The Ethics of Phase 0 Oncology Trials

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Abstract

Recent guidance from the Food and Drug Administration supports the conduct of a new type of exploratory clinical trial, commonly called phase 0 clinical trials. Proponents argue that phase 0 clinical trials have the potential to expedite the development of new oncology drugs while exposing fewer research subjects to the risks of experimental treatments. At the same time, phase 0 oncology trials raise important ethical concerns that have received little attention. In particular, there is a question of whether it is ethical to enroll individuals in research that offers them no potential for clinical benefit. Further concern focuses on the inclusion of terminally ill and consequently vulnerable cancer patients in these trials. To evaluate these concerns, this article considers relevant empirical data from phase 1 oncology trials and develops several recommendations regarding the conduct of phase 0 clinical trials in oncology.

Standard evaluation of oncology drugs involves in vitro and animal testing followed by phase I studies in humans to assess toxicity and establish a dose for future phase II and III trials. Because preclinical studies often do not provide an accurate estimate of the pharmacokinetics and toxicity of candidate agents in humans (1–3), many phase I agents ultimately are abandoned (1–3). The resulting costs in time and resources raise the need for alternative methods of drug development (3–5).

In response, the US Food and Drug Administration recently issued guidance on exploratory investigational new drug trials.3 These trials are defined as ones that occur before traditional phase I dose escalation, safety, and tolerance studies and, hence, have been labeled phase 0 studies (5–7). Phase 0 oncology trials focus broadly on defining the pharmacokinetic and pharmacodynamic properties of investigational agents or confirming the mechanism of action, biodistribution, or target modulation of an agent. They typically involve administration of a single dose or a short course of microdoses to a small cohort of volunteers and may require multiple blood draws and, at times, biopsies of relevant organs or tissue (1–4).

Proponents argue that phase 0 trials have the potential to make drug development both more efficient, through earlier development of target assays and more informed phase I starting doses, and less resource intensive, as unsuccessful candidate agents are eliminated earlier in the process (1–5). This issue of CCR Focus explores several crucial aspects of phase 0 clinical trials, including goals, trial design, feasibility, community acceptance, and ethics (8–13). This last topic is the subject of the present analysis. In particular, we consider whether it is ethical to enroll individuals in research that offers them no potential for clinical benefit and also consider the ethical concerns raised by the inclusion of terminally ill and consequently vulnerable cancer patients in these trials (1, 2, 4, 6, 14).

Ethics of Phase I Oncology Trials

Given the small size and recent development of phase 0 oncology trials, there are almost no empirical data available on which to evaluate the ethical concerns they raise. Accordingly, we begin by looking to the phase I oncology literature, as such studies are closely related to phase 0 cancer trials and have been the focus of a good deal of ethical analysis. Similar to phase 0 trials, commentators argue that phase I oncology trials raise three primary ethical concerns: (a) their risk to benefit ratio is inherently unfavorable for subjects; (b) they enroll patients...
whose ability to provide valid informed consent may be compromised; and (c) they may take advantage of vulnerable subjects (15, 16).

Risk to Benefit Ratio. A longstanding controversy concerns whether phase I oncology trials offer subjects a chance of clinical benefit that justifies the risks and burdens they incur (15, 17–22). In response, a number of empirical studies have attempted to quantify the risk to benefit ratio of phase I oncology research. Estimates of response rates in phase I cancer studies do not pertain to phase 0 oncology trials, which hold out no potential for personal medical benefit. Conversely, the risk data from phase I trials may be relevant, although the extremely limited exposure to study drug in phase 0 trials should ensure lower (likely significantly lower) risks (1, 2, 4).

Meta-analyses find toxic death rates of ~0.5% in phase I cancer trials (23–26). The most recent study also reports that, of the subjects for whom specific toxicity information are available, ~14% experienced at least one grade 4 toxic event (23). Because most phase I studies are designed to escalate the dose until toxicity is observed, the relatively high rate of toxicity in these trials is not surprising. In contrast, phase 0 trials do not use toxicity as an end point, nor do they involve dose escalation. Thus, phase I meta-analyses likely provide an exaggerated estimate on the upper limit of risk in phase 0 trials.

The few studies that have assessed quality of life and performance status of phase I oncology subjects suggest that trial participation does not negatively affect either measure, at least compared with support care alone (27–29). Others report that early-phase oncology research subjects sometimes feel burdened by the repetitive procedures and time commitment involved (30, 31). These same routines and research interactions, however, may also provide some psychological benefits, such as feelings of comfort and increased control (17, 32).

Because the time commitment in phase 0 oncology studies is much shorter, subjects are much less likely to feel burdened by their participation, although some phase 0 procedures (e.g., biopsies) can be onerous, even invasive (2). Furthermore, the abbreviated nature of phase 0 trials will likely limit the extent to which phase 0 subjects experience indirect or collateral benefits from their routines and contact with research staff (14). Nevertheless, phase 0 oncology subjects may derive some psychological benefit from participating, similar to oncology subjects whose involvement in an early-phase study provided “a purpose in their lives” (31).

In general, clinical research should be conducted only when the risks are minimized, the potential benefits to subjects have been enhanced, and the potential benefits to subjects and society justify the risks and burdens to subjects (33). Thus, clinical trials that do not offer the possibility of personal medical benefit, exposing subjects to some risks for the benefit of others, can be ethically permissible (18). Net risks to subjects, however, should not be excessive. Although the absence of sufficient data on the effect of phase 0 studies makes evaluation difficult, the phase I risk data, together with the assumption that the risks of phase 0 trials will be significantly lower, suggests that the net risks of most phase 0 should be acceptable, assuming the study is scientifically valid and socially valuable.

Informed Consent. Most clinical research trials require informed consent. Concern, however, has been raised that the subjects of phase I cancer trials may not provide valid consent (16, 19–21, 34–38). In particular, some commentators worry that subjects of phase I cancer trials have an exaggerated estimate of the chance of therapeutic benefit (34, 36, 39, 40). Empirical studies find that phase I oncology trial subjects are highly optimistic about their chance of personal benefit (17, 32, 34, 39, 41–44) and are motivated by hope for clinical improvement (32, 34, 36, 40, 43–47). Altruism, on the other hand, is much less frequently identified as driving their decision to enroll (34, 36, 40, 43, 45); when cited as a motivating factor, it typically is not the main reason for participation (32, 39, 46, 47). In one study, 61% of phase I oncology subjects were doubtful that altruism would motivate advanced cancer patients to enroll in non-beneficial research (34), and several phase I subjects in another study indicated “surprise” at the idea of participation based solely on altruism (45). Studies find, however, that individuals in other types of trials often participate in hope of helping others. For instance, Schaeffer and colleagues (44) report that “hope others benefit” is one of the two most common motivational factors for healthy volunteers and phase III trial subjects.

Independent of whether it is problematic for patients to enroll in phase I oncology trials for personal medical benefit, such motivation is inappropriate in the phase 0 context. At first glance, the phase I literature seems to indicate that most end-stage cancer patients are not motivated to participate in research based on altruism or a desire to contribute to medical science. It is difficult to draw conclusions about altruism of the terminally ill with regard to clinical trial participation from these data; however, as subjects were typically asked only about their primary reason for participation. It seems reasonable and not at all surprising that cancer patients who have exhausted their standard care options will be focused principally on their last chance (however small) of benefit (15, 17, 48). Furthermore, the nature of phase 0 oncology trials (less burdensome than phase I but with no promise of personal medical benefit) might facilitate more altruistic participation. As Kimmelman (6) recognizes, further inquiry is needed into the willingness of the terminally ill to undergo risks and take on burdens solely for the benefit of others.

Other empirical studies show that phase I oncology subjects are generally satisfied with the information they receive (45, 46) and the vast majority report that they understand most (if not all) of the trial information (34, 36, 39, 40, 46). There is no reason to think that, provided the informed consent process is procedurally similar and has adequate content, phase 0 oncology subjects should not be similarly satisfied. It is worth noting, however, that phase I subjects less frequently recall having discussed key aspects of trial participation than do the investigators who accept them.
In empirical evidence that oncologists overestimate the probability of success of the investigational therapy (48, 50–52). There is a degree of fiduciary duty and when there is a potential conflict of interest on the part of the investigator (49). The nature of the research may influence the subject's enrollment decision insofar as they flavor the presentation of trial information. It is also important to note that physicians overestimate the risks of trial participation as well (40, 42).

Objective assessment of phase I trial subjects' understanding suggests that subjects may know and appreciate far less than they themselves perceive (34, 36, 39, 40, 46). A commonly used surrogate marker for objective understanding is the subject's ability to state (or recall) the purpose of the trial as that of toxicity and dose determination. Most empirical reports estimate that no more than 50% of phase I subjects are able to correctly describe the aims of the trial (34, 36, 39, 40, 49). Many critics thus conclude that subjects do not understand or appreciate the information material to their decision to participate in phase I oncology trials (16, 40). Others have declined to draw such conclusions given the paucity of the data and the fact that many empirical evaluations likely are testing individuals recall rather than their understanding, especially when several days, weeks, or months have passed since consent (14, 17).

