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Original article

Uncertainty about effects is a key factor influencing institutional review boards' approval of clinical studies

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ABSTRACT

Purpose: To investigate factors, which influence institutional review boards' (IRBs') decision to approve or not approve clinical studies, a nationwide vignette-based online survey of IRB members was conducted.
Methods: A factorial design was used, whereby seven aspects of each hypothetical study were randomly varied in 15 phrases in each vignette to produce unique vignettes. Participants indicated the degree of study approval and described factors influencing approval decision. Qualitative responses were thematically content analyzed.
Results: Sixteen themes were obtained from 208 participants from 42 institutions. Uncertainty, adherence, study design, and harms were frequently and intensely cited to influence study approval. Analysis of two extreme subgroups (approvers vs. nonapprovers) showed that uncertainty influenced approval decisions, odds ratios (OR) = 3.5 (95% confidence interval [CI], 1.3–9.8) and OR = 3.2 (95% CI, 1.1–8.9), respectively, based on theme frequency and theme intensity, ignoring multiple observations per person. Taking into consideration multiple observations per person, similar results were obtained for uncertainty: OR = 8.9 (95% CI, 0.93–85.4).
Conclusions: Perceived uncertainty about benefits and harms of a proposed intervention is a key driver in IRB members' approval of clinical trials. This, in turn, calls for improved standardization in the communications of information on benefits and harms in the research protocols considered by the IRBs.
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Introduction

Institutional review boards (IRBs) are locally administered groups that undertake review of research protocols involving humans to ensure they adhere to federal regulations, adequately protect human participants' rights and welfare, and are ethically sound.[1] In the United States, the federal law mandates [2] that the Office of Human Research Protections and the Food and Drug Administration authorize IRBs to review research protocols and related materials to decide whether to approve, require modifications in planned research before approval, or disapprove the research. Despite the pivotal role IRBs play in research conduct, little is known about what factors influence IRBs' decision to approve or not approve a study.

If the proposed study is deemed ethical and approved by one IRB, then one would expect another IRB to draw a similar conclusion. However, research show that when IRB members at multiple sites are presented with the same research proposal, their reactions vary [3,4]. Variations have been noted in the acceptable methods for recruitment of study participants [5,6], designation of risk level [4,7], type of concerns expressed or changes required [5,8–11], and more importantly, approval versus disapproval decision [11,12]. Empirical evidence from a systematic review of 43 studies found that the same clinical study, which has been approved by one IRB in the United States gets disapproved by another IRB, and vice versa [3].

Given the inconsistency in IRB's reactions to the same proposal, it is imperative to examine what factors influence IRB members' decision to approve or not approve a study protocol. According to Henderson et al. [13], factors such as scientific purpose, level of uncertainty about efficacy of intervention under investigation, competing interest of a clinician (e.g., to advance scientific knowledge vs. provide best care to patients) may influence approval decision. IRB members also may differ on approval decisions based on perceived benefit of the treatment to current patients versus future patients. According to the Belmont Report [14] and Declaration of Helsinki [15], the primary goal of research is to help develop new

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health intervention that will help future patients; however, research ethics require that risks to subjects posed by participation in research is justified by the anticipated benefits to the current patients [16]. Similarly, health care professionals are duty bound not to subjugate their duties to (current) patients' best interest to the utilitarian goals for the good of others (future patients) [17,18]. Thus, enrollment into clinical studies is justified only if it can benefit study patients more than treating them outside of the trial [17]. In sum, a number of factors may affect IRB members' approval decision. To date, there has not been any systematic investigation of factors that impact IRB members' approval decision. Accordingly, the goal of this study was to identify factors that influence IRB members' decision to approve or not approve clinical studies.

Method

Research design

This study comprises the qualitative component of a larger study employing mixed methods approach to examine factors that influence IRB members' decision to approve or not approve a study protocol. Specifically partially mixed concurrent dominant status design [19] was used, whereby quantitative and qualitative components are conducted concurrently, the quantitative component being accorded more weight in addressing the research question, and mixing occurring at the data interpretation stage.

