Patient Perspectives on Phase 0 Clinical Trials

Martin Gutierrez\(^1\) and Deborah Collyar\(^2\)

Phase 0 clinical trials are considered first-in-human studies that require extensive agent characterization and target assay development before administration. Phase 0 clinical trial goals can include assessing the pharmacokinetic-pharmacodynamic relationships of an investigational drug. They cover the rational transition from preclinical to clinical drug development, which includes an assessment of drug effect on the target or surrogate biomarker and relationship between the biological effect and the pharmacokinetics of the drug. The main goal of a phase 0 clinical trial is to acquire information that supports the decision to continue clinical development and accelerates the design and success of subsequent larger phase I/II trials. The anticipated outcome of any specific phase 0 clinical trial must be deemed a benefit to society; that is, it should contribute to efforts of drug development and have scientific validity. This issue of CCR Focus is dedicated to exploring the issues surrounding the implementation of phase "0" trials in medical oncology (1).

**Patients as Participants**

From a patient’s perspective, the introduction of the phase 0 concept offers the opportunity to help improve how some drugs can be evaluated. Their involvement can help researchers and future patients identify possible treatment paths quickly—to either discard drugs that will not work or promote those that show activity. Patients can act as participants instead of research subjects and they play a valuable role in the search for better ways to detect diagnose, treat, and ultimately prevent cancer. There are, however, major ethical concerns associated with conducting early-phase clinical trials, in particular phase 0 trials, including the risk-benefit ratio, the lack of treatment intent, and the participant’s understanding of the informed consent document. Thus, attention to these issues is essential to the success of the approval and execution of phase 0 trial. The limited study drug exposure and risk of potential interventions are real challenges to participation. From a survey of phase 0 participants at the National Cancer Institute (NCI), we have learned that altruism, prior physician-patient relationship, and the participant’s general understanding of clinical trials will likely be important when considering how best to approach eligible patients about enrollment in phase 0 trials.

Patient risk and the risk to benefit ratio of the phase 0 trial are major considerations. The risks of participation in a phase 0 trial include those from required research-related interventions, such as serial tumor biopsies and computed tomography scans, and potential delay or possible future exclusion from participation in additional clinical trials that do offer the possibility of therapeutic benefit. There is no chance of direct medical benefit to participants who enroll in phase 0 trials, although this is balanced by the fact that there is limited study drug exposure with very little likelihood of toxicity. For phase 0 trials to be considered ethical, they must minimize risk to participants while offering important scientific value to society. Specifically, the samples obtained from participants for research must be used in validated assays with the goal of establishing whether the agent being evaluated is having its anticipated effect. This knowledge may improve the quality and efficiency of the subsequent clinical development of the investigational agent, making it available more quickly for future patients.

Because of the risk to benefit ratio of phase 0 trials, participant understanding is critical. In particular, the research participant must understand that, although his/her participation will contribute to the scientific effort, there is no possibility of direct therapeutic benefit. Investigators must consider the risks and benefits involved for people considering participation who may be especially vulnerable due to their health status or competence. It is also reasonable to exclude patients who are eligible to participate on a trial with therapeutic intent (i.e., phase I or II), as well as those for whom participation might eliminate future participation in a phase I or II trial.

**Informed Consent**

Once the social value and appropriate risk to benefit ratio has been determined, participant understanding becomes a priority. We know from previous studies on clinical trials in general that research participants are often motivated to enroll based on their interest in maintaining their positive relationship with their primary physician. Consequently, there is a clear and imperative need for the Investigator to carefully explain the differences between experimental research and therapeutic care with as much objectivity as possible. Word-processing programs can also help investigators simplify their language through grammar and readability statistics and tools.

Ensuring and documenting that a patient fully understands the objectives, procedures, risks, and benefits of a clinical trial inherently implies respect for a person. Providing this

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**Authors’ Affiliations:** 1Center for Cancer Research, National Cancer Institute, Bethesda, Maryland, 2PAIR: Patient Advocates In Research, Danville, California

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**Requests for reprints:** Martin Gutierrez, Center for Cancer Research, National Cancer Institute, Bethesda, MD 20892. Phone: 301-435-0591; Fax: 301-402-2553; E-mail: mgutier@mail.nih.gov.

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information in a way that promotes understanding respects the individual’s ability to make an informed decision. Investigators recruiting potential participants to a phase 0 trial must present the information about the expected risks and benefits of participation in the research in a realistic and straightforward way to reduce the incidence of a therapeutic misconception on behalf of the research participant.

Based on empirical evidence from the phase I literature, we know that the patient, the physician, and the patient-physician dynamic can influence the informed consent process. This is discussed extensively in Abdoler et al. (2) in this issue of CCR Focus. When asked, a phase I trial participant tends to believe they understand the trial objectives, but the majority are unable to correctly state the purpose of the study. In addition, many participants eligible for phase I studies enroll with the hope of direct medical benefit. In many cases, it is the desire or hope for direct benefit or a positive physiologic response that motivates people to participate in medical research. There is also evidence that principal investigators may overstate the likelihood of benefit in their presentation of the option of enrollment in phase I trials, which may contribute to the potential participant’s hope for benefit. To assure that an eligible phase 0 patient has understood the information provided, measurements of understanding are recommended. In fact, it may be prudent to raise the standards for early-phase studies to include documentation of understanding. It will be important as phase 0 trials are introduced and conducted to study their unique informed consent process. The results of such studies may also benefit the conduct of phase I and other clinical trials.

