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Therapeutic Misconception

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Henderson et al[1] define therapeutic misconception as follows: "Therapeutic misconception exists when individuals do not understand that the defining purpose of clinical research is to produce generalizable knowledge, regardless of whether the subjects enrolled in the trial may potentially benefit from the intervention under study or from other aspects of the clinical trial." To help counter this misconception, they have identified 5 key aspects of research that trial participants should understand (Table).

This boundary between practice and research echoes a similar distinction in the Belmont Report: "For the most part, the term 'practice' refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. By contrast, the term 'research' designates an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective."[2]

In a clinical care scenario, we trust that physicians have our best interests at heart and are recommending treatments they think are best for us as individuals and that have a reasonable chance of success. In research, however, physician-investigators follow a research protocol that is uniformly applicable to all participants in determining what treatment is given. The primary purpose of the trial is to answer the research question, not to individually help the participant. Because our personal physician may often be the physician-investigator, the trust we have that our physician has our best interests at heart may carry over into the research context.

Clinical trials may be phase I in which benefits are nil to the research subjects, phase IV in which the US Food and Drug Administration (FDA) has already found the drug to be safe and effective for the labeled indications, or in between these 2 extremes. Many clinical trials may provide some benefit to the participant, but some trials may not be beneficial, some may involve harms, or the participant might be assigned to a placebo arm. Treatments are often randomized and are therefore not tailored or adjusted to what an individual needs. The potential harms and lack of any guaranteed benefits are acknowledged in the consent form. Generally, the consent forms approved by institutional review boards (IRBs) honestly and transparently convey to the participants the risks and the limited, if any, potential benefits of the trial.

Pentz et al queried 95 participants in phase 1 trials to obtain an estimate of how many participants had therapeutic misconception.[3] Sixty-five of 95 respondents (68.4%) had therapeutic misconception, associated in a multivariate analysis with lower education and family income (P=0.008 and P=0.001, respectively), but therapeutic misconception "was not associated with the vulnerability of having hardly any treatment options."

What does this finding say about the ethics of the consent process if those signing the consent form have a perception of the meaning that is very different from what the investigators intended?

Researchers are aware that consent is a process, and the written form is only one aspect of that process. The study team leads a discussion, often a long one, to explain the consent form, answer questions, and evaluate a participant's understanding of the content. This discussion continues throughout the study. Nevertheless, a participant's perceptions are often different than the consent form content.

From a legal perspective, all applicable consent requirements—those of the FDA,[4] of the Department of Health and Human Services,[5] and of each state's particular consent law[6]—emanate from the basic ethical tenet that every adult of sound mind has the right to make an informed decision about healthcare. For the consent process to be considered legally effective, sufficient information—not only about risks but also about the purpose and nature of the research—must be communicated to the subject during the consent process with content and in a manner understandable to a layperson. The FDA regulations state that one of the basic elements of informed consent that must be provided to a subject is a "description of any benefits to the subject or to others which may reasonably be expected from the research."[7] Further FDA guidance provides as follows:

> The description of benefits to the subject should be clear and not overstated. If no direct benefit is anticipated, that should be stated. The IRB should be aware that this element includes a description not only of the benefits to the subject, but to "others" as well. This may be an issue when benefits accruing to the investigator, the sponsor, or others are different than that normally expected to result from conducting research. Thus, if these benefits may be materially relevant to the subject's decision to participate, they should be disclosed in the informed consent document.[8]

Table. Five Draft Dimensions of Research That Trial Participants Understand[1]

Dimension 1. Scientific Purpose
Clinical research is designed to produce generalizable knowledge and to answer questions about the safety and efficacy of intervention(s) under study to determine whether or not they may be useful for the care of future patients.
Dimension 2. Study Procedures
Participation in a trial may involve procedures or tests, in addition to the intervention(s) under study, that are intended only or primarily to generate scientific knowledge and that are otherwise not necessary for patient care.
Dimension 3. Uncertainty
For intervention(s) under study in clinical research, there often is less knowledge and more uncertainty about the risks and benefits to a population of trial participants than there is when a doctor offers a patient standard interventions.
Dimension 4. Adherence to Protocol
Administration of the intervention(s) under study is typically based on a strict protocol with defined dose, scheduling, and use or avoidance of concurrent medications, compared to administration of standard interventions.
Dimension 5. Clinician as Investigator
Clinicians who are in healthcare settings provide treatment; in a clinical trial setting, they are also investigating the safety and efficacy of an intervention.

The failure of a physician-investigator to obtain a meeting of the minds from the subject as to benefits of the research will result in a per se legally ineffective consent.

Research participants want a good outcome. Even in the face of a phase I consent form warning of potential harms and no benefits, many participants want to believe in a good personal outcome. Our perceptions are formed in a context in which we tend to trust our doctors and study teams, and this trust makes us less influenced by the consent form wording. In the consent process for research studies, study teams should work against therapeutic misconception. A useful technique is to highlight the 5 key aspects of research proposed by Henderson et al and to ensure that participants understand them.

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