by increasing the potential scientific benefit. But IRBs also struggle with whether the benefits should be maximized further (e.g., that the science be as good as it can). Committees don't appear routinely to consider which goal they are pursing, or have consistent policies within or between IRBs. Moreover, the metrics and calculus involved in weighing risks *vs.* benefits are inherently subjective – e.g., exactly *how much* benefit justifies a 5% or 20% risk of subject harm. IRBs frequently have to judge how much potential benefit to many future patients justifies how much risk to a relatively small group of subjects.

These interviews provide preliminary data that helps to identify and elucidate these boundaries and tensions. IRB chairs and members often have dual goals: as researchers (advancing science) *vs*. as IRB chairs/members (following regulations). Based on either role, IRBs sometimes clash with PIs concerning whether the committee has adequate scientific expertise to make certain alterations. Deciding what standard to use in evaluating a protocol's potential future benefits is difficult, and researchers and IRBs can disagree. Though regulations require that IRBs have adequate scientific expertise, this is undefined. IRB members typically have partial knowledge of many areas of research, but sometimes lack in depth knowledge about subfields in which research occurs.

Prior research has documented variations in IRBs' decisions.[27] This study raises the question of whether these differences result partly from variable perceptions of scientific quality and of IRB roles and standards.

This preliminary study has several potential limitations, such as lack of observations of IRB meetings, lack of complete or structured data from each IRB, and inability to quantitate responses. It was designed to reveal and elucidate issues, phenomena and practices,, and suggest research questions and hypotheses that future studies can explore, using larger samples designed to measure rates of these attitudes and practices, and statistical associations.

These data suggest a need for OHRP, PRIM&R or other groups to clarify issues, and develop guidance and consensus concerning definitions, thresholds and appropriate scope for IRBs, and examples where these groups think scientific changes are legitimate. These data have implications also for future research: to explore among larger samples of both IRBs and researchers how often, when, how and why IRBs alter studies; how legitimate, helpful, or costly such changes are; how often IRBs face difficulties concerning the science, and seek science being "good enough" *vs.* as good as possible; what constitutes "less interesting science," and how that concept should be evaluated; how often scientific review occurs outside the IRB, and of what it consists.

These data confirm that IRBs face ambiguities and conflicting goals in assessing scientific quality, and questions about whether to improve the science beyond what the regulations mandate, with concomitant implications for practice, education, research, and policy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: The National Institutes of Health [R01-NG04214] and the National Library of Medicine [5-G13-LM009996-02] supported this work.

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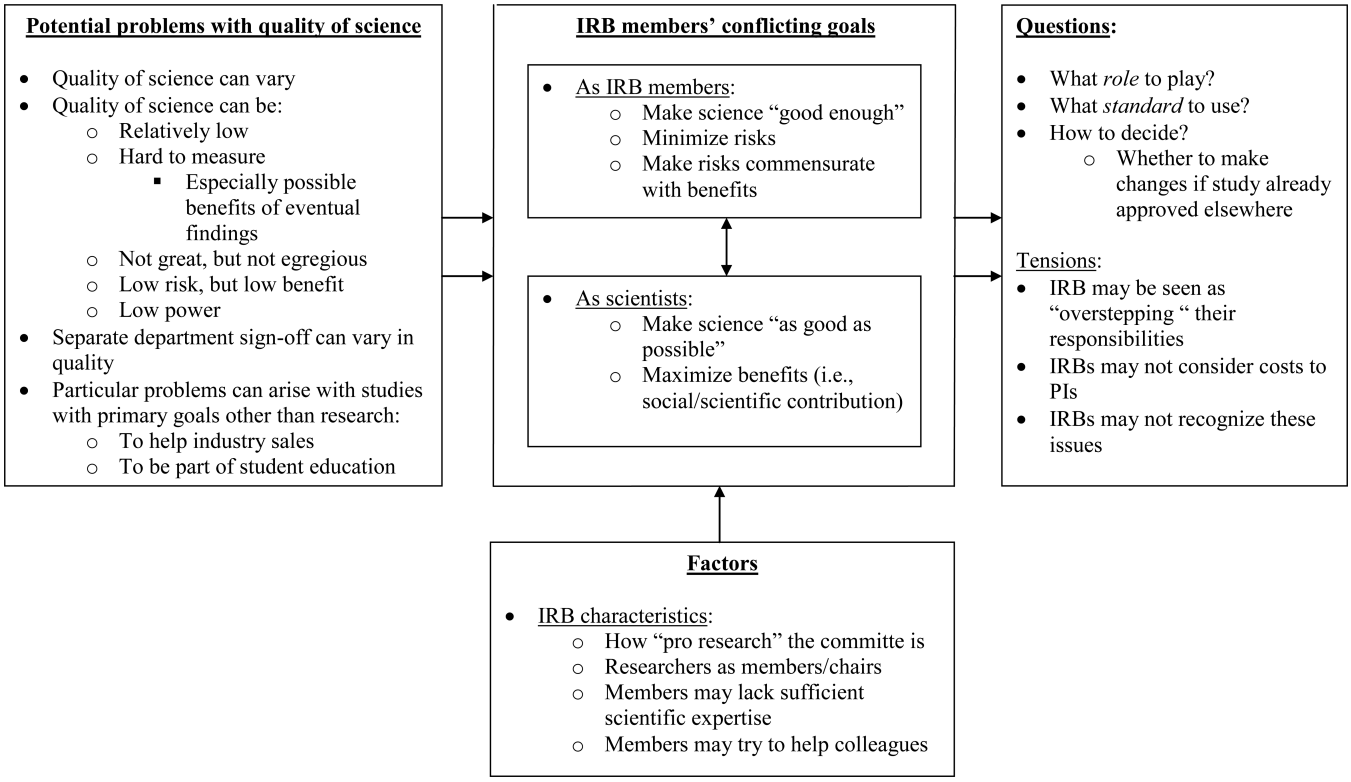

Figure 1.
Themes Concerning IRB Views of the Quality of Science