Assessing Research Benefits: Practical Ethicist

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Dear Practical Ethicist,

There has been much discussion about the assessment of risks in considering clinical protocols. We also struggle with the assessment of benefits, as part of the consideration of weighing whether the risks are reasonable in relation to the benefits. How do we consider benefit to a study participant when there is little information known yet about the investigational product, and it could have little or no benefit, or great benefit? Should payment for participation in studies (above reimbursement of expenses) be categorized as a benefit?

Sincerely,
Ben Eficence

Dear Ben,

You raise some important questions. As you note, to approve research, Institutional Review Boards/Research Ethics Boards (IRBs/REBs) have to determine that the research has a favorable relationship of risks and benefits. Commonly, this is codified by the rule that risks to subjects must be reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result (Institutional Review Boards, 2009; Protection of Human Subjects, 2009a). Aside from the regulatory criteria, researchers should also seek to ensure that the research they are considering conducting will have a greater chance of doing good, overall, than doing harm, which is consistent with the Belmont report principle of beneficence (Belmont Report, 1979).

To evaluate risks and potential benefits, the IRB/REB needs information about what the risks to subjects are, what the anticipated benefits to subjects are, and what the knowledge that may reasonably be expected to result ia. To obtain this information, IRB/REB members need input from individuals with scientific expertise who can ascertain whether the risks, anticipated benefits, and knowledge to be gained are accurately described in the protocol, and if not, provide this information to the IRB/REB members. This is the role of scientific review, which is a specialized function of the IRB/REB and a core component of ethics review (Cooper & McNair, 2014). Although discerning the risks, anticipated benefits, and knowledge to be gained requires scientific expertise, judging the *importance* of that knowledge and whether risks are *reasonable* in relation to potential benefits is a determination that can be made by all IRB members regardless of their level of scientific expertise.

Like potential risks, anticipated benefits are possible, but not certain. This is important to remember, as IRBs/REBs—as well as other research stakeholders—can often fall into the habit of considering just the administration of a novel investigational product to be a benefit of research. Certainly, this perspective has been promulgated by marketing efforts for medical centers, which often promise that patients can "gain access to new research treatments before they are widely available." Such promises ignore the reality that the vast majority of investigational products (>80%) will fall out of the drug development process (The Center for Information and Study on Clinical Research Participation, n.d.) for reasons of safety or lack of efficacy, and that an experimental regimen may actually have less benefit and/or more safety issues than the standard therapy. The habit of assuming a benefit of receipt of the most novel product can be seen in, for example, requests that protocols provide a cross-over option for control arm participants to get the investigational product, which confounds the ability of the study to accurately assess endpoints like overall survival, even though there is no evidence yet that the investigational product is better—or even as good as—the control regimen.

When analyzing potential benefits, IRBs should consider two categories of benefits: benefits to subjects and importance of the knowledge expected to result. Some research has no anticipated direct benefit to subjects and can be ethical if risks to subjects are reasonable in relation to the importance of the knowledge that may reasonably be expected to result. This assessment is applicable to healthy volunteer studies. Another category of benefits which may be particularly relevant in international research or in research in medically underserved communities is often referred to as "ancillary benefits." This term refers to the access to medical care (physical examinations, care or referral for the treatment of co-morbid conditions, access to standard therapies) provided by trial participation, regardless of whether the participant receives an investigational product (Belsky & Richardson, 2009; Slack, 2014).

IRBs/REBs should evaluate the anticipated benefits to subjects as opposed to the anticipated benefits to other individuals that are not subjects. The broader benefits to society should be evaluated in terms of the importance of the knowledge that may reasonably be expected to result, rather than direct benefit to individuals who are not subjects. Research is commonly defined as "a systematic investigation designed to

develop or *contribute* to generalizable knowledge" (Protection of Human Subjects, 2009b). The definition acknowledges that research does not always *contribute* to generalizable knowledge. Sometimes research *develops* important knowledge that is not generalizable, but lays the foundation for future studies that can be designed to contribute to generalizable knowledge. Common examples are pilot studies and exploratory research. In addition, research is always uncertain. Experts and peer reviewers may agree that research is properly designed to develop or contribute to generalizable knowledge, but due to unforeseen circumstances, research may not work out as planned. Studies that do not provide conclusive answers, or that provide negative study results—sometimes unfortunately referred to as "failed trials"—still contribute to knowledge, because researchers can use this information to design better research in the future.

IRBs/REBs often question whether payment for participation in research should be considered—and described in the informed consent process—as a benefit of participation; in the generally used definition of the word, getting paid for taking part in research is a benefit. However, regulatory agencies and ethicists generally do not agree with the description of payment as a benefit that can justify risk, and instead consider it a recruitment incentive (U.S. Food & Drug Administration, n.d.). IRBs/REBs should not consider payment as a benefit in the analysis of risks and benefits. One way to consider this is that an unfavorable relationship of risks and benefits cannot be made favorable by paying subjects more money; therefore, payment should not be weighed against potential risks.

In summary, to approve research, IRBs/REBs have to determine 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. IRBs/REBs should consider two categories of benefits (anticipated benefits to subjects and the importance of the knowledge that may reasonably be expected to result), and acknowledge that ethical research does not need to have both categories of benefits. IRBs/REBs should consider all expected knowledge as a benefit, not just generalizable knowledge. IRBs/REBs should have scientific expertise to ascertain the risks to subjects, the anticipated benefits to subjects, and the knowledge that may reasonably be expected to result. However, all IRB/REB members, including non-scientific members, can judge the importance of the knowledge and determine whether risks are reasonable in relation to benefits.

P. Ethicist

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