Are the Criteria for Approval Sufficient to Protect Research Participants?

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Dear Practical Ethicist,

In our Research Ethics Committee (REC) meetings, we sometimes have a committee member raise a concern about a protocol that seems to be outside the standard set of criteria for protocol approval—for example, requiring that compensation for study participants must be in the form of gift cards and not in cash. When the chair points out that the concern does not seem to be based on the criteria for approval, the response is usually "the criteria for approval are the floor, not the ceiling!" This is generally interpreted to mean that additional requirements are appropriate as the basis for decisions. This sometimes results in frustration from our investigators, who point out that protocol or study conduct elements that were acceptable in one submission are found unacceptable in a subsequent submission. In multicenter studies with more than one REC/IRB (Institutional Review Board) reviewing the same protocol, we also hear that we are requesting changes that no other REC/IRB has requested. How should we address "additional" approval criteria?

Signed,
Additional Criteria Really Exasperating

Dear ACRE,

The statement that the criteria for approval are the floor, not the ceiling, is often heard in the world of RECs and IRBs. The implication is that the criteria for approval are sometimes (or always) insufficient to protect research participants. REC/IRB members who believe that the criteria for approval are a floor say that research ethics must be individualized; RECs/IRBs must be given the latitude to expand beyond a fixed set of criteria. Those who disagree with the statement believe that the criteria for approval are sufficiently flexible to handle all types and kinds of research, and new criteria are unnecessary. Which is correct?

To answer this question, it is best to look at ethical decision making as a process that takes an input and delivers an outcome. The input is the submission materials describing the research, including the protocol, consent, investigational product data, principal investigator information, and site information, as well as other materials. The output is a decision to approve the research, require modifications to secure approval, or disapprove the research. In this sense, the process of ethics review is no different than any other standard process.

Once we look at ethics review as a standard process, we can state a fundamental tenet that high-quality processes have minimal variability of the outputs given identical inputs. With a quality ethics review, decisions should not vary substantially based on the composition of the board reviewing the protocol, the meeting at which the protocol is reviewed, or the order in which the protocol is placed on the agenda. Differences among review decisions unrelated to the content of the materials submitted for review are referred to as "special cause variation" (Montgomery, 2000) because the variation is related to special differences in the underlying review process and not based on variations in the input. A quality process must be consistent to minimize special cause variation. Consistent processes still vary in outcome, but the variation is called "common cause variation" (Montgomery, 2000) because it is related to variation that occurs despite a consistent process. "Necessary variation" occurs because the inputs vary. For example, in a multicenter protocol differences in local issues, such as laws, qualification of personnel, and standard of care, result in necessary variation. Special cause variation can be removed by following a consistent process, and quality processes always eliminate special cause variation. Common cause variation can never be eliminated, but quality processes strive to minimize it. Necessary variation is of course necessary.

One component of the ethics review process is the approval criteria used to determine whether research can be approved. If the REC/IRB uses one set of approval criteria at one meeting and a different set at another, review of the same submission materials could result in different decisions. These different decisions represent special cause variability since differing criteria for approval applied to the same protocol represents a variation in underlying process of decision making. When there is special cause variation, a quality systems approach considers three possibilities for improvement:

1. One set of approval criteria better protects research participants and should be used at all meetings.
2. Both sets of approval criteria are equally protective of research participants, but one set is easier to apply, simpler, or more efficient. In that case, the approval criteria that are easier to implement and minimize wasted time and effort better protect subjects.
3. There is no difference between the participant protection values of the sets of approval criteria, and

> both sets of approval criteria are equally easy, simple, and efficient. If so, we should flip a coin and use one set of approval criteria at all meetings because operational consistency better protects subjects.

One symptom of varying approval criteria is that when a specific REC/IRB member is present at a meeting, a certain issue is raised and changes to the protocol or consent are made or requested, but when that member is not present, the issue is not raised and the changes are not requested. You might have one member who raises concerns about the methods of statistical analysis and frequently requires a different statistical plan or a revised power analysis as a condition of approval. Another member might insist on changes to the research design to improve the level of scientific rigor, or that safety monitoring plans include specific stopping criteria, or that audio tapes of interviews must be destroyed after transcription. However, when these members do not attend meetings, the review committee does not look for these factors or, if they are not there, require these changes prior to approval. The Practical Ethicist knows of examples in which RECs/IRBs came to refer to specific requests as "the Smith criterion" because it was applied only when Dr. Smith was present for the meeting.

When review decisions vary based on the presence of one member that suggests that the one member is using personal approval criteria not being used by other members. As before, there are several possibilities.

1. The personal approval criteria better protect research participants and should be used by all members or the personal approval criteria are less protective and should not be used.
2. There is no difference in participant protection, and the personal approval criteria should be used if they are simpler, easier, or more efficient.
3. There is no difference at all, and the personal approval criteria should not be used.

The principle that a high-quality process results in the same output given identical inputs supports the idea that the approval criteria used by an ethics review committee ought to be both necessary and sufficient to protect subjects. That is, the criteria should be both the ceiling and the floor. An ethics review panel that consistently uses the same approval criteria may still generate inconsistent opinions. For example, two committees might disagree on whether the exclusion of pregnant women from a study represents equitable selection. However, if both committees are asking the question, "Is selection of participants equitable, considering the purpose and setting of the research and being cognizant of the issues of vulnerable populations?" the difference represents common cause variation. Common cause variation is expected during ethics review because ethical review requires a committee with diverse members who have varying backgrounds where the members are expected to bring a unique perspective.

To ensure use of consistent approval criteria, ethics review panels should codify their criteria in writing. Written policy should indicate that research meeting the approval criteria gets approved, and research not meeting approval criteria does not get approved unless changes are made that allow the research to meet approval criteria. To promote this approach, committee members should express their concerns by indicating the approval criterion that is not met and why. If the committee cannot justify a concern with an approval criterion, the concern should be taken off the table. The committee should express controverted issues as areas where members disagreed about whether the issue affected an approval criterion, rather than a disagreement over the issue, or whether it is important enough to affect approval.

Using a consistent set of approval criteria does not make the approval criteria static. Approval criteria can change to minimize common cause variation. For example, a rewording of a criterion might lead to a better and more consistent interpretation by REC/IRB members. Approval criteria can change as research or technology changes. For example, the need for research on cardiac resuscitation challenges long-held criteria regarding informed consent. Preimplantation genome editing that leads to germ line changes challenges our criteria for acceptable risks and benefits. However, such changes to approval criteria should not be *ad hoc*. Instead, the change should be made as a deliberative policy-making process that systematically considers the effect of the change on future research and future REC/IRB operations. Once the change is made, the new approval criteria should be applied consistently across all RECs/IRBs.

In summary, the purpose of having criteria for approval is to protect research participants. In a quality process that optimally protects subjects, the process is followed consistently. Therefore, RECs/IRBs should consistently follow their criteria for approval. Approval criteria ought to be the floor and the ceiling; RECs/IRBs should take steps to eliminate *ad hoc* criteria to eliminate special cause variation and to recognize that the elimination of special cause variation better protects research participants.

P. Ethicist

Reference

Montgomery, D. C. (2000). *Introduction to statistical quality control* (7th ed.). Hoboken, NJ: John Wiley.

Author Biographies

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Lindsay McNair, MD, MPH, MSBioethics, is a physician, clinical investigator, and former academic IRB member who has spent most of her career working in clinical research for the pharmaceutical and biotechnology industry, with a specific interest in ethical drug development research. She is an adjunct faculty member at Boston University and is currently the chief medical officer for the WIRB-Copernicus Group.