In terms of phase 0 oncology trials, the subjects' ability to explicitly state the scientific purpose of the study does not seem essential. For example, an individual's failure to recall that the purpose of the trial is to determine the exact correlation between a particular surrogate marker and the deposition of drug in tissue is not worrying. In contrast, it is crucial for phase 0 subjects to understand the lack of potential clinical benefit. The likelihood that phase 0 subjects will fall prey to the therapeutic misconception seems lower than phase I subjects, as the shorter and less intensive and interactive research experience (1) will less resemble previous treatment or care. Nonetheless, subjects should have a clear understanding of the risks and, more importantly, the lack of potential for clinical benefit.

A final aspect of informed consent that has been given much attention is the voluntariness of the subject's enrollment decision. As Franz Ingelfinger argued:

"Incapacitated and hospitalized because of illness, frightened by strange and impersonal routines, and fearful for his health and perhaps life, he [the patient-subject] is far from exercising a free power of choice when the person to whom he anchors all his hopes asks, 'Say, you wouldn't mind, would you, if you joined some of the other patients on this floor and helped us to carry out some very important research we are doing?" (50).

A legitimate concern about voluntariness in phase I oncology research stems from the influence or pressure physician-investigators may place (intentionally or not) on patient-subjects, especially when the relationship is characterized by a degree of fiduciary duty and when there is a potential conflict of interest on the part of the investigator (48, 50–52). There is empirical evidence that oncologists overestimate the likelihood of medical benefit to patients on phase I trials (40, 42, 53), which may play a role in how they present information to patients (35). As Emanuel notes, "There is no implication that these physicians are intentionally lying or dissembling, only that, like the rest of us, they believe in their therapies and tend to perceive benefits of therapy as greater than actually demonstrated in published trials" (16). Oncologists relay information about the trial to patients who then make a decision about enrollment based, in part, on the information they receive; thus, the oncologist's own expectations for success may influence the subject's enrollment decision insofar as they flavor the presentation of trial information. It is also important to note that physicians overestimate the risks of trial participation as well (40, 42).

Empirical studies disclose, however, that physicians are not as influential in the phase I oncology subject's decision to enroll as one might expect. For instance, only 7% of phase I oncology subjects feel moderate or significant pressure from physicians to participate (17), and only 9% think that patients, in general, are subject to enrollment pressures (54). Whereas trust in or advice from the physician-investigator does seem to be a relatively important factor in a subject's decision to enroll in early-phase oncology research, the majority of studies report that it is not the main reason for participation (39, 40, 43, 46, 48). Indeed, approximately half or less of phase I subjects list the physician-investigator as the primary person with whom they discussed their enrollment decision, a relatively low percentage given the importance of the information the physician-investigator imparts (34, 40, 55). The claim that physician-investigators do not inappropriately influence early-phase oncology subjects is further supported by evidence that the majority of subjects consider themselves the primary decision maker with regard to their choice to enroll (34, 40, 48).

Whatever pressure phase I subjects feel to enroll, phase 0 subjects should experience even less. Given the inherently nonbeneficial nature of phase 0 oncology trials, both terminally ill cancer patients and their physicians should be less susceptible to the therapeutic misconception. Participation in phase 0 cancer studies represents not a last chance for therapeutic response but rather an altruistic contribution to medical science unlikely to significantly affect the subject's life. Conversations and deliberations regarding the decision to enroll should thus be characterized by less pressure.

**Vulnerability.** A final ethical issue related to phase I oncology trials is the perceived vulnerability of terminally ill cancer patients (19, 22, 34, 35, 38, 41, 42, 51, 52, 55–57). Although closely linked to the previous concerns, worries regarding vulnerability may be present even when "there is sufficient disclosure, and the patients are making an informed and voluntary decision" to participate (15, 16). If indeed present, such vulnerability could cause subjects to be less able to protect their own interests and more susceptible to being exploited (52). For this reason, it has even been suggested that the terminally ill should be excluded from nonbeneficial studies that involve any risk (38).

Extensive phase I oncology research demographic information finds that subjects typically are not "economically,
educationally, or otherwise socially disadvantaged;” indeed, they oftentimes are highly advantaged individuals (56). A large, multicenter study of phase I subjects reports similar characteristics (17). Furthermore, after examining data on performance status and therapeutic experience, Seidenfeld and colleagues (56) conclude that compared with terminally ill cancer patients as a whole, phase I oncology subjects are not “the most ill, inexperienced, or ill informed.”

