Ethics and Clinical Research: Improving Transparency and Informed Consent in Phase I Oncology Trials

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Informed consent is a basic ethical principal and requirement of clinical trials discussed in the Belmont Report[1] and the World Medical Association's Declaration of Helsinki[2] where "each potential subject must be adequately informed of the aims, methods, … anticipated benefits, and potential risks of the study and the discomfort it may entail." The purpose of this commentary is two-fold: (1) to share our observation that when a phase I cancer trial uses a risk-targeting design in dose-finding, that target is not generally disclosed in the written informed consent document and (2) propose simple ways to improve the informed consent process starting with individual phase I studies and extending to the larger research enterprise to help create a more transparent environment for clinical research.

Phase I studies set the foundation and dose for subsequent phase II-III studies, with 4,263 phase I cancer clinical trials recruiting patients per ClinicalTrials.gov on May 11, 2022. The consent process for phase I studies is always challenging because of divergent perspectives on the prospect of benefit in a phase I trial.[3,4] In addition, the stress and variable cognitive condition of patients with advanced cancer who enroll on such studies requires extra effort to properly assist the patient in understanding the benefit and risks of participation.[5] The written consent form assists in that interactive and iterative process and needs to reflect the risks and benefits of participation in the specific study which may differ considerably from studies in the past.

Given the challenges assessing the relationship between dose and clinical activity in early drug development, phase I designs commonly focus on toxicity when identifying candidate phase II doses. Some phase I designs (eg, the traditional 3 + 3 design, Accelerated Titration design, the Rolling 6 design, and IQ 3 + 3, IQ Rolling 6) seek to explore escalating dose levels subject to rules intended to limit patient risk for unacceptable toxicity[6-9]; others are risk-targeting designs (eg, the Continually Reassessment Method [CRM], Bayesian Logistic Regression Method [BLRM], modified Toxicity Probability Interval [mTPI], and the Bayesian Optimal Interval design [BOIN]).[10-13]

Between 1991 and 2006, only 1.6% of phase I oncology studies used risk-targeting designs[14] in dose-finding, whereas a sample of the last 3 months (May 24, 2022-August 24, 2022) of phase I publications shows nine of 35 (25.7%) used such methods. Risk-targeting designs specifically seek to find and focus on a dose that is expected to cause rapidly emerging severe or life-threatening adverse events in a predetermined percentage of patients, most commonly targeting one in four.[15]

With the emergence of risk-targeting designs, the consent process needs to adapt appropriately to ensure that the patient has a sufficiently clear understanding of the risks. In considering the ethical review of such trials, we identified two issues: (1) at the individual protocol level, a comparison of study protocols and associated consent forms, to the extent permitted, suggests that the written consent forms routinely fail to state the targeted risk when the study is specifically designed to escalate the risk exposure to a prespecified target and (2) at the research enterprise level where we note a systematic evaluation of the consent process is not possible because of the lack of any requirement to include a model consent or supply the protocol-specified toxicity goals (or more generally sufficient detail regarding the expected toxicity) in ClinicalTrials.gov or the European clinical trials registers (clinicaltrialsregister.eu or euclinicaltrials.eu).

At the individual protocol level, we note that almost all oncology phase I dose-finding designs use dose limiting toxicity (DLT) information occurring in a defined time period (usually the first treatment cycle) to find the maximum tolerated dose (MTD). Protocols define which treatment-related adverse events are considered DLTs. Typically, DLTs are severe or life-threatening adverse events, although reversible severe adverse events may be excluded from the DLT definition by the protocols. For the traditional 3 + 3

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on November 18, 2022 and published at ascopubs.org/journal/jco on February 1, 2023: DOI https://doi.org/10.1200/JCO.22.01736

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design, the MTD is the highest dose level where zero or one DLT is observed when six patients are treated at that dose level (empirical DLT rate 0% or 16.7%). For the newer risk-targeting designs, the MTD is defined based on a preset DLT target rate, and the design seeks to find the dose that achieves that DLT target rate and treat a high percent of patients near or at that target during dose-finding. In a review of these risk-targeting designs, the median DLT target was 25%, with a range of 10%-33%.[15] As the target usually exceeds the empirical DLT rate of the traditional 3 + 3 design, risk-targeting designs, especially those with elevated planned risk, are of heightened concern.

Whether targeting toxicity is an appropriate design objective or a particular toxicity target is clinically reasonable should be thoroughly discussed by the principal investigator and clinical team at the time of protocol development and before opening a study and starting the consent process with patients. The purpose of the target should also be clear, as reflected in the US Food and Drug Administration new Project Optimus that notes the distinction between the MTD and the recommended phase II dose (RP2D). They suggest considering all available preclinical and clinical data in the determination of the RP2D and question the broad use of the *more is better* paradigm, especially with modern molecularly targeted or immune-based therapies. Furthermore, they suggest that multiple RP2Ds may often be appropriate to advance for further evaluation.[16] Regardless of the toxicity target and design details, a necessary condition is that patients agree to participate in the phase I study.

Routinely, the Possible Risk section of the informed consent form details approximate frequencies of individual expected side effects associated with the agents used (or theoretical risks if a new compound). This listing, however, does not capture the aggregate nature of the DLT assessment. When a phase I protocol specifically targets a DLT rate and tests new or escalating doses to achieve it, there is no confirmation that this toxicity risk target is communicated to the patient. In our experiences serving on Institutional Review Boards, the consent form initially submitted to the Institutional Review Board rarely specifies the toxicity risk target, even when the explicit objective of the trial is to find a dose that results in DLTs in a substantial fraction of patients (eg, one in four) in just the first cycle of treatment. Some review committees have started to require clear language in the consent form on the toxicity risk target as more attention and questions have been raised on this topic[16,17]; however, a uniformly applied or stated policy does not exist.

In our opinion there is little downside to such transparency. It is unlikely that a more thorough disclosure of risks will dissuade patients from enrolling in such studies *if the level of risk is appropriate*. This includes studies where the target DLT rate is very high. For some select phase I studies, curative intent, short treatment duration, preclinical data, specific cancer details, or the drug class may support a high-risk approach to achieve a breakthrough treatment—where, if successful, long-term disease control will more than offset the short-term risk of high toxicity.[18] In such cases, with no other known good options for a rapidly progressing terminal disease, many patients will accept the tradeoff between high-risk/high-toxicity and the potential, albeit unproven, benefit over other treatment options that are still available to the patient considering enrollment onto a phase I setting. In other cases, the toxicity risk target may be perceived as inappropriate and dissuade participation. Regardless of the design, patients should be provided a clear description of the risk to make a more informed decision. A minimum necessary requirement is for this description to be included in the informed consent document. That the principal investigator and clinical team may choose to be more conservative than the statistical design in the protocol to mitigate that patient risk is not a compelling reason to limit transparency of the stated phase I target toxicity in the consent process.

At the research enterprise level, we focus on ClinicalTrials.gov because adult phase I trials were excluded from the public site by rule in the European registry,[19] and the updated system is still in transition. Of the 4,263 active oncology phase I trials on ClinicalTrials.gov, there were only nine (0.2%) where the model consent form was available on that public trial registry. Furthermore, only 15 (0.4%) of the phase I trials list the full protocol on that site. Phase II and III entries are similarly lacking in either model consents or full protocols. For phase I studies, it is clear that the protocol summaries as currently provided are not sufficient. To demonstrate, we restricted our search to the limited cases where an other terms search found phase I key design words, specifying DLT target rate design names of BOIN, CRM, mTPI, or BLRM. In this subset of studies that both used DLT-targeting methods *and* provided those key words in the summary, the ClinicalTrials.gov records provided information about the DLT target rate in 6/36 BOIN studies, 13/27 CRM studies, 1/14 mTPI designs, and 1/9 BLRM designs or only 21/86 (24.4%) of the records even when DLT rate targeting methods were clearly identified by the study team in their ClinicalTrials.gov posting.

Looking beyond ClinicalTrials.gov, local research staff can examine protocols and consent forms where they have access. Unfortunately, any such effort would represent a very small sample of the total studies nationwide or worldwide. Furthermore, protocols are commonly covered by confidentiality agreements and/or nondisclosure agreements, and while consent forms need not be confidential, this combination of factors results in a lack of transparency at the enterprise level that prevents a data-driven and verifiable discussion on the topic of the appropriateness of the consent process. Posting the relevant information on the targeted toxicity to improve transparency is a minimal burden, as ClinicalTrials.gov already requires a

synopsis of the study. For phase I studies, it only requires the sponsor add a short description of the phase I study in the summary to convey the risk limiting approach (eg, 3 + 3 design) or the target DLT rate (eg, targeting a 25% DLT rate), along with a brief DLT definition. The consent form can vary over sites and evolve, but uploading a single-model consent should be encouraged.

In conclusion, use of newer risk-targeting phase I designs without commensurate changes to the informed consent document has motivated this commentary. Institutional Review Boards or equivalent committees should require that consent forms state the targeted risk when specified in the protocol design. Clarifying the targeted toxicity rate from a clinical perspective, absent the statistical language, can: (1) minimize undisclosed risks to patients participating in phase I clinical trials; (2) improve communication between patient, principal investigator, and statistician; and (3) ensure alignment between the clinical goals and the statistical language in the protocol.

Improving transparency of the study goals in phase I cancer trials will continue the historic advances made in ethical human subject research to better serve both current and future patients. The public registries can contribute to this effort. As transparency issues are not unique to phase I studies, these issues should also be evaluated and discussed in the context of later phase clinical trials.

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PRIOR PRESENTATION

Presented in part at the 2020 ASCO annual meeting, virtual, May 29-May 31, 2020.

SUPPORT

Supported by UM1CA186690 (J.H.B.), P30CA047904 (J.H.B.), P30CA033572 (P.H.F.).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.22.01736.

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Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

We would like to thank John Zaia, MD, Rex Greene, MD, and C. Michael Jones, MD, for their careful review and comments.

REFERENCES

1. The Belmont Report (April 18, 1979). hhs.gov/ohrp/regulations-and-policy/Belmont-report
2. World Medical Association Declaration of Helsinki - Ethical Principals for Medical Research Involving Human Subjects, 2022. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects
3. Miller FG, Joffe S: Benefit in phase 1 oncology trials: Therapeutic misconception or reasonable treatment option? Clin Trials 5:627-623, 2008
4. Adashek JJ, LoRusso PM, Hong DS, et al: Phase I trials as valid therapeutic options for patients with cancer. Nat Rev Clin Oncol 16:773-778, 2019
5. Hlubocky FJ, Sachs GA, Larson ER, et al: Do patients with advanced cancer have the ability to make informed decisions for participation in phase I clinical trials? J Clin Oncol 36:2483-2491, 2018
6. Storer BE: Design and analysis of phase I clinical trials. Biometrics 45:925-993, 1989
7. Simon R, Friedlin B, Rubinstein L, et al: Accelerated titration designs for phase I clinical trials in oncology. J Natl Cancer Inst 89:1138-1147, 1997
8. Skolnik JM, Barrette JS, Jayaraman B, et al: Shortening the timeline of pediatric phase I trials: The rolling six design. J Clin Oncol 26:190-195, 2008
9. Frankel PH, Chung V, Tuscano J, et al: Model of a queuing approach for patient accrual in Phase 1 oncology studies. JAMA Netw Open 3:e204787, 2020
10. O'Quigley J, Pepe M, Fisher L: Continual reassessmenet method: A practical design for phase 1 clinical trials in cancer. Biometrics 46:33-48, 1990
11. Neuenschwander B, Branson M, Gsponer T: Critical aspects of the Bayesian approach to phase 1 cancer trials. Stat Med 27:2420-2439, 2008
12. Ji Y, Liu P, Li Y, et al: A modified toxicity probability interval method for dose-finding trials. Clin Trials 7:653-663, 2010

13. Liu S, Yuan Y: Bayesian optimal interval designs for phase I clinical trials. J R Stat Soc Ser C Appl Stat 64:507-523, 2015
14. Rogatko A, Schoeneck D, Jonas W, et al: Translation of innovative designs into phase I trials. J Clin Oncol 25:4982-4986, 2007
15. Iasonos A, O'Quigley J: Adaptive dose-finding studies: A review of model-guided phase I clinical trials. J Clin Oncol 32:2505-2511, 2014
16. Shah M, Rahman A, Theoret MR, et al: The drug-dosing conundrum in oncology—When less is more. N Engl J Med 385:1445-1447, 2021
17. Frankel PH, Chung V, Xing Y, et al: Untenable dosing: A common pitfall of modern DLT-targeting phase I designs in oncology. Curr Probl Cancer 44:100583, 2020
18. Garrett-Mayer E: The continual reassessment method for dose-finding studies: A tutorial. Clin Trials 3:57-71, 2006
19. Goldacre B, DeVito NJ, Heneghan C, et al: Compliance with requirement to report results on the EU Clinical Trials Register: Cohort study and web resource. BMJ 362:k3218, 2018

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This author is an Associate Editor for *Journal of Clinical Oncology*. Journal policy recused the author from having any role in the peer review of this manuscript.
Stock and Other Ownership Interests: Asensus Surgical, Geron
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Research Funding: AbbVie (Inst), TriSalus Life Sciences (Inst)
Patents, Royalties, Other Intellectual Property: Sulphoraphane for melanoma chemoprevention (Inst)
Expert Testimony: Pfizer, Spectrum Pharmaceuticals, AstraZeneca/Merck, Astellas Pharma, Taiho Pharmaceutical
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Research Funding: Boehringer Ingelheim, Merck, Ignyta, Genentech/Roche
Travel, Accommodations, Expenses: AstraZeneca, Boehringer Ingelheim, Takeda, Genentech/Roche, Pfizer, Merck

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No other potential conflicts of interest were reported.