Sample selection and participant recruitment

Potential participants included IRB members from 128 colleges and universities representing 317 IRBs, which are members of the Association of American Medical Colleges and members of the Public Responsibility in Medicine and Research. We obtained the list of Public Responsibility in Medicine and Research members and then cross verified these members with the list of active IRB members affiliated with 128 colleges and universities to discard duplicates. We contacted potential participants via postal mail, e-mail, and phone calls. An initial advance letter alerting recipients to the upcoming survey was used when a mailing address was available. E-mail was the primary mode of contact. An announcement e-mail echoing the language of the letter was sent with the intent to reach respondents about the same time as the letter. Follow-up e-mail reminders, along with post cards and telephone reminders, when possible, were also used. The study was approved by the University of South Florida IRB (No: 107911).

Survey development, piloting, and administration

We developed a web-based survey employing vignettes. The vignettes depicted clinical study scenarios in which uncertainties and other factors potentially influencing approval of proposed research studies were used. We used a factorial design, whereby seven aspects of each scenario (Table 1) were randomly varied in 15 phrases in each vignette to produce unique vignettes for each respondent (see P1–P15 in Fig. 1). At the end of each vignette participants responded to the following three questions based on a seven-point Likert-type scale (1 = definitely not, 2 = most likely not, 3 = likely not, 4 = may or may not, 5 = likely, 6 = most likely, and 7 = definitely):

- extent to which IRB members believed the proposed study will generate knowledge about medical treatment that will benefit future patients;
- extent to which IRB members believed the treatment in the proposed study will improve outcomes in the study patients; and
- likelihood to approve the proposed study.

Table 1
Variable included in questionnaire vignettes

Variable	Value (description)
1. Condition	Metastatic pancreatic cancer (deadly cancer, affect survival) or rheumatoid arthritis (disabling arthritis, affect quality of life)
2. Uncertainty	Effects of the treatment/intervention, ranging from 1% to 100%
3. Therapy type	May be over the counter, gene therapy, or other
4. Study procedures	A study that requires additional testing/treatment, including invasive procedures or a study that does not require testing/treatment
5. Adherence to protocol	A study that requires stopping treatment in progress (strict protocol) or a study that does not require stopping treatment in progress
6. Scientific purpose	Either an explanatory trial (under ideal conditions of a research) or pragmatic (in a real medical practice)
7. Interest of a clinician	Either to advance scientific knowledge (scientific focus) or to provide best care for patients (patient care focus)

Participants also responded to the open-ended question, Please briefly describe what factors influenced your decision to approve or not approve the proposed study. Responses to this question constitute the qualitative data on which our report is based. Participants were asked to assume that the described study was scientifically sound and appropriate, although not described in detail. We pilot tested the vignettes and the web-based survey among University of South Florida IRB members and the members from our study team. A sample of IRBs members at academic institutions across the United States, not part of the study participants, provided expert review of the vignettes and the questions asked.

We administered the survey electronically to support the intricate branching and variable randomization of the vignettes. We programmed the survey in Sensus, an Internet survey tool licensed from Sawtooth Technologies, Northbrook, IL. Each respondent was presented with four pairs of vignettes, with each pair representing one of the four types of clinical studies (phase I, phase II, randomized controlled trial [RCT], and a cohort study) and one randomly selected vignette. A randomized sequence of five integers was generated, one for each respondent to be sampled, which controlled the sequence of study design types to be presented in the four pairs and the additional vignette. For each of the nine vignettes, seven random digits were used to set the values for each of the experimentally varied factors in the vignettes. Thus, a total of 68 random digits were set in advance for each respondent, so that vignette content and sequencing were fully randomized across the respondents. The random digits were edited before use to eliminate the possibility of showing to a respondent two identical vignettes within the same questionnaire. Participants were emailed the link directing them to their own copy of the survey. Participants were not directly compensated; however, we inserted a $5 gift card into all advance letters sent as a small token of appreciation to create the expectation of reciprocity.

Data analysis

We used thematic content analysis, whereby two members of our research team coded independently participants' significant statements in response to the open-ended question. By significant