**Recruitment Experience in a Phase 0 Trial**

The NCI was successful in recruiting research participants to its first phase 0 clinical trial (3, 4). The objective of the study was to determine the dose level of ABT-888, an oral poly ADP-ribose) polymerase inhibitor that potentiates the cytotoxic effect of DNA-damaging agents in vitro and enhances the antitumor activity of cytotoxics in xenograft tumor models (3). This trial is discussed in more detail elsewhere in this issue of CCR Focus (5, 6). The protocol was approved by the NCI scientific review committee, Institutional Review Board, and Cancer Therapy Evaluation Program, and was reviewed by the NIH Bioethics Department. As a result of Institutional Review Board and Ethics Committee reviews, an explicit statement was added to the informed consent to acknowledge the nontherapeutic, nonpersonal benefit nature of the study: This clinical study does not intend to treat your cancer. Your participation in this study may delay (up to a period of 6-8 weeks) or exclude your ability to participate in other clinical trials. Research participants who agreed to participate were asked to initial this statement to confirm that they understood the purpose of the study: I understand that participating in this study will be of no therapeutic benefit to me but may be of benefit to others.

Study accrual began in June 2006; 24 participants were screened and 14 enrolled on the clinical trial. Referrals originated from prior participation in NCI studies (9) and prior patient-NCI physician relationship (5). The characteristics of screened participants are presented in Table 1. Nine of 14 participants underwent serial biopsies as required by the protocol. The most common protocol-related barriers described by those who declined to participate in the phase 0 study of ABT-888 included potential side effects, fear that study participation would preclude future participation in other studies, transportation or distance to the trial site, and lack of family support and primary physicians’ attitude toward participation in the trial (4). An assessment was also conducted to learn why patients chose to participate or not to participate in the phase 0 clinical trial. A total of 24 participants took the survey; 10 declined to participate in the clinical trial, whereas 14 agreed to participate. Reasons for declining participation included nontherapeutic study (2), biopsy requirement (2), recommendation by oncologist (2), family member influence (2), or condition requiring treatment (2). Reasons for participation included altruism (6), and altruism and waiting for another study (8).

The time from start to completion of the phase 0 trial of ABT-888 was 12 months. The information collected for this first phase 0 clinical trial conducted at the NCI informed the development and design of several combination phase I studies of ABT-888 with chemotherapeutic agents. The average time from a first-in-human single-agent phase I trial to a phase I combination trial is normally 2 to 3 years; however, the ABT-888 combination trials were started within 18 months. It is thought that the phase 0 trial helped shorten this timeframe.

**Role of the Patient Community**

The concept of phase 0 clinical trials is currently not widely known among investigators, patient advocates, or patients. Researchers like the possibility of screening multiple agents and multiple doses as early as possible in the clinical development process to evaluate whether they modulate the intended biological target. The patient community, however, is traditionally more interested in the clinical implications of a new drug than whether or not it modulates its biological target. The latter simply does not translate into a direct, positive clinical outcome for patients with cancer. In a small poll of patient advocates,3 they saw the potential for faster targeted drug

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3 Eleven patient advocates who are part of Patient Advocates in Research and work with Special Program of Research Excellence and Cancer and Leukemia Group B answered a short survey that was sent out before the September 5, 2007 NCI Workshop on Phase 0 Trials in Oncologic Drug Development.
development but were also concerned about multiple biopsies, the critical need to validate markers that correlate with disease outcome, and opportunity costs that patients would weigh between a phase 0 with no therapeutic potential compared with a phase I that might offer minimal benefit. All agreed that phase 0 trials are too new to offer educated opinions. One key question repeatedly surfaced. Is phase 0 about the patients or the drug? It is important, therefore, to explain the importance of early-phase studies to clinical drug development and assessment, even without the prospect of direct benefit to participants and patients. Patient advocates point out that many research participants have a clear understanding of their situation and can be quite savvy about clinical trials. They believe patients should be offered an opportunity to participate as long as the benefits and risks are clearly and effectively articulated. In fact, some patient advocates have helped develop better communication tools.

Patients and patient advocates are in favor of efforts to speed the drug development process but will need solid evidence rather than policies based on enthusiasm to understand and support the phase 0 paradigm. Exploratory investigational new drugs and phase 0 clinical trials may save money and time in drug development, but from the vantage of advocacy groups, it is currently unclear how participants will benefit. It is crucial to create a dialogue with the patient advocacy community about how phase 0 trials may expedite the pharmacologic and biological understanding of new drugs in the development process and perhaps translate into greater likelihood of therapeutic success. Only through such interaction and collaboration will the patient advocate community feel comfortable assisting investigators in recruiting patient volunteers to phase 0 clinical trials.

Because the drug development process confuses many in the medical, advocacy, and patient communities, materials that clearly state the conceptual framework of phase 0 clinical trials are imperative to create a healthy dialogue that delineates the advantages and challenges of this innovative approach. The experience and success of the first phase 0 study (ABT-888) at the NCI may help assure these communities that this concept, and patient participation, is valuable. At a minimum, any site that conducts phase 0 studies should have standard operating procedures that can be shared with participants to assure them that their efforts will contribute important information about potential new agents. One way to encourage this approach is for investigators to share the results of such studies in real-time as much as possible, especially at the end of the trial. Tools such as slide presentations, published articles, or other documentation will ensure that participants can clearly see the value of the study and how their contributions help. It is also recommended that phase 0 trials be called exploratory research instead of a clinical trial to help eliminate therapeutic misconceptions.

**Conclusion**

In sum, recruitment to phase 0 trials is feasible but dependent on patient altruism, prior physician-patient relationship, and careful planning and implementation of standards for communication and procedures. These studies can be ethically conducted and accrual completed in a timely fashion provided that interventions are of minimal risk, the study experience is commensurate with patient expectations, and the results are valuable to subsequent participants and society. Investigators who conduct phase 0 trials should create special procedures that complement the unique scientific opportunities while clearly explaining the lack of therapeutic benefits.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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**References**

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