Because most phase 0 oncology subjects are likely to be drawn from the same population as phase I subjects, such conclusions should extend to them as well. Although further research into this area is warranted, the discovery that terminally ill cancer patients are vulnerable would not necessarily render phase 0 oncology studies unethical. Even vulnerable populations are capable of understanding and appreciating information and expressing voluntary preferences, although additional safeguards may help protect them in the context of nonbeneficial research with more than minimal risk (15, 51).

**Recommendations**

Although the preceding analysis discloses no issues that render phase 0 oncology studies inherently impermissible, it suggests several strategies to minimize the risks and address the concerns associated with this new research paradigm.

1. **Evaluate the Value of Phase 0 Trials**
   In theory, phase 0 trials offer significant potential social benefits. It is too early, however, to determine whether these benefits will be realized in practice (2–4, 6, 14). To provide the necessary data, and determine whether phase 0 oncology trials should be continued, present conduct of phase 0 trials should include systematic evaluation of their value (6). Do phase 0 trials result in fewer individuals being exposed to nonviable oncology drugs; do they expedite the drug development process?

2. **Formally Evaluate Potential Subjects’ Understanding**
   Concerns about misunderstanding have led to the call for formal evaluation of subject understanding in a variety of clinical research contexts (44). The design and study population of phase 0 trials make this an attractive safeguard. To distinguish problems of understanding from problems with recall, such evaluation should occur soon after the study has been explained to the subject and before the subject is asked to consent. This evaluation should focus on assessing whether subjects understand five important concepts:
   - They are being asked to contribute to an effort to collect information that might help others in the future.
   - Participation offers no prospect of personal medical benefit.
   - Even when the risks are low, there is typically a high degree of uncertainty.
   - Participation is entirely voluntary.
   - Their enrollment decision will not affect their individual care.

3. **Reconceptualize the Investigator/Subject Relationship**
   Some of the misunderstanding that characterizes early-phase clinical trials likely arises from the fact that physician-investigators and subjects often regard clinical research as a context in which investigators help subjects with their illnesses. In phase 0 trials, however, investigators are not helping subjects; rather, subjects are helping investigators answer a scientific question. Taking steps to emphasize this aspect of the investigator-subject relationship may help to reduce misunderstandings and mitigate the effect of any vulnerability on the part of the subjects.

   A reasonable first step would be to require that someone other than the subject’s own clinician solicit consent (51, 58). In addition to eliminating Kimmelman’s (6) worry that subjects will feel obliged to enroll, this approach may minimize the chances that subjects regard themselves, in the context of the trial, as patients. Investigators also should treat subjects as contributors, not patients. A simple test investigators can use in this regard is to consider whether it makes sense, given the nature of their relationship with subjects, to share research results with them (57). If it does, the parties are less likely to regard themselves as physician and patient. In practice, the offer to share and the practice of sharing research results with subjects may help to underscore the experimental nature of phase 0 clinical trials. This approach also may encourage subjects’ sense of making a valuable contribution and is in line with the preferences of early-phase oncology research subjects (31, 46).

4. **Consider Modest Payments**
   Paying phase 0 subjects deserves consideration (14). Certainly, it seems reasonable to compensate subjects for any expenses or costs they incur. Many commentators view payment as problematic and warn that excessive payments may unduly induce individuals to participate. In the case of nonbeneficial research involving patients, however, payment, especially a small payment above and beyond expenses and costs, may help reinforce the idea that subjects are volunteers (not patients) who will receive no medical benefit from their participation.

5. **Reconsider the Appropriate Study Population**
   One last strategy to minimize the ethical concerns surrounding phase 0 oncology trials involves reconsideration of the study population. In phase I oncology studies, the enrollment of terminally ill cancer patients is justified by the fact that they are positioned to capitalize on whatever benefits may result from exposure to highly toxic drugs (21, 57). In phase 0 oncology studies, the risk of serious adverse events is much lower and the risk-benefit profile more closely resembles those of nononcology phase I trials; accordingly, consideration should be given to enrolling healthy volunteers. Although not feasible in all types of phase 0 oncology studies (such as those that focus upon characterization of the drug within tumor
Conclusions

The ethical issues that arise with regard to phase 0 oncology trials, although significant, are not insurmountable. Provided the phase 0 design is scientifically valid and subjects understand that such trials offer them no potential for medical benefit while exposing them to small (but uncertain) risks, it seems ethically permissible to conduct phase 0 studies. Although verification of the value of the phase 0 design remains the purview of the scientific community, the recommendations described here may help to mitigate concerns regarding subject vulnerability and consent.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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