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Thirteen Questions for IRBs to Ask About Risk Disclosure

By Dennis J. Mazur and Norman M. Goldfarb

Once an institutional review board (IRB) has assessed the risks in a clinical study[1] and determined that they are acceptable, the risk section of the informed consent form can be reviewed. It is very important for this document — and the accompanying discussion — to objectively and clearly communicate the risks so potential study participants can make an informed decision about participating in the study.

The Belmont Report

Extracts from the Belmont Report that are most relevant to risk disclosure are as follows:

> Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied…
>
> Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include:… risks and anticipated benefits…
>
> One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation…
>
> While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Considerations

In its review, the IRB needs to determine to its own satisfaction whether the correct risks are included and whether they are explained so potential participants can understand their nature, severity and likelihood.

While risks with moderate to high severity and moderate to high probability should be included, the question remains as to what extent, if any, risks with low severity and low probability can be excluded? In addition, what, if any, risks with moderate to high severity

and low or very low probability can be excluded? What if a risk can present in a variety of severities? What if the probability is very uncertain or essentially unknown?

In addition to the known risks, there might be unknown risks that cannot unanticipated. How should the possibility of unknown risks be disclosed?

Some medical conditions are difficult to explain concisely and correctly in lay language. Should that affect the decision as to whether they should be disclosed? For each such risk, is it better to provide a concise explanation in lay language that a medical professional would find lacking, a lengthy explanation in technical terms, some compromise, or both lay and technical explanations? Should a supporting document provide the lengthy, technical explanations? For example, psychiatric drugs might cause side effects like neuroleptic malignant syndrome (muscle rigidity, fever, autonomic instability, and cognitive changes such as delirium) or tardive dyskinesia (involuntary, repetitive body movements that have a slow or belated onset).

If too many risks are disclosed, the important ones can get lost in a lengthy document. If there are numerous risks, how should the less important ones be disclosed? Should the list be split into important and less-important risks, perhaps with the less-important ones presented in a supporting document? Similarly, long descriptions of the risks can be burdensome. If the long descriptions are limited to just some risks, it raises the question as to why the other risks did not deserve long descriptions.

Different potential participants will be interested in different risks and different disclosures about those risks. To what extent should these different interests be accommodated, and how should that be accomplished? For example, if one of the risks is breast cancer, the risk might be much higher for women than for men, but the risk to men might be greater than zero.

The nature of a risk can be complicated. First, what pathophysiology (physical or mental effects) is causing the risk? For example, in a study of a cardiovascular drug for hypertension, do participants understand that "heart failure" does not mean "heart attack"? What are the quality of life outcomes? What are the financial consequences? Will it manifest in the short or long term? Will it be a one-time or recurrent effect? Will it be reversible or permanent?

How should probability be communicated? Research in health and medical communication has demonstrated that that patients' quantitative interpretations of terms like "probable," "possible" and "rare" can vary 10-fold or more. Instead of saying "rare," would it be better to say "one in a thousand"? If data is lacking to provide a precise quantitative probability, would saying "one in a thousand" give a false impression of accuracy? Would it be better to say "roughly one in thousand" or "less often than one in a thousand"? If probability (or severity) depends on factors like gender, age or disease state, how should that information be explained?

How should risk severity be communicated? Different people have different pain thresholds, different levels of concern about losing their hair, etc. Different people care more or less about certain risks. For example, a pianist is more likely to be concerned about damage to fine motor skills than a jackhammer operator, who might be more concerned about carpal tunnel syndrome. Different cultures also have different attitudes toward risk — how should that be handled?

Should the severity of the medical condition affect how the severity of the risks are presented? For example, if a participant is likely to die of cancer in six months, is dying a month sooner a low, moderate or high severity risk?

Clinical research sometimes poses risks to the participant's family or community. For example, if the study drug might damage the participant's genetic material, it would affect the spouse's wish to have healthy children. An attenuated-virus vaccine might escape into the community. To what extent should those risks be disclosed to potential participants, as opposed to the family or community directly?

45 CFR 46.116 and 21 CFR 50.20 state: "The information that is given to the subject or the representative shall be in language *understandable* to the subject or the representative." ICH E6 4.8.7 states: "The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be *understandable* to the subject or the subject's legally acceptable representative and the impartial witness, where applicable." (Italics added.) In other words, there is no regulatory requirement that potential participants actually *understand* the information provided. However, as the Belmont Report notes, "…when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension." Thus, how should understanding of the risks be confirmed?

The primary purpose of some consent forms appears to be minimizing the litigation risk of the investigator and sponsor, rather than informing the study participants. While the two objectives do not necessarily conflict, the responsibility of the IRB is to protect study participants.

Thirteen Questions

When IRB members are assessing the risk section of an informed consent form, they can ask the following questions:

1. Are the appropriate risks disclosed?

2. Are the natures of the risks presented accurately and clearly in lay language, e.g., including the pathophysiology and potential quality of life consequences?

3. Are the severities of the risks presented accurately and clearly in lay language, e.g., with an explanation of terms like "moderate"?

4. Are the probabilities of the risks presented accurately and clearly in lay language, e.g., with an explanation of terms like "rarely"?

5. Is the severity of the risks described appropriately, given the nature of the medical condition under experiment?

6. If the probability or severity of a risk varies significantly based on participant characteristics, is this variation clearly and accurately explained?

7. Is it clearly disclosed to what extent the risks are uncertain or even unknown?

8. Is the description of the risks too long? For example, is the consent form cluttered with low severity or very unlikely risks that could be covered in an addendum? Or, are the explanations too wordy?

9. Should there be an addendum that explains the risks in more detail or in more technical language for potential participants who want more-sophisticated explanations?

10. Are any risks to family members or the community appropriately disclosed?

11. Does the risk disclosure appear to be written to help potential participants or to protect the investigator and study sponsor from litigation?

12. To what extent is verbal explanation expected to supplement the consent form?

13. Are there important risks for which the potential participant's understanding should be confirmed and, if so, how?

Conclusion

Asking the right questions is half-way to getting the right answers. By asking these questions, IRBs can increase the probability that risks will be adequately disclosed. By asking them across a broad range of studies, IRBs can develop experience, policies and principles that support a consistent, high-quality review of risk disclosures in consent forms.

Reference

1. Mazur D J, Goldfarb N M. Thirteen Questions for an IRB to Ask When Evaluating Risk. Journal of Clinical Research Best Practices, February 2015. http://firstclinical.com/journal/2015/1502_Risk_Assessment.pdf

Authors

Dennis J. Mazur, MD, PhD, is the author of *Evaluating the Science and Ethics of Research on Humans: A Guide for IRB Members,* published by the Johns Hopkins University Press, Baltimore Maryland, 2007. Contact him at mzrdj11@gmail.com.

Norman M. Goldfarb is Managing Director of First Clinical Research LLC, a provider of clinical research best practices information services. Contact him at 1.650.465.0119 or ngoldfarb@firstclinical.com.