Continuing to Broaden Eligibility Criteria to Make Clinical Trials More Representative and Inclusive: ASCO–Friends of Cancer Research Joint Research Statement

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ABSTRACT

Purpose: Restrictive clinical trial eligibility criteria (EC) limit the number of patients who can enroll and potentially benefit from protocol-driven, investigational treatment plans and reduce the generalizability of trial results to the broader population. Following publication of expert stakeholder recommendations for broadening EC in 2017, the American Society of Clinical Oncology (ASCO) and Friends of Cancer Research (*Friends*) convened working groups to produce additional recommendations and analyze the potential impact on clinical trials using real-world data.

Experimental Design: Multistakeholder working groups were appointed by an ASCO-*Friends* leadership group to propose recommendations for more inclusive EC related to: washout periods, concomitant medications, prior therapies, laboratory reference ranges and test intervals, and performance status.

Results: The four working groups, ASCO Board of Directors, and *Friends* leadership support the recommendations included in this statement to modernize EC related to washout periods, concomitant medications, prior therapies, laboratory references ranges and test intervals, and performance status to make trial populations more inclusive and representative of cancer patient populations.

Conclusions: Implementation of the recommendations is intended to result in greater ease of determining patient eligibility. Increased opportunities for patient participation in research will help address longstanding underrepresentation of certain groups in clinical trials and produce evidence that is more informative for a broader patient population. More patients eligible will also likely speed clinical trial accrual.

See related commentary by Giantonio, p. 2369

Introduction

Accelerating advances in cancer treatment requires efficient clinical trials that produce clinically meaningful outcomes and generalizable knowledge. Clinical trials are not possible without patients, whose eligibility to participate is determined by inclusion and exclusion criteria. Trial eligibility criteria (EC) are designed to protect participant safety and define an appropriate study population. Following approval, patient safety may be compromised if a trial generates insufficient evidence to inform care for specific patient groups, for example, those underrepresented among trial participants. Furthermore, restrictive EC limit clinical treatment options for patients who weigh the potential risks, benefits, and alternatives of a protocol-driven investigational treatment plan and opt to participate in studies.

Exclusion of certain patient populations or disease characteristics is common in oncology clinical trials and is often not founded on current evidence-based scientific justification. This leads to underrepresentation of older adults (1), racial/ethnic (2–4) and sexual/gender minorities (5–7), and patients with well-managed comorbidities (8). An estimated 17%–21% of patients are not able to enroll on clinical trials due to restrictive EC, among other reasons (9, 10). In the era of biomarker-driven therapies where the pool of potential study participants may be very low due to low biomarker prevalence, the negative impact of excessively restrictive EC is magnified (11).

The desire to mitigate safety concerns and ensure trial integrity is paramount, but EC are often replicated from earlier trials and may date back to concerns about cytotoxic chemotherapy. A 2017 review by the FDA concluded that clinical trial EC can be expanded without compromising patient safety (12). To ensure that only criteria relevant to safety concerns about the specific agent are included and extraneous EC are excluded, scientific rationale should be included to justify any exclusion criteria.

ASCO-*Friends* Eligibility Criteria Initiative

Eliminating overly restrictive EC is a priority for the American Society of Clinical Oncology (ASCO) and Friends of Cancer Research (*Friends*), as well as many other patient groups (such as the American Cancer Society Cancer Action Network), researchers, sponsors, regulators, and the National Academy of Medicine (9, 13–18). Enacting

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Translational Relevance

Cancer clinical trials are critical for developing safety and efficacy evidence to advance cancer care. Narrow clinical trial eligibility criteria can compromise the relevance of results to the broader population of patients with the disease. Studies should employ the principles of distributive justice to help ensure appropriate inclusion of underrepresented groups in research, where safety permits. Equitable access to research will also help ensure external validity of results. ASCO and Friends of Cancer Research worked with stakeholders throughout the cancer research community to develop evidence-based, consensus recommendations that are focused on expanding eligibility criteria to make trial populations more reflective of the general cancer population. Implementation of the recommendations is intended to result in greater efficiency of trial conduct and quicker clinical trial accrual, and will provide increased opportunities for patient participation and more informative evidence to guide appropriate uses of new therapies.

changes will optimize trial enrollment and ensure that benefits to patients and the broader scientific community are maximized. In addition, broadening EC is desirable to improve accrual and prevent trial delays and failures, which are a significant strain on human and financial resources during development of new therapies (19–21).

Through this work, ASCO and *Friends* propose a new cancer clinical trial paradigm, in which:

(i) Patients are eligible for a trial by default and excluded only when there is scientific rationale and/or evidence demonstrating that enrollment would compromise the patient's safety.
(ii) In all cases, protocol development begins with informed consent as the only eligibility criteria. Any inclusion/exclusion criteria are tailored to the scientific objectives of the study, based on the investigational treatment and study population, and address only substantiated participant risks.
(iii) Trial participants more closely resemble the population intended to receive the therapy and no group is excluded without scientific justification based on current evidence.

