Phase 0 Trials: Are They Ethically Challenged?

T. Patrick Hill

The answer to this question depends on how this emerging clinical research model challenges the standard expectations of clinical trials and whether ethics itself has to formulate a new critique to account for the novel aspects of phase 0 trials. In addition, providing an answer is a matter of some urgency because the expectation is that the number of phase 0 trials being conducted will only increase. Speaking of the Food and Drug Administration's guidance document on phase 0 trials, Colin Garner, CEO of Xceleron, described it as "a great boost and vote of confidence in innovative new techniques such as microdosing that can help pharmaceutical companies to develop products faster and more efficiently."1

According to the Food and Drug Administration,2 a phase 0 or exploratory Investigational New Drug study is designed to take place "very early in phase I, involves very limited human exposure, and has no therapeutic intent (e.g., screening studies, microdose studies)." The Food and Drug Administration notes further that such studies precede "the traditional dose escalation, safety and tolerance studies that ordinarily initiate a clinical drug development program." Typically, phase 0 trials enroll few patients, perhaps 10 or less, and involve administration of small doses of an experimental drug over a shorter period of time. This means that because patients are receiving doses that are subtherapeutic, or that produce a pharmacologic rather than a toxic effect, their risk of harm is much less than in a conventional phase I trial. However, unlike phase 1 cancer trials in which drug administration continues if there is evidence of clinical benefit, phase 0 trials lack even therapeutic intent.

The scientific justification for phase 0 trials includes determining sooner whether a new drug is capable of modulating its intended target in humans, and/or generating pharmacokinetic data, such as the biodistribution and metabolism of a drug. This knowledge is often critical in drug development and may avoid larger phase I and II trials for drugs shown to have unfavorable pharmacologic properties in phase 0 trials. In one significant respect (i.e., the involvement of human subjects), the phase 0 trial is no different from the conventional clinical trial. However, in another equally significant respect (i.e., the use of the human body as a pharmacokinetics and pharmacodynamics laboratory), the phase 0 trial is markedly different from the conventional clinical trial. Reconciling these two respects constitutes the basic ethical challenge posed by phase 0 trials.

As a necessary but not sufficient condition ethically justifying human involvement in clinical research, the experiment has to be scientifically valid, based on a reasonable hypothesis and a research methodology that can be expected to reach its stated end points. This may be where phase 0 cancer trials are questionable, for now at least. As one commentator puts it, we may think that we have the biological, pharmacological, or imaging capabilities to measure the effect of the drug on its target (1). "But in oncology, we just don't have that for many of our targets now." And because validation of these assays in patients is often difficult, phase 0 trials are at serious risk of failure. The same commentator notes that they run the risk of concluding that a drug is inactive when in fact it is active. Under such circumstances of futility, it would be unethical to involve human subjects, especially seriously ill human subjects, because there is no possibility of any benefit, direct, indirect, or even to others. Thus, an essential requirement for the validity of phase 0 trials would be the availability of assays reasonably validated in earlier animal and in vitro studies for the purposes of subsequent clinical studies.

As a necessary and sufficient condition, justifying human involvement in clinical research, the experiment has to of benefit to those participating. In clinical research, the term benefit can mean benefit that is direct, indirect, or "to others." Given the design and purpose of phase 0 trials, there can be little expectation of either direct or indirect benefit from them. In the absence of therapeutic intent, it would be naive to anticipate any direct benefit to a human subject from a microdose, for example, of the immediacy that would qualify benefit as direct. And because phase 0 trials are designed to last between 7 and 14 days, it is difficult to see how they can be expected to provide indirect benefit that usually includes the physiologic and psychologic benefits derived from simply participating in a trial.

This seems to leave "benefit to others" as the sole possible benefit to be associated with phase 0 trials, suggesting how they are breaking new ethical ground by challenging the long-standing principle that the interests of human subjects always take precedence over the interests of society (2). The National Bioethics Advisory Commission captured the essence of the challenge when it observed that the notion of "benefit to others" derived from trials in which the probability of direct benefit is virtually nonexistent "poses in the most dramatic form the conflict between the societal interest in the conduct of important and promising research and the interests of potential subjects (3)."

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1 http://www.xceleron.com/metadot/index.pl?id=2222&isa=Newsitem&op=show

2 http://www.fda.gov/cder/guidance/6384dtf.htm
One reasonable resolution of the conflict is to acknowledge a moral obligation to participate in clinical research. In a recent article (4), John Harris advances two separate but complementary arguments for such an obligation, the first of which is considered here. This argument is based on the principle of “do no harm” applied to situations where, according to Harris, it is reasonable to think that our actions will, or will probably, prevent serious harm. That is, if we can reasonably act, despite the risk of harm to ourselves, but with the likelihood of benefit to others, we should act or accept responsibility for the harm that follows from failing to act. Peter Singer’s formulation of the principle (“If it is in our power to prevent something very bad happening, without thereby sacrificing anything of comparable moral significance, we ought to do it”) also has applicability (5).

As Harris has put it, most diseases generate needs in those affected, needs in their relatives, friends, health care providers, and society at large. But because medical research is necessary for relieving such needs, furthering clinical research, when it is within your power, becomes a moral obligation (4). Cancer patients are uniquely positioned to contribute to the research undertaken in phase 0 trials, thereby helping to prevent the harm of cancer from others in the future.

A similar argument may be made for non-oncology phase I trials, which involve healthy volunteers who cannot benefit from the drug even as they expose themselves to some risk of harm. These healthy-volunteer trials exemplify the significance of altruism in clinical research. Altruism is possibly more explicit as a motive in such trials and may explain why participants are often paid as reward for their participation. It may also explain in part why we have not recognized sufficiently how they depart from the orthodox ethics formula for clinical trials with their emphasis on altruism. The NIH list five benefits of volunteering for clinical research. Three are “benefit to others”; one is “indirect benefit”; and one is compensation. No direct benefit to participants is listed.

In contrast, participants in phase 0 oncology may be sick. Although they consent to participate, it is reasonable to think they do so reluctantly. Under these circumstances, giving moral weight to altruism to justify participation is understandably more troubling and explains the emphasis on direct benefit. However, were we to do so, we might also consider compensating participants financially.

It seems clear from this analysis that phase 0 cancer trials are both ethically challenged and ethically challenging. Success in overcoming the former is largely a matter of meeting the long-standing requirements of scientific validity. However, success with the latter means winning the unfamiliar argument that there is a moral obligation to participate in clinical research. Key to that is a reassessment upwards of the moral weight of “benefit to others” sufficient in itself as benefit to warrant the conduct of phase 0 cancer trials. Success on both counts is necessary to show that phase 0 trials represent a departure, legitimate both ethically and scientifically, from conventional clinical research that bodes well for clinical science, participating human subjects, and society at large.


References

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