What Is the Role of a Statistician on the IRB?

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Dear Practical Ethicist,

We recently had a new faculty member with IRB experience join our institution and begin to serve on the IRB. He immediately noticed that we do not have a statistician as a member of our IRB, and he has been very vocal about the need for one. So my IRB recently appointed a new IRB member who is a statistician. The statistician often raises concerns with power and sample size calculations and frequently wants us to ask the researcher to make changes for a "better" statistical analysis. Are these legitimate issues for the IRB? What is the role of a statistician on the IRB?

Signed,

Sighing Over Statistics

Dear SOS,

Reviewing the statistical components of the research such as the sample size calculations and the proposed data analysis plan can help determine whether the protocol meets the criteria for approval. Statistical methods primarily affect two criteria:

- Risks to subjects are minimized by using procedures consistent with sound research design that do not unnecessarily expose subjects to risk; and
- Risks to subjects are reasonable in relationship to anticipated benefits to subjects, if any, and the importance of the knowledge expected to result.

A component of the first criterion is that to approve research, the IRB must determine that risks to subjects are minimized by using procedures consistent with sound research design, which do not unnecessarily expose subjects to risk. The IRB must ascertain the risks of the research, the aims of the research, and the research methods. The IRB must then judge whether alternative methods to perform the research would reduce the risks to subjects and still allow the research to achieve its aims. An important factor is whether the researcher plans to study a larger number of subjects than required to answer the scientific question. "Right-sizing" the number of subjects can minimize risks to subjects and be consistent with sound research design. If the research involves no more than minimal risk to subjects, this may not be a major consideration; there is little valuable reduction in risk if we decrease the number of surveys or one-time blood draws from 1,000 to 800. When the risks are greater, like in a study of an implantable artificial heart, it makes sense to more rigorously consider the reduction of even one or two subjects if they are more than are needed to answer the research question.

The second criterion is that risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. The IRB must judge whether the risks they identify are justified by the sum of two benefits: (a) the benefits that subjects may experience and (b) the importance of the knowledge reasonably expected to result. For this criterion, the issues are whether the number of subjects to be studied will be sufficient to answer the scientific question and whether the data analysis will lead to important knowledge. One point often missed with this criterion is that it refers to "knowledge" not "generalizable knowledge." Often research does not provide a definitive answer to the study question for reasons that are not readily foreseeable at the study start. For example, the variability in response among the study participants is greater than expected, or incorrect assumptions (perhaps about the response rate of the control group) were made in the study design. However, seldom does that research fail to lead to important knowledge; even studies that fail to detect the effects that they were designed to investigate are important when they provide information to improve the design of future studies, or they lead researchers to stop exploring a therapeutic idea that isn't going to be effective. Researchers learn as much from their mistakes as from their successes. Good IRBs know that knowledge may result from both success and failure and consider the importance of that knowledge when judging whether this criterion is met. If the research involves no more than minimal risk to subjects and no benefit to subjects, minimally important knowledge can justify this risk. Minimally important knowledge might be an answer to questions, such as, "Is this research feasible? Is there something interesting here to pursue?" Again, when the risks include death and disability but no benefit to subjects, IRBs should allow that only when there is overwhelming importance of the knowledge expected to result.

Many IRBs, and particularly academic IRBs, choose to have a statistician on the IRB. There is no requirement for this, but they find it helpful in the assessment of protocols

to have statistical expertise readily available when needed. Importantly, the role of the statistical expert is the same as any other IRB member, which is to review submitted materials in a sufficient depth to determine whether the regulatory criteria for approval are met.

When an IRB member raises issues regarding the sample size and power of the study to detect the anticipated result, useful questions the IRB can pose are as follows: How many subjects would you say are required? How much uncertainty is there in the researcher's estimate and in yours? What knowledge (not necessarily generalizable knowledge) will be expected if the number of subjects proposed by the researcher is studied? To what extent will that knowledge increase if the number of subjects you propose is studied?

If the concern is that there are *too many subjects* in the study as proposed, a useful question to ask is, "Are the differences between the two estimates large enough (relative to the uncertainties around sample size estimation) to minimize risk in a way that is reasonable to impose on the research?" If the issue is that there are *too few subjects* in the study as proposed, a useful question to ask is, "Are risks to subjects justified by the benefits to subjects, if any, and are those risks justified by the importance of the knowledge expected to result from the number of subjects proposed by the researcher?" If so, a change in the number of subjects is not required. If not, are risks justified by the benefits to subjects, if any, and by the importance of the knowledge expected to result from the increased number of subjects?

When an IRB member raises issues regarding the planned data analysis, useful questions the IRB can pose are as follows: What knowledge (not necessarily *generalizable* knowledge) will be expected if the statistical analysis proposed by the researcher is used? To what extent will that knowledge increase if a different statistical test or analysis method is used instead? If the risks are justified by the benefits to subjects, if any, and by the importance of the knowledge expected to result from the statistical analysis proposed by the researcher, then a change should not be required, even if an IRB member thinks a different analysis method might be "better."

IRBs may find situations where there is controversy over the statistical methods of a protocol. Sometimes there are members who want to improve every statistical analysis, insist that all analyses be performed in a particular way, or demand quantitative analysis of qualitative research. This can lead to contention on the IRB about the role of statistical analysis in the review of research. One can avoid this contention with a careful analysis of the criteria for approval. Just as there are uncertainties, preferences, and biases among research methods, there are also uncertainties, preferences, and biases among statistical methods. As with any component of the scientific review of protocols, the IRB always has to assess whether their comments affect the regulatory criteria for approval. IRBs should require changes to the statistical analysis when the criteria for approval are affected. Once the criteria for approval are met, changes intended only "to make the study better" should not be required.

P. Ethicist

Author Biographies

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Jeffrey A. Cooper, MD, MMM, is a physician, basic science investigator, clinical investigator, and manager with many years of ethical review experience as a member and chair of an IRB. He left medical practice in 2002 to help start the Association for Accreditation of Human Research Protection Programs, Inc. (AAHRPP), where he was responsible for the development and operation of the accreditation process. He is currently vice president for Global Consulting at WIRB-Copernicus Group.

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 and president of Consulting Services for the WIRB-Copernicus Group.