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Fourteen Questions for an IRB to Ask When Evaluating Risk

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Assessing risk is a fundamental institutional review board (IRB) responsibility. To reach the right conclusion about risk, IRBs must first ask the right questions, since risk is a complicated matter in clinical research.

Risks have two main components: severity and probability. Severe, high-probability risks are of major concern. Even unlikely severe risks are of concern, precisely because they are rare events, so less is understood about them. Study participants will also want to understand risk of relatively minor severity, e.g., temporary confusion, disorientation and nausea. Other combinations of severity and probability also need to be sorted out by the IRB. Assessing the severity and probability of risks is challenging — after all, we're talking about research — but IRBs must do the best they can under the circumstances.

When IRB members talk about risks, they need a vocabulary to discuss the risks. Objective, quantitative descriptors, e.g., "a likelihood of 10%" or "one week in the hospital" are best, but are seldom available. In most cases, only qualitative descriptors, such as "unlikely" or "severe" are at hand. If such descriptors are used, they should be defined as precisely as possible (e.g., "unlikely" might mean "a 1-10 chance out of 1,000"), since such terms mean different things to different people. The description of the risk is also important, e.g., "stroke" or "stroke that might cause irreparable physical or cognitive damage."

Risk and uncertainty are two different concepts. The existence of a *risk* implies both severity and probability. To the extent these statements are imprecise, there is *uncertainty*. For practical purposes, there is always some level of uncertainty, so the question is whether there is *enough* certainty. It is much easier to assess risks for which the severity and probability are well-known. If both parameters are very uncertain for a Phase III study, and the IRB has reason to be concerned, the study drug or device might not be ready for Phase III testing.

The 14 Questions

When assessing the risk of a study, the IRB should ask the following questions:

1. **What are the risks?** Mental or physical injury to the study participant is an obvious concern, but are there also, for example, privacy risks, or risks to others, such as family members or study team members? IRBs should not assume that the absence of known risks means there are no risks. Even with an approved drug or device, very rare risks might not become apparent until many thousands of patients have been treated. Thus, even apparently safe studies should have some scientific merit to be approved.

2. **How well understood are the severity and probability of each risk?** For example, how much is known about the pertinent physiology? Do previous studies provide adequate information on the risks? Can information be extrapolated from other drugs or devices in the same class? How are the researchers assessing the risks of a newly developed drug (with a new mechanism of action) that has barely been tested on human research subjects?

3. **Does the IRB have adequate expertise to objectively assess the risks?** If the expertise of the Board members is insufficient, can outside experts, other IRBs, or

federal regulators provide advice? Does the IRB need to hear a pro/con discussion among experts?

4. **Is the IRB able to assess risk in an objective and unbiased manner?** An expert's bias can be caused by a conflict of interest, a particular past experience, or simply by his or her attitude toward risk in general — "better safe than sorry" or "nothing ventured, nothing gained."

5. **Do the potential benefits to study participants and generalizable knowledge justify taking the risks?** Potential benefits have their own significances and probabilities. If participating in a study might, in fact, benefit study participants, how does the consent form explain the potential benefits? Not disclosing potential benefits is a disservice to potential participants.

6. **Will potential study participants understand the risks?** Are the risks accurately described in non-technical language? Are the risk descriptors quantitative, qualitative or absent? Are the real risks obscured by a cloud of unlikely or inconsequential risks? Does the consent form understate the risks? On the other hand, erring on the side of overstatement does not help if it unduly frightens potential participants from enrolling in the study.

7. **Do patient preferences vary with respect to risk?** Are some patients more risk adverse than others? Does the consent form enable patients to assess the risks based on their personal preferences?

8. **What treatment options do study subjects have outside the study?** Is the risk/benefit ratio of standard-of-care treatment higher or lower than the study treatment? Does the study's informed consent form adequately explain the pros and cons of clinical treatment versus research participation?

9. **Does the protocol minimize the risk to each participant and to the study population as a whole?** For example, is liver enzyme, genomic and other testing adequate to screen out vulnerable participants? Does the consent form adequately explain any limitations in screening out participants subject to particular risks?

10. **Who in the potential study population is vulnerable to the risk?** Excluding vulnerable patients from research participation may protect them, but it interferes with creating generalizable knowledge.

11. **When does the risk occur?** If it occurs within an hour of treatment, subjects should be kept for observation. If it occurs within a day of treatment, a call the next day makes sense. If it might occur after months or years, a monitoring plan should be created.

12. **If harm occurs, how will it be identified?** What is the impact on the study participant if it is not identified in a timely manner?

13. **If harm occurs, how will it be handled?** What suffering, cost and inconvenience will the study participant experience? Who will perform the treatment? Will treatment provide a cure?

Example Risks for IRB Members to Consider

As an exercise, draft consent form language that explains the following severe but rare risks:

- Malignant hyperthermia
- Neuroleptic malignant syndrome
- Tardive dyskinesia

Should each consent form have the same explanation?

How will it be determined whether the harm was caused by the study? Who will pay for the treatment? Will any compensation be paid for the injury to the study participant? By whom? Who will participate in these determinations?

14. **Taken as a whole, are the risks acceptable?** Is there a single risk that is unacceptable or a set of risks that, in aggregate, are unacceptable? What is it about the unacceptable risks that make them unacceptable?

Conclusion

Asking the right questions is halfway to getting the right answers. With the 13 questions above, IRBs can discuss the risk of clinical studies in a structured way that is likely to draw out the real risks and assess their significance.

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