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Twelve Questions for an IRB to Ask When Assessing Risk vs. Benefit in a Research Study Proposal

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Clinical research studies are designed to advance scientific knowledge, not to benefit the study subjects. However, they should not harm the subjects. IRBs must therefore assess the potential benefits and harms (principally, the *risks* of harm) in determining whether to approve a study. Logically, if a study provides no benefits to the subjects, any risk at all can be justified only on the basis that society will benefit from knowledge generated by the study.

Federal Regulations

When reviewing a clinical study, an IRB must decide whether the ratio of risks to benefits is acceptable. However, the Code of Federal Regulations is vague on this question. It says that risks should be "reasonable in relation to anticipated benefits." However, it does not define the term "reasonable." Apparently, the IRB has the discretion to decide whether reasonable means the risks are "smaller" than anticipated benefits, "comparable" to anticipated benefits, or any other ratio that the IRB deems reasonable.

Similarly, the regulations are vague on how to weigh various risks and benefits. Certainly, "anticipated benefits, if any, to subjects" should be included in the calculation, but what weight should be given to "the importance of the knowledge that may be expected to result"? Is it acceptable to put subjects at great risk if great knowledge may be expected to result?

> 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. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility. (21 CFR 56.111(a)(2)) (*45 CFR 46.111(a)(2) adds the word "reasonably.")

"Possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy)" might cover a vaccination study that could lead to a policy of universal vaccination that causes adverse effects for a small percentage of the population. Or, a study might lead to increased insurance costs for people with a certain gene variant. Or, a study might cause a change in public policy on the acceptability of a controversial type of research.

The FDA has not provided guidance on risk/benefit ratios other than to restate that risks should be reasonable in relation to anticipated benefits.

The Belmont Report

The Belmont Report (which is *not* a regulation or even a guidance), says that, "Previous codes and Federal regulations have required that risks to subjects be outweighed by the

sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research." However, it does not recommend this standard for *future* regulations. The Report further discusses what is "commonly" considered to be an acceptable risk/reward relationship: "balanced" or "in a favorable ratio," but does not propose these terms as standards.

The Report does say that "the risks and benefits affecting the immediate research subject will normally carry special weight," but gives IRBs leeway to consider "interests other than those of the subject," provided "the subjects' rights [i.e., safety and welfare] have been protected." However, since risks inherently carry the potential to injure, exposing a subject to *any* risk that does not provide direct benefit to the subject, would appear to violate that subject's rights.

The regulations do not specify who is included in "interests other than those of the subject." Presumably, people with the medical condition to be studied are included. However, the benefits of the potential treatment might be unavailable to segments of the population (including study subjects after the study) because it is unsafe for that segment, too expensive, or impractical to provide for logistical reasons.

> **The Nature and Scope of Risks and Benefits.** The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term "risk" refers to a possibility that harm may occur. However, when expressions like "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.
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> The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harm and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.
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> Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.
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> **The Systematic Assessment of Risks and Benefits.** It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making

precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: (i) Brutal or inhumane treatment of human subjects is never morally justified. (ii) Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. (iii) When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject — or, in some rare cases, to the manifest voluntariness of the participation).

Potential Benefits

Possible benefits to study subjects might include:

- Treatment of the medical condition during the study (at no charge)
- Better understanding by the subject of his or her medical condition
- Healthcare services like physical exams and lab tests during the study (at no charge), with the possibility of detecting and perhaps treating other medical conditions
- Availability of the treatment, if it eventually reaches the market, to the subject and his or her family members
- The satisfaction of performing an altruistic act

Possible benefits to society might include:

- Availability of the treatment if it eventually reaches the market
- Generalizable knowledge (including negative results that avoid useless research in the future
- Reduction in the cost of providing medical care to subjects during and possibly after the study

In "Payment to Research Subjects – Information Sheet," the FDA states: "Payment to research subjects for participation in studies is not considered a benefit, it is a recruitment incentive." While most subjects probably consider receiving a payment to be a benefit, IRBs should not consider payments when assessing the risk/benefit ratio.

Risks have been considered in a previous article.[1]

IRB Review

Each IRB must establish its own standards for determining what constitutes a "reasonable" ratio of risks to benefits and how various risks and benefits are to be weighed. Common sense, although not the regulations, suggest that benefits should exceed risks. Weight should be given to societal benefits (especially since they may be the *only* benefits), but not to the point that the significant rights of study subjects are sacrificed to the greater good.

Further, although the regulations do not explicitly address risk/benefit ratios for specific subjects, as opposed to subjects in general, common sense suggests that eligibility criteria should exclude those for whom the risk/benefit ratio is unacceptably high.

As the Belmont Report states, "Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols." Thus, it is unlikely that an IRB will be able to calculate a numeric risk/benefit ratio. Instead IRBs must make a qualitative analysis: Do the potential benefits exceed the risks (a risk/benefit ratio less than 1)?

IRBs have the option to approve a study provided the investigator improves the risk/benefit ratio. And, even if improving the risk/benefit ratio is not necessary to approve a study, the IRB can still recommend ways to improve it.

In addition to assessing risk/benefit ratios, IRBs must also review informed consent forms to ensure that the risks and benefits are clearly presented without coercion or undue influence. Clarity of presentation might include limiting the risks that are disclosed (or emphasized) to only the most significant. Blanket clauses like, "The following risks may or may not apply to you" are not recommended since they suggest that all the risks are equally important and may not, in fact, be risks at all.

Twelve Questions

When IRB members are assessing the risk/benefit ratio of a study, they can ask the following questions:

- What potential benefits for the subject and for society should be considered, and what are their magnitude and likelihood?
- What risks should be considered, and what are their severity and likelihood?
- What weight should be given to unknown risks, especially if the study is in a novel area?
- Are there any risks so major that no level of benefit justifies the research (perhaps for certain subpopulations)?
- Are the risks so minimal that benefits are not required?
- How do the risks and benefits compare to those of treatments (if any) that subjects would receive in the absence of the study?
- How well understood are the risks and benefits, so their magnitude and likelihood can be accurately estimated? (Can any of them be quantified?)
- How do the risks and benefits vary across potential subject populations, including those that are vulnerable?
- How can the benefits be enhanced, without becoming unduly influential?
- How can the risks be avoided or mitigated?
- How likely is the study design to advance generalizable knowledge?
- How will society otherwise benefit from the study?

Conclusion

Asking the right questions is half way to getting the right answers. By asking these questions, IRBs can assess the risk/benefit ratio of a study and possibly find ways to improve it. By asking these questions across a broad range of studies, IRBs can develop experience, policies and principles that support a consistent, high-quality review.

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

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