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# Evaluating the Strategies on Ethical Grounds for Phase 0 Oncology Clinical Trials

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**Abstract**

Since the release of Exploratory IND guidance by FDA, phase 0 clinical trials have been criticized on many ethical grounds. Ethical concerns associated with phase 0 clinical trials include patients' recruitment without any therapeutic benefit, delay in treatment and delay for participation in other clinical trials, therapeutic misconception, invasive biopsy procedures, and risks of research-related interventions. Various approaches have been identified to enhance the ethical stature of these trials but still there is need felt for newer approaches to develop an effective ethical agenda for phase 0 clinical studies. This article provides newer insights and perspectives on phase 0 ethics and explores the various ethical concerns, with distinction from each others, involved in phase 0 trials, and put forward a critical review and ethical agenda of the best possible approaches for enhancing the ethical stature of phase 0 oncology clinical trials.

**Keywords:** Phase 0; Ethics; Exploratory IND; Clinical trials; Oncology

Traditional new drug development model has remained largely unchanged since last many decades with no productive innovation, which can be traced long back in the history [1]. Identifying the compelling need for innovative changes in traditional drug development paradigm, to enhance the efficiency and success rate of new drug development program, US FDA issued guidance on *Exploratory IND Studies* [2]. This guidance document provided legitimacy to the conduct of phase 0 studies, with flexibility of reduced preclinical testing requirements, intended for testing, via pharmacokinetic (PK) and pharm acodynamic (PD) assessment, of new agents in humans prior the traditional phase I dose escalation, safety and tolerability studies. To summarize, Exploratory IND (Exp IND) studies or phase 0 clinical trials are studies conducted with very limited human exposure (10-15 patients for a period of ≤ 7 days) and are non-therapeutic in nature as these use low doses of investigational agent unlikely to have any therapeutic effect for the study participants.

Inclusion of phase 0 studies in drug development process is still questionable since these do not replace traditional phase I trials, and also not provide any evidence for clinical efficacy and safety [3]. For the question, "Why not just include PD end-points in Phase I trials in order to avoid unnecessary addition of phase 0 trials to the drug development process?" it was proposed that incorporation of PD endpoints in phase I trials would, then, require full range of preclinical studies with the additional extensive resources for PD assay development and validation, which would, in turn, lead to the late initiation of phase I trials unlike to phase 0 trials [4].

It is claimed, by defenders of phase 0 trials, that these trials might help early elimination of the doomed molecules from further clinical development, thereby saving significant cost, time and valuable patient resources which would otherwise have wasted over non-promising molecules; and provides, so called, an opportunity for the development of validated biomarkers as a tool for expediting the new drug development pathway. Beginning from the release of this guidance document and initiation of phase 0 clinical trials by some institutions, a still ongoing criticism and debate have aroused, mainly because of their non-therapeutic nature, pertaining to various ethical concerns associated with the conduct of these studies.

## Ethics in Phase 0 Clinical Trials

Ethics in clinical research can be expressed as a product of morality and materialism (Box 1). Morality in clinical trials can be expressed as something related to humane moral values that restrain researchers to do anything wrong to the research study participant i.e. putting their lives on unnecessary risk. A respect for the lives of study participant is the inherent value to the morality. Moral values are required to be considered prior to initiation, while conducting and after the completion of a clinical trial. On the other hand materialism can be expressed as something related to the significance of the study results obtained from or the questions addressed by the study, in terms of the present or future benefits of society and scientific research.

In case of phase 0 trials, materialism can be expected to remain high for the benefits to society, scientific research and industry in terms of more efficacious and safer drugs reaching faster to society, development of biomarkers making drug development paradigm more efficient, and savings in terms of cost and time respectively. On the contrary, this seems to be the most valuable criticism of phase 0 trials evidencing the favor of the industry, research and society over the study participants by FDA, and some authors, therefore, criticize the patient participation into non-therapeutic studies [5,6]. The morality on the other hand in conducting phase 0 trials seems to be low because of no therapeutic

Ethics = Morality x Materialism

**Box 1:** Ethics in clinical research.

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benefit to participants, delayed participation of study participants in other therapeutic clinical trials, therapeutic misconception, invasive study procedures, and risks of research-related interventions including biopsies.

Ethical principles of biomedical research in humans state that the interest of patients prevails over society [7]. This basic principle is challenged by phase 0 trials where *benefit to others* takes precedence over the benefit to study participants because of low morality involved [8]. However, the comprehensive analysis of phase 0 ethical issues by Abdoler did not disclose any issue making these trials inherently impossible [9]; therefore, it becomes of significant importance to make every possible effort to increase the morality, involved in phase 0 studies, by lessening of factors, as much possible as, contributing to the low morality. Various strategies and approaches, to increase the moral value, were identified and implemented successfully in ABT-888 phase 0 trial at National Cancer Institute (NCI); however, still there is a compelling need to develop newer strategies to enhance the ethical stature of phase 0 trials.

## Study Patients: Research Subjects vs. Study Participants

Patients who get enrolled into a typical phase 0 study indeed are potential contributors to the research and help the study investigators to address a specific research hypothesis, but not the investigators are helping them because patients don't seem to receive any therapeutic benefit out of the study in exchange of participation in the study. Enrolled patients in phase 0 trials, therefore, are required to be recognized as *study participants* rather than *research subjects* [10]. This is the first and foremost attitude that needs to be acquired by phase 0 researchers toward the study participants. This issue is closely linked with the study's moral value as it involves an inherent respect for the study participants. Sharing the study results, on contemporary basis and after the study completion, with study participants would further reinforce the above idea, i.e. to make participants feel themselves as research contributors rather than just patients. Results of phase 0 trials should also be published or made available at publicly accessible electronic database [11].

## Patients' Participation in Phase 0 Clinical Trials

Patients' participation, in a study which does not provide any therapeutic benefit to the participants and involves invasive study procedures too, is the major ethical concern pertaining to phase 0 clinical trials [4]. This leads the risk-benefit ratio for phase 0 trials toward higher end. Some critics have questioned the ethical acceptance of recruiting patients in such studies where no direct patient benefit is offered [12]. Why, then, to put patients' lives unnecessarily on risk and delay their treatment? The debate is still on and this question remain unanswered adequately yet; however proponents of phase 0 trials argue that involved risk and treatment delay are balanced by much lower doses of study agent and shorter duration of exposure and drug wash-out period. Since the non-therapeutic nature of phase 0 trials cannot be overcome by the researchers; it is, therefore, required to minimize the risks, associated with investigational study agent, treatment delay and invasive biopsies, to lower, as much as possible, the risk-benefit ratio.

Factors identified as potential barriers to patients' participation in phase 0 studies may include (a) lack of therapeutic benefit; (b) invasive biopsies; (c) potential side effects deemed by patients; (d) fear in patients for delayed participation in or exclusion from other clinical trials that would otherwise provide therapeutic benefit; (e) decreased feasibility associated with distant trial site from home; (f) lack of support of family members; (g) negative opinion of primary physician; and (h) immediate treatment requirement [13]. On the other hand probable reasons for the patients' participation in phase 0 trials include (a) altruism; (b) prior patient-physician relationship; (c) prior participation in other trials with enhanced understanding of the research element and clinical trials; and (d) proven research orientation of the recruiting institution [9].

Patients' willingness to support research and help future patients is obviously the most important factor, being truly altruistic in nature, for participation in phase 0 trials and better patient participation could be expected with patients who have had prior participation in other research trials, as they can better understand the importance and element of research [14]. Altruism in this said population is evident from the successful accrual by NCI in ABT-888 phase 0 trial [13]. In addition to altruism prior physician-patient relationship is an important factor influencing patient participation and a good prior physician-patient relationship is expected to have better patient participation with duly improved appreciation of the risks involved in the study. It is hoped that better accrual can be obtained in the institutions with adequate infrastructure, dedicated research facilities, proven research orientation and past research track in comparison to general oncology clinics and hospitals; since the phase 0 research opportunity can be best utilized there with due commitment of obtaining useful results from each tumor specimen.

The opinion of primary physician of the patient may have potential implications on the patient's participation in a phase 0 study by appreciating the extent of risks to which patient may be exposed with study participation and by carefully judging the current treatment needs for the patient. Also there is a need felt to educate and spread awareness among patient and medical community so as to make them familiar with the concept of phase 0 trials. Apart from the above approaches enrollment of healthy volunteers should also be considered at least in those phase 0 trials that do not aim for the characterization of an anticancer drug in tumor tissues [9]. However, in case of healthy volunteers, potential restrictions posed by certain prohibitive properties of the study agent, such as mutagenicity and carcinogenicity for example, are required to be taken into consideration and should be investigated adequately prior the study initiation.

## Informed Consent and Therapeutic Misconception

For phase 0 studies, being a departure from typical therapeutic studies, obtaining a well justified and adequately documented voluntary informed consent from study participants is another critical ethical concern [4]. Therapeutic misconception could be said to happen when phase 0 participants do not understand the non-therapeutic nature of the study explicitly and might think of therapeutic benefit which is generally expected from the typical clinical trials. Special precautions are, therefore, required to be taken during informed consent procedure in phase 0 studies. Investigator should carefully explain the experimental research in comparison to therapeutic care so that non-therapeutic nature is clearly understood by the study participants. Also the phase 0 trials are required to be documented and titled as *exploratory research* rather than as *clinical trials* to avoid any minimal misconception [10]. It is required to ensure that participants have understood fully that (a) there is no personal medical benefit; (b) study could only help others in future; (c) unforeseeable risks are possible; and (d) decision is entirely voluntary which is not going to affect their medical care [9]. The understanding of the participants is required to be documented that could be done by addition of an explicit statement to the informed consent document requiring participants' initials, and which should acknowledge clearly that participation in study could lead to a possible

delay in the treatment and no personal treatment benefit is expected out of the participation in study. The statement that was added to the informed consent document in ABT-888 phase 0 trial at NCI, as a result of ethics committee review, could be used as an appropriate phrase for this purpose: "*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*". Agreed participants should be asked to initial this statement confirming that the purpose of the study is fully understood by them: "*I understand that participating in this study will be of no therapeutic benefit to me but may be of benefit to others*" [10].

In addition, options of other clinical trials, which are likely to provide medical benefit, are also need to be discussed clearly during the informed consent process of phase 0 studies. Modest payments should be considered since excessive payments may unduly influence the decision of participants [9]. Exclusion of vulnerable patient population from the study and inclusion of impartial witness during the informed consent process, as a general practice, could possibly enhance the ethical stature of phase 0 trials.

## Delayed Participation in Other Clinical Trials

Risks of phase 0 participation include delayed participation in or exclusion from other clinical trials, which might otherwise provide therapeutic benefit. This sets forth another ethical concern associated with phase 0 studies, which goes severe, particularly where immediate medical care is required for a patient. Proponents of phase 0 trials, however, argue that treatment delay is minimized by limited duration of exposure (≤7 days) and shorter drug wash-out period (≤ 2 weeks). In ABT-888 phase 0 trial with 2 weeks washout period, all patients without significant delay participated in other trials.

For each patient required a defined plan for overall clinical care integrated with phase 0 participation and not to exclude phase 0 participants from later phase trials of same or similar agents [3,4]. Allowing enrollment of phase 0 participants in other clinical trial, of therapeutic nature, of their choice will require an acceptance of phase 0 participants as altruistic research contributors across the oncology community with changing study eligibility criteria [4]. A plan for overall clinical care for individual patient should be devised with a firm commitment to implement with due responsibility. If required, the discussion of overall clinical are plan with patient and primary physician could help a great deal. The clinical care plan needs to define what extent of medical care is required for the patient, how and when the medical care would be provided either by institution itself or by helping the patients to be enrolled in other suitable clinical trials of therapeutic nature. Patients requiring immediate medical care and patients whose participation in phase 0 trials might eliminate participation in other trials should be excluded from phase 0 trials [15,16].

## Study Design and Scientific Validity

Careful designing of phase 0 trials is required so as to make full utilization of tissue samples for the research purposes. Pharmacodynamic assay and biomarker should be validated and clinical modeling of standard operating procedures (SOPs) for obtaining tissue sample, handling and storage is required prior study initiation to obtain maximally useful results from the human tissue samples. Based on sound scientific principles and preclinical evidences study should be so designed that minimizes the possibility of invasive tumor biopsies. The ABT-888 phase 0 trials at NCI were designed with a minimum possible number of biopsies, i.e. only one pre- and one post-treatment biopsy. Post-treatment tumor biopsy was done only after the confirmation of both threshold/minimum level of target expression in pretreatment sample required to adequately detect the drug effect and achieving the post-treatment threshold plasma drug level required to show target effects as defined with animal models. This minimized the requirement of post-treatment biopsy procedures [15]. Pocard et al. recently proposed an exploratory methodology involving the patients with advanced or metastatic disease in phase 0 trials, who are waiting for surgery. This approach could have several potential advantages including: post-treatment biopsies can be merged with typical surgical procedure; and in situ dosage of the drug could be practiced thereby allowing the drug directly to the tumor tissue [17]. Furthermore definition of endpoints is required to be in real time to avoid any possible treatment delay.

Three obvious arguments can be raised over the scientific validity of phase 0 trials. First, whether the PK results obtained from a micro dose study will, in true sense, predict the PK results of a full-dose study. Because for the PK evaluation, if non-linearity of PK exists for the molecule under investigation, this may impose serious challenges for extrapolation to the PK profile at therapeutic doses. This is a major concern related to PK studies because various practical aspects can deviate the PK results at micro doses [18,19]. Therefore, prior confirmation of the validity of dose extrapolations in preclinical studies, and expert analysis while interpretation and extrapolation of micro dose PK results, are required to make phase 0 studies scientifically useful. Secondly, whether the biomarker employed, for the pharmacodynamic assessment, is reliable, valid and robust enough to assess the PD effects of the study agent at the molecular level. Evidences and reasons are there in literature that, if the study agent works through a different molecular mechanism in humans or the mechanism of action of a study agent fails to produce a desired downstream event of a series of molecular reactions, such as apoptosis which is actually being measured by the biomarker assay, as it may require other additional events which are not a direct consequence of agent's mechanism, then it may lead to termination of further clinical development of the molecule [4,20]. Thirdly, since there is always a possibility of false negative results particularly with small and heterogeneous patient population, to rule out the possibility of false negativity, larger trials with higher doses and other possible biomarkers may be required [4,20,21]. Therefore, the question that still stood before investigators is that, with challenges of micro dose PK results, questionable reliability of biomarkers, and possibility of false negative results; is it justified enough to conduct the phase 0 studies with non-therapeutic intent? This article may not be an appropriate conclusive referee for this debate; however, it is noteworthy that to enhance the scientific validity of phase 0 studies, validity of dose extrapolations is required to be confirmed prior to study initiation and a valid biomarker should be employed in the study.

## Unforeseen Adverse Events

The possibility of occurring unforeseen adverse effects caused by research related interventions including of tumor biopsies, in phase 0 clinical trials, could not be denied completely, and this may count as another risk of participation in phase 0 trials in addition to delayed participation in other trials. Researchers comment that the probability of adverse effects is, however, expected to be minimized since phase 0 trials use relatively much lower drug dose, with approximately 100x safety margin, which otherwise have evaluated as safe in preclinical testing. From the ABT-888 phase 0 trial it is evident that low doses of drug were well tolerated and trial reported mild dizziness and nausea for only one patient, having a history of recurrent nausea and dizziness

| Issue / problem | Approaches |
|---|---|
| Patients as research subjects | Recognize patients as participants and contributors in research rather than research subjects<br>Share study results with participants<br>Make results availability at publicly accessible database |
| Patient participation | Good prior patient-physician relationship<br>Approach patients who have had prior clinical research participation experience<br>Choose Institutions with proven research orientation, research facilities and infrastructure<br>Increase awareness of phase 0 concept among patients and physicians community<br>Devise and implement an overall clinical care plan for individual patient<br>Discuss overall clinical care plan with patient, family and primary physician<br>Consider patients with advanced or metastatic disease waiting for the surgery<br>Consider enrollment of healthy volunteers in phase 0 trials those do not aim for the characterization of an anticancer drug in tumor tissue |
| Informed consent and therapeutic misconception | Carefully explain to patients: non-therapeutic nature, study procedures and benefit to others<br>Document phase 0 trials as exploratory or experimental research rather than as clinical trials<br>Add an explicit statement in ICD acknowledging no personal benefit and treatment delay<br>Document participants' understanding of study objectives and nature<br>Consider modest payment<br>Exclude vulnerable patient population<br>Include impartial witness as a general practice<br>Inform patients of limited preclinical testing done |
| Delayed participation in other clinical trials | Acceptance of ≤ 2 weeks washout period of phase 0 trials in other therapeutic clinical trials<br>Help enroll phase 0 participants in other clinical trials without any delay<br>Devise and implement an overall clinical care plan for individual patient<br>Exclude patients requiring immediate medical care<br>Allow phase 0 participants in later studies of the molecule, if found beneficial |
| Study design and scientific validity | Make full utilization of each tissue sample for the research purpose<br>Use validated and optimized PD assay<br>Confirm validity of dose extrapolations prior to study initiation<br>Use validates biomarker, if available<br>Establish and follow SOPs for assay and tissue handling procedures<br>Minimize possibility of invasive biopsies<br>Devise novel statistical designs with required power<br>Use scientifically justified drug doses<br>Consider patients with advanced or metastatic disease waiting for the surgery to merge post-treatment biopsies with typical surgical procedure |
| Unforeseen adverse effects | Use lower doses with greater safety margin<br>Monitor closely of any possible adverse effect<br>Provide adequate medical care |
| IRB review quality and efficiency | Seek review from IRBs experienced in phase 0 trials<br>Mutual acceptance of the review proposals between IRBs |
| Abbreviation: ICD, informed consent document; PD, pharmacodynamic; SOPs, standard operating procedures; IRBs, institutional review boards. | |

**Table 1:** An ethical agenda for phase 0 oncology clinical trials.

with narcotics use with receiving regular dose of narcotic during the trial, and mild dysgeusia not associated with anorexia for another one patient [22].

With any investigational therapy, however, the probability of occurring unforeseen adverse events can never said to be zero; no matter how lower the drug dose is administered. Further, since the safety foundation of phase 0 studies relies on limited safety studies, the possibility of adverse event cannot be ruled out completely. Some skeptics, on the other hand, comment that there are studies where potential toxicity occurred at very low doses [6]. Study participants are, therefore, required to be informed of limited safety and toxicology testing done prior to phase 0 studies. A close monitoring approach for any possible unforeseen adverse event is needed similar to other typical clinical trials [16]. Also, if required adequate medical care should be provided.

### Ethical Review

The concept of phase 0 trials is increasingly being accepted at both academic and industrial level [23]. The institutional review boards (IRBs) involved in ethical review of phase 0 protocols are, therefore, required to develop novel approaches balancing between non-therapeutic nature of these studies on one hand and productive research and rights, safety and well-being of participating patients on another. There is a need felt for qualitative studies which can evaluate the various positive and negative factors associated with phase 0 studies as well as the understanding of participants toward the nature and concept of these trials. Also there is a need for assessment scientific complexity involved in with adaptive and innovative statistical and clinical designs and use of surrogate markers and PD endpoints in phase 0 studies to enhance the review capacities of ethics committees for phase 0 trials [11]. These future assessment propagations are expected to clarify many of the ethical concerns of phase 0 studies, and also to enhance, then, the review capacity of the IRBs. It is advisable that researchers may seek review from IRBs having experience of reviewing phase 0 protocols. Furthermore IRBs newer for phase 0 trials could also sought expertise from the IRBs experienced in phase 0 protocol review.

## Conclusion

Conduct of phase 0 clinical trials has been criticized for various ethical concerns associated either directly or indirectly with phase 0 clinical trials. This criticism, however, does not prove that phase 0 trials are inherently impossible. It is hoped that these ethical challenges could be dealt with adopting and developing novel ethical approaches and better study designs. It is proposed that there is a need for developing, and progressive improvement of, an effective ethical agenda for the phase 0 studies (Table 1). IRBs involved in the phase 0 protocol reviews are required to develop newer approaches balancing between ethical issues and conduct of phase 0 studies. Studies, examining and focusing

on various ethical concerns, their qualitative effects and their probable solutions, are needed to be conducted by biomedical ethicists. Phase 0 trials have the potential to shift drug development paradigm towards a positive direction; and it is hoped that, on the cumulative side of future, patient community could be expected to be treated better and sooner with new more safe and efficacious drugs.

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