ASCO, *Friends*, and FDA first formed a collaboration to address overly restrictive cancer clinical trial EC in 2016, which led to publication of recommendations for more inclusive EC for brain metastases, minimum age for enrollment, human immunodeficiency virus (HIV) status, organ dysfunction, and prior or concurrent malignancies (13–17).

In 2019, project leadership consulted with stakeholder experts, including ASCO's Cancer Research and Health Equity Committees, to select additional categories of common EC that pose significant barriers to clinical trial enrollment. These topics were selected with an eye for how many patients they impact and how they affect special populations, as well as their potential impact on evaluation of safety and efficacy if relaxed.

Representatives from academic and community research sites, regulatory agencies (FDA and NCI), patient advocacy groups, NCI Network Groups, and the pharma-biotech industry were invited to join the project work groups. The work groups finalized their consensus recommendations after convening with additional patient and industry representatives to discuss their draft recommendations. ASCO and *Friends* herein recommend broadening approaches to clinical trial enrollment related to the following five EC:

(i) Washout periods
(ii) Concomitant medications
(iii) Prior therapies
(iv) Laboratory reference ranges and test intervals
(v) Performance status (PS)

ASCO-*Friends* Recommendations

This statement provides a high-level summary of additional ASCO-*Friends* recommendations for more inclusive clinical trial EC (**Table 1**). Detailed discussion of each recommendation and supporting rationale is presented in separate manuscripts.

There are three common themes across these recommendations. First, clinical trial designers should launch every trial with a goal of inclusion and should add exclusions only where safety concerns warrant exclusion of patients with certain characteristics. Protocols should be living documents; that is, over the course of new agent development from first-in-human through phase III studies, EC should be examined critically and revised to allow for the enrollment of patients who may have previously been excluded because of safety concerns, but for whom new information provides sufficient evidence to support their inclusion.

Second, inclusion of all populations who are anticipated to benefit from the therapy based on the mechanism of action early in clinical development is both equitable and necessary. This will ensure that patients who may ultimately benefit from the treatment being studied are not excluded because of lack of safety data for that population. If representative populations are not included, dose, tolerance, risk of adverse events, and therapeutic benefit remain unknown. The inclusion of exploratory cohorts with broader eligibility in early-phase trials will help to inform and enable revisions to the protocol EC based on these earlier risk-benefit analyses. These exploratory cohorts should help sponsors strike a balance between more rapid patient accrual with broader criteria, time associated with enacting protocol amendments later in development, and number of postmarketing requirements and commitments to expedite trial completion and submission of more complete study findings to regulatory agencies, ultimately leading to broader knowledge in clinical use. At minimum, participants in trials leading to marketing authorization should be inclusive of the patients in the intended use population.

Finally, study design should consider both internal and external validation. In phase I studies, safety is paramount and EC are based on existing knowledge. More stringent EC may also be appropriate in early-phase studies conducted to establish principles of management or to explore a biological question. Including an exploratory cohort in early-phase trials through broadened EC will provide safety information to expand participation in the next phase of study. Registration trials can include participants that resemble the entire population of patients who may use the therapy after approval more closely, that is, improving external validity. Including broader populations also helps fulfill the principle of distributive justice, ensuring appropriate representation of groups who are underrepresented in research, where safety permits.

Washout periods

A washout period is a time between most recent treatment and trial enrollment that is intended to prevent confounding the interpretation of the effect of a new treatment by a persistent effect of an immediately prior

Table 1. Summary of Work Group Recommendations.

Eligibility criteria category	Recommendation
Washout periods	1. Time-based washout periods should be removed from protocol eligibility criteria in most cases. Any inclusion of time-based washout periods should be scientifically justified and clearly specified. 2. Relevant clinical and laboratory parameters should be used in place of time-based washout periods to address safety considerations. 3. Potential trial participants should have recovered from clinically significant adverse events of their most recent therapy/intervention prior to enrollment.
Concomitant medications	1. Concomitant medications use should only exclude patients from trial participation when clinically relevant known or predicted drug–drug interactions or potential overlapping toxicities will impact safety or efficacy.
Prior therapies	1. Patients are eligible for clinical trials regardless of the number or type of prior therapies and without a requirement to have received a specific therapy prior to enrollment unless a scientific or clinically based rationale is provided as justification. 2. Prior therapy (either limits on the number and type of prior therapies or requirements for specific therapies before enrollment) could be used to determine eligibility in the following cases: a. If the agents being studied target a specific mechanism or pathway that could potentially interact with a prior therapy. b. If the study design requires that all patients begin protocol-specified treatment at the same point in the disease trajectory. c. In randomized clinical studies, if the therapy in the control arm is not appropriate for the patient due to previous therapies received. 3. Trial designers should consider conducting evaluation separately from the primary endpoint analysis for participants who have received prior therapies.
Laboratory reference ranges and test intervals	1. Laboratory test results should only be used as exclusion criteria when scientifically justified and when abnormal test results confer safety concerns. 2. Laboratory reference values should account for potential normal variations due to race, ethnicity, age, sex, and gender identity (i.e., due to surgical and/or hormonal changes). 3. Routine reassessment of laboratory test-based exclusion criteria should be conducