Eligibility in Cancer Clinical Research: The Intersection of Discovery, Generalizability, Beneficence, and Justice

Bruce J. Giantonio

SUMMARY

Eligibility criteria in clinical trials limit the study population for safety and scientific purposes. The American Society of Clinical Oncology and The Friends of Cancer Research collaboration reconsidered common eligibility criteria in cancer trials and found many to be unnecessarily restrictive. The current recommendations further their efforts to facilitate accrual and improve the generalizability of research results to practice.

See related articles, p. 2394, 2400, 2408, 2416, 2424, and 2430

Clinical research is the foundation for evidence-based high-quality medical care, with the randomized controlled trial accepted as the gold standard for providing data to guide clinical practice. Yet, research results derived from a study-defined population might not be reproducible in a target population encountered in clinical practice; that is, the statistical validity of a clinical trial's result (internal validity) may not fully extend to the target population (external validity). The gap between internal and external validity is influenced by a number of factors, including how the study population is defined by the eligibility requirements for participation in the research. A series of articles in this issue of *Clinical Cancer Research* is the result of an on-going collaboration between the American Society of Clinical Oncology and The Friends of Cancer Research (ASCO-*Friends*) that reevaluates eligibility criteria common in cancer clinical trials with the dual purposes of facilitating the pace of discovery by increasing accrual to cancer clinical trials and improving the external validity of the research findings (1–6).

In 2016, ASCO-*Friends* in collaboration with representatives from the FDA, the NCI, the pharmaceutical industry, and patient advocacy organizations, undertook a multidisciplinary reevaluation of eligibility criteria regarding coexisting human immunodeficiency virus (HIV) infection, allowable organ dysfunction, comorbidity and concurrent malignancy, coexisting brain metastases, and the minimum age for trial participation, and published a series of articles with recommendations on how to safely broaden those criteria (7–10); and the recommendations have been adopted by the NCI's National Clinical Trials Network (NCTN). In the current series of articles, a similarly thoughtful and multidisciplinary reevaluation is conducted of eligibility criteria for performance status (PS), prior cancer-directed therapies, laboratory-based criteria and their testing intervals, and washout periods for prior therapies, with recommendations developed for their use in clinical cancer research trials.

As described previously (11), research participants are at risk of harm, yet their involvement in clinical research is essential for advancing our knowledge of disease. Regulations and guidelines for performing clinical research balance the common good of scientific advancement with protecting the rights and welfare of individuals. The Belmont Report (12) delineates the boundary between practice and research and describes three basic principles relevant to the ethics of research involving human subjects: respect of persons, beneficence, and justice.

An ethical justification for less restrictive clinical trial eligibility criteria exists in the justice principle of the Belmont Report. The principle of distributive justice in clinical research addresses the fair allocation of society's benefits and burdens such that no one group receives a disproportionate benefit from or bears a disproportionate burden for that research. Yet, the safe conduct of human subjects research requires that the justice principle is balanced against the principle of beneficence: the obligation of research to maximize possible benefits and minimize possible harm; it is in the balancing of distributive justice and beneficence against each other that we find the challenges of clinical trial design that impact generalizability to a target population.

A distributive justice argument is germane to the work of the ASCO-*Friends* collaboration, and similar efforts by others. Motivated by concern for both participant safety and study integrity, eligibility criteria can exclude whole groups of individuals, at times unintentionally, and inappropriately. Often these restrictions have their basis in empiricism, or even speculation, and too often such criteria become adopted norms across the cancer clinical research enterprise without a full reconsideration of their relevance to the specific research question and impact on outcomes. With time and experience it has become clear that some of these restrictions are not only unnecessary, but can violate the distributive justice principle. For example, laboratory-based criteria for organ function that do not accommodate population-based variation have been shown to inadvertently exclude Black men from prostate cancer clinical trials (13). The initial work of the ASCO-*Friends* collaboration and others found the categorical exclusion of people with well-controlled HIV disease from cancer clinical research, and thus those populations more affected by the disease, to be unnecessary (10, 14).

Yet, our definitive and practice-changing studies will always require inclusion and exclusion criteria to ensure the safe and sound conduct of the research, and result in study populations that do not precisely mirror the populations encountered in practice. The degree to which internal validity can be deemphasized will depend on the nature of the study, and how the data are to be used. Rigorously defined study populations will be necessary in specific settings. For example, the importance of safety in phase I studies and signal finding in phase II studies argue for more restrictive criteria to insure both the safety of

Division of Hematology and Oncology, Massachusetts General Hospital, Boston, Massachusetts.

Corresponding Author: Bruce J. Giantonio, Division of Hematology and Oncology, Massachusetts General Hospital, Bartlett Hall, 2nd Floor, 55 Fruit St., Boston, MA 02114. E-mail: giantonb@me.com

Clin Cancer Res 2021;27:2369–71

doi: 10.1158/1078-0432.CCR-21-0085

participants and study integrity, than perhaps would be necessary for a large randomized phase III study.

Eligibility criteria that are too broadly inclusive, however, can introduce prognostic heterogeneity into the study population and require larger accrual goals to conduct subgroup analyses, thus extending accrual times; an impact counter to the intended goal of facilitated trial completion. But when done cautiously, the impact can be marginal. In an accompanying article, Magnuson and colleagues conducted a simulation trial to model the impact on outcomes and accrual times for the inclusion of a proportion of PS-2 participants. They found that when inclusion of PS-2 participants accounted for a small proportion of total accrual (e.g., 10%), the effects on the estimated HR and power were modest. But they recognize that broader inclusion can increase risk to participants or compromise the efficacy assessment (6).

As discussed above, even with improvements in the selection of participants for research studies, the portability of the results of that research to a target population will remain limited to some degree as we cannot entirely dispense with eligibility criteria. Methodology exists to test the generalizability of clinical trial results, which can be done during the design of the study (*a priori*) or following its completion (*a posteriori*; reviewed by He and colleagues; ref. 15). The testing methods vary and can be tailored to the research. While the preferred methods and their appropriate use are yet to be defined, the now prevalent use of electronic health records, and the development of "real-world" databases ostensibly mirroring practice populations can enable generalizability testing. These large analyzable datasets can be utilized to more accurately define clinical and epidemiologic features of a target population for comparison with the proposed study-defined population. An argument can be made for the application of generalizability testing at two timepoints: the *a priori* determination of generalizability during trial development to aid in assessing the clinical relevance of the research, and *a posteriori* testing to assist clinicians in the applicability of the research findings to their clinical practice.

Using the ASCO CancerLinQ database, a limited *a posteriori* generalizability analysis was conducted of nearly 10,000 individuals with advanced non–small cell lung cancer reported from practices participating in the CancerLinQ program. The study applied differing sets of eligibility criteria to the dataset: creatinine clearance, prior cancer diagnosis, and presence of brain metastases; one set of criteria being less restrictive than the other. The authors found that the more commonly used and more restrictive criteria for those three clinical features would exclude roughly one half of the individual records evaluated. The less restrictive yet acceptable criteria increased the potential candidates to 99% of the records analyzed. In addition, the authors found that accrual of women and older individuals would occur at higher levels with the less restrictive criteria, supporting the hypothesis that overly restrictive eligibility criteria can result in underrepresentation of certain populations affected by the disease (2).

Making cancer clinical trials less restrictive is viewed as one means of improving trial enrollment. But restrictive eligibility to cancer clinical trials is only one part of a large and interrelated complexity of barriers to clinical trial participation, not all of which are patient related. A meta-analysis of 13 qualifying studies of nearly 9,000 participants evaluating the trial decision-making pathway found overall trial participation to be about 8%, and that both structural and clinical barriers were the reasons for nonparticipation in more than 3 of 4 patients studied. Interestingly, that improvement in trial participation from the commonly cited 2%–3% of patients with cancer was largely the result of accrual to industry-sponsored trials (16). A clinical trial completion prediction model developed using data from a retrospective analysis of 297 cancer clinical trials conducted at a single institution found industry sponsorships to be one of four predictors for trial accrual completion. The authors postulate that rigorous accrual plans, trial monitoring, and adequate supporting resources that are common to industry-sponsored trials may explain the finding (17). In comparison, NCI-funded trials, which are not supported to the same degree as industry-sponsored trials, may have lower rates of trial completion (18, 19). Yet, NCTN-sponsored research can be more inclusive of a diverse study population. A recent analysis comparing the accrual of Black patients to pharmaceutical company–sponsored and NCTN-sponsored trials found a 3-fold higher proportion of Black participants in NCTN trials (2.9% vs. 9%; ref. 20). These data suggest that carefully considered eligibility criteria can reduce disparity in cancer clinical research, but that restrictive eligibility criteria might not be the dominant barrier to timely trial completion.

The intersection of discovery, generalizability, beneficence, and justice that exists in the eligibility sections of cancer clinical trials requires a careful balance of those concepts to protect participants and preserve the scientific value of the study as we conduct the foundational research that advances cancer care.

The ASCO-*Friends* collaboration has been thorough in its review of eligibility criteria commonly used in cancer research, challenging accepted norms and promoting broader access to clinical trials that can improve both the pace of discovery and the generalizability of research findings to patients encountered in practice, without compromising participant safety and research integrity.

These efforts can be argued as issues of social justice as eligibility criteria can contribute to disparities in clinical research. As social justice is a form of distributive justice, this argument is as reasonable as it is important, and it adds a sense of immediacy to the efforts being taken by the ASCO-*Friends* collaboration.

But it cannot be left to the NCTN and other federally funded research organizations to be the only ones to respond to these reforms: unless all involved in the cancer clinical research enterprise share in doing so, little progress will be made on these critical issues.

Author's Disclosures

No disclosures were reported.

Received January 27, 2021; revised February 9, 2021; accepted February 15, 2021; published first February 18, 2021.

References

1. Kim ES, Uldrick TS, Schenkel C, Bruinooge SS, Harvey RD, Magnuson A, et al. Continuing to broaden eligibility criteria to make clinical trials more representative and inclusive: ASCO-Friends of Cancer Research joint research statement. Clin Cancer Res 2021;27:2394–9.
2. Harvey RD, Bruinooge SS, Chen L, Garrett-Mayer E, Rhodes W, Stepanski E, et al. Impact of broadening trial eligibility criteria for patients with advanced non-small cell lung cancer: real-world analysis of select ASCO-Friends recommendations. Clin Cancer Res 2021;27:2430–4.
3. Spira AI, Stewart MD, Jones S, Chang E, Fielding A, Richie N, et al. Modernizing clinical trial eligibility criteria: recommendations of the ASCO-Friends of Cancer Research Laboratory Reference Ranges and Testing Intervals Work Group. Clin Cancer Res 2021;27:2416–23.

4. Harvey RD, Mileham KF, Bhatnagar V, Brewer J, Rahman A, Moravek C, et al. Modernizing clinical trial eligibility criteria: recommendations of the ASCO-Friends of Cancer Research Washout Period and Concomitant Medication Work Group. Clin Cancer Res 2021;27:2400–7.
5. Osarogiagbon RU, Merino Vega D, Fashoyin-Aje L, Wedam S, Ison G, Atienza S, et al. Modernizing clinical trial eligibility criteria: recommendations of the ASCO-Friends of Cancer Research Prior Therapies Work Group. Clin Cancer Res 2021;27:2408–15.
6. Magnuson A, Bruinooge SS, Singh H, Wilner KD, Jalal S, Lichtman SM, et al. Modernizing clinical trial eligibility criteria: recommendations of the ASCO-Friends of Cancer Research Performance Status Work Group. Clin Cancer Res 2021;27:2424–9.
7. Gore L, Ivy SP, Balis FM, Rubin E, Thornton K, Donoghue M, et al. Modernizing clinical trial eligibility: recommendations of the American Society of Clinical Oncology-Friends of Cancer Research Minimum Age Working Group. J Clin Oncol 2017;35:3781–7.
8. Lichtman SM, Harvey RD, Damiette Smit MA, Rahman A, Thompson MA, Roach N, et al. Modernizing clinical trial eligibility criteria: recommendations of the American Society of Clinical Oncology-Friends of Cancer Research Organ Dysfunction, Prior or Concurrent Malignancy, and Comorbidities Working Group. J Clin Oncol 2017;35:3753–9.
9. Lin NU, Prowell T, Tan AR, Kozak M, Rosen O, Amiri-Kordestani L, et al. Modernizing clinical trial eligibility criteria: recommendations of the American Society of Clinical Oncology-Friends of Cancer Research Brain Metastases Working Group. J Clin Oncol 2017;35:3760–73.
10. Uldrick TS, Ison G, Rudek MA, Noy A, Schwartz K, Bruinooge S, et al. Modernizing clinical trial eligibility criteria: recommendations of the American Society of Clinical Oncology-Friends of Cancer Research HIV Working Group. J Clin Oncol 2017;35:3774–80.
11. Giantonio B. Investigator responsibilities. In: Piantadosi S, Meinert CL, editors. Principles and practice of clinical trials. London, United Kingdom: Springer Nature; 2020.
12. U.S. Department of Health and Human Services.Belmont Report. Ethical principles and guidelines for the protection of human subjects of research. 1979.
13. Vastola ME, Yang DD, Muralidhar V, Mahal BA, Lathan CS, McGregor BA, et al. Laboratory eligibility criteria as potential barriers to participation by black men in prostate cancer clinical trials. JAMA Oncol 2018;4:413–4.
14. Persad GC, Little RF, Grady C. Including persons with HIV infection in cancer clinical trials. J Clin Oncol 2008;26:1027–32.
15. He Z, Tang X, Yang X, Guo Y, George TJ, Charness N, et al. Clinical trial generalizability assessment in the big data era: a review. Clin Transl Sci 2020;13:675–84.
16. Unger JM, Vaidya R, Hershman DL, Minasian LM, Fleury ME. Systematic review and meta-analysis of the magnitude of structural, clinical, and physician and patient barriers to cancer clinical trial participation. J Natl Cancer Inst 2019;111:245–55.
17. Iruku P, Goros M, Gelfond J, Chang J, Padalecki S, Mesa R, et al. Developing a model to predict accrual to cancer clinical trials: data from an NCI designated cancer center. Contemp Clin Trials Commun 2019;15:100421.
18. Schroen AT, Petroni GR, Wang H, Gray R, Wang XF, Cronin W, et al. Preliminary evaluation of factors associated with premature trial closure and feasibility of accrual benchmarks in phase III oncology trials. Clin Trials 2010;7:312–21.
19. Tang C, Sherman SI, Price M, Weng J, Davis SE, Hong DS, et al. Clinical trial characteristics and barriers to participant accrual: the MD Anderson Cancer Center experience over 30 years, a historical foundation for trial improvement. Clin Cancer Res 2017;23:1414–21.
20. Unger JM, Hershman DL, Osarogiagbon RU, Gothwal A, Anand S, Dasari A, et al. Representativeness of black patients in cancer clinical trials sponsored by the National Cancer Institute compared with pharmaceutical companies. JNCI Cancer Spectr 2020;4:pkaa034.