Upholding the Principles of Autonomy, Beneficence, and Justice in Phase I Clinical Trials

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In this issue, Kurzrock and Stewart explore the challenges faced by investigators and study subjects in adhering to protocol mandates in the phase I clinical trial setting [1]. The authors highlight the peculiarities of early-phase anticancer agent testing—in particular, the need for intensive monitoring that is required for patient safety and to position the compound for possible regulatory approval requirements in the future. The authors report the outcome of a review of 49 institutional phase I clinical trials activated between 2004 and 2007, which demonstrated an average of 45 mandated events per subject within the first 4 weeks on study. Even more concerning was the average number of 105 events observed in their review of 15 industry-sponsored phase I studies at the same institution. The authors see a direct link between increasingly complex study designs and failure to comply with protocol mandates. Given the current lack of clear regulatory guidance on how to handle protocol deviation that may arise from disparate patient factors and circumstances, fear of unwarranted regulatory sanctions creates the potential for subject coercion to ensure study compliance, which is a real threat to the ethical conduct of human subject research.

The significant progress made in the treatment of cancer in the last two decades owes as much to the increased understanding of the molecular underpinnings of cancer as it does to rationally designed, well-conducted human subject trials [2]. Carefully conducted clinical trials are essential for establishing the efficacy of novel agents prior to regulatory approval. By establishing the safety (or lack thereof) of promising new agents and by defining the optimal dose to be employed for future efficacy trials, the phase I trial setting is particularly critical to the success of this multistage process. Phase I studies therefore attract the most stringent degree of scrutiny at all levels of regulatory review and approval prior to study conduct. An appraisal of the core principles underlining ethical conduct of clinical research is timely given the work of Kurzrock and Stewart in this issue [1].

Beginning with the Nuremberg code through the Declaration of Helsinki to the Belmont Report, clinical research ethics has been distilled down to three core principles: autonomy, beneficence, and justice [3, 4]. Autonomy (or respect for people) demands that the ability of competent subjects to make their own decisions be recognized and respected, while also protecting the autonomy of the vulnerable by preventing the imposition of unwanted decisions. This basic principle gave life to the practice of informed consent, whereby a competent sub-

ject or legally authorized representative is allowed to make an informed decision to participate in a study or not. Although the consent process may be misconstrued as the mere physical act of getting the subject's signature on a document, granting consent should be understood as a continuous process that does not come to an end until a subject has reached a predefined status in the study or ceased participation. A challenging issue is how to strike a balance between a subject's autonomy and study compliance by a consenting subject already enrolled and actively participating in the study. Human subject clinical trials are research processes that seek generalizable knowledge. Therefore, conducting the studies in a methodical and controlled manner ensures reliability and validity of the results. The protocol document represents a well-thought-out process for achieving this ultimate research goal and should be strictly complied with.

Beneficence and the twin concept of nonmaleficence demand that subjects should not be harmed through the conduct of the study. Because most phase I studies are considered high risk for potential harm, it behooves all involved to ensure that the design and conduct of these studies minimize the possibility of harm given the limited chance of benefit for the vast majority of enrolled subjects [5, 6]. Risk mitigation should address both the probability and the severity of potential harm to study participants. Although investigators and institutional review boards appear to have a reasonable *modus operandi* for ensuring risk minimization, the degree of discomfort that subjects are required to bear in order to conform to protocol-mandated procedures are often underestimated and frequently overlooked. For instance, routine procedures such as blood draws may be considered to have no more than minimal risk, but the repeat visit required for the procedure may impose an unreasonable level of discomfort that is difficult to accurately quantify because of the differing clinical and social circumstances of study subjects.

Finally, justice in clinical research demands that all subjects be treated fairly. Thus, equals must be treated equally. The burden placed on the subjects should be commensurate with the probability of benefiting from the outcome of the research within the limits possible. This may be specific to the subject, although general benefit to a group, the whole society, or to the advancement of knowledge is also acceptable. Because the majority of investigational anticancer agents fail to gain approval (indicating that these agents turned out to be unsafe, ineffective, or both), the phase I trial setting is one area of clinical research in which a

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reasonable likelihood of individual benefit is difficult to estimate [7, 8]. Yet, thousands of patients with cancer enroll in these studies annually. Altruism may be a valid reason for patients to enroll in phase I studies, but truly separating this motive from therapeutic misconception and misestimation, which can be prevalent in patients with incurable disease, is challenging [9]. Moreover, the increasing need to obtain as much information as possible from a single study by using the same study to establish safety and proof of concept prior to efficacy testing restricts the equitable sharing of the burden across all patient groups who are likely to benefit should the investigational agent obtain regulatory approval.

Because human events rarely go as exactly planned, the feared outcome of protocol deviation or violation is inevitable in human subject research. Any unplanned departure from the protocol-required study conduct carries the risk that it will violate one or more of the ethical bedrocks of research. In addition, it may jeopardize the safety of the patient and/or the quality or validity of the results. Such acts of departure do happen despite the best efforts and intentions of an investigator. However, coherent policy guidance on how to best address such occurrences is currently lacking.

Recognizing the peculiar circumstances that surround unplanned deviations or violations may help in developing a management approach that is fair to all parties without jeopardizing the ethical conduct of human subject research. For instance, an intentional but preventable departure from the protocol by knowingly enrolling an ineligible patient is an egregious form of deviation that should warrant serious and immediate sanctions. On the other hand, a nonpreventable deviation may be beyond the control of all parties, even when recognized before it occurs, such as a patient's inability to make a required appointment due to a transportation problem. Certain deviations may even share some attributes of both examples, such as failure to obtain critical data mandated by the protocol due to willful neglect or preventable or unpreventable factors. Depending on the specific circumstance, certain types of protocol deviation may not warrant immediate sanction and can be managed through a well-thought-out and feasible corrective and preventative action (CAPA) plan reviewed and approved by the oversight committee. Failure to adhere to the approved CAPA plan would then constitute evidence of willful non-compliance that, if egregious enough, should result in appropriate sanctions against the study subject (usually through withdrawal from study) or the investigator (through referral to regulatory authorities or suspension from participating in the research study).

Although most protocols and consent information documents consider a study subject's failure to comply with protocol-mandated procedures as sufficient grounds for withdrawal from a study, judicious use of this provision requires that it should not be viewed as an instrument to coerce compliance. Threatening a subject with termination from the study to ensure compliance may violate patient autonomy and could be perceived as a form of retribution, especially for situations in which the protocol mandates are patently impractical. However, if the subject's clinical or social circumstances do not allow for reasonable compliance

with the protocol, termination of further participation is a fair and equitable course of action. Hopefully, such a decision would be preceded by a respectful discussion to determine the reason(s) for the subject's noncompliance with the protocol mandate, as well as alternative studies that may be appropriate for the patient's circumstance in the future. When the responsibility for a recurrent deviation lies with study staff, retraining or reassignment may be in order. Frequently, any remedial action or sanction falls on the subjects or the investigators, although study sponsors may be partly culpable through complex study design and an inordinate number of research-driven procedures that are irrelevant to the primary aim of the study. A deviation that results from impractical study design is best addressed proactively through a formal protocol amendment. In the case of industry-sponsored studies, investigators should maximize opportunity of the site initiation visit to identify any aspects of the protocol that may benefit from an amendment prior to enrollment of subjects.

The procedures for handling protocol deviations are plagued by divergent opinions among institutions, study sponsors, investigators, and institutional review boards. Without consistent guidance from the U.S. Food and Drug Administration (FDA) or the Office for Human Research Protections in the U.S. Department of Health and Human Services (DHHS), ad hoc definitions and guidance continue to be employed across institutions. Commonly employed definitions recognize a protocol deviation as an unintentional departure from protocol-specific study procedures or schedules that does not affect patient autonomy, safety, or study validity. On the other hand, a protocol violation (also called substantive deviation) refers to a significant divergence from the protocol by the patient, the investigator, or the sponsor that has a high likelihood to affect autonomy, safety, or study validity, including acts of omission or commission that affect subject consent, protocol-specified inclusion or exclusion criteria, primary objective endpoints, and/or good clinical practice guidelines. In recognition of this challenge, the DHHS Secretary's Advisory Committee on Human Research Protections has produced a set of recommendations that hopefully will be adopted by the DHHS and FDA to provide consistent definition and review processes for unplanned excursions from protocol-mandated study conduct [10].

The explosion in the number of purely research-driven procedures increases the likelihood of unplanned deviations during the conduct of the study [11]. Limiting the frequency and complexity of such procedures will serve a dual purpose: reducing the likelihood of protocol deviation and ensuring fairness. Performing some research-driven procedures in the phase II or III setting is an alternative approach that will also promote equitable sharing of the burden of research-related risk and discomfort. Although the concepts of autonomy, beneficence, and justice are well-enshrined in the clinical trials lexicon, integrating these ethical pillars into real-world practice is a continuing task. The firsthand experience shared by Kurzrock and Stewart in this issue [1] is a timely reminder through which we continue to mature from "know" to "know-how" so that attitude and practices conform not just to the letter but also to the spirit of these guiding principles.

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C/A: Consulting/advisory relationship; RF: Research funding; E: Employment; H: Honoraria received; OI: Ownership interests; IP: Intellectual property rights/inventor/patent holder; SAB: scientific advisory board

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EDITOR'S NOTE: See the accompanying article on pages 308–313 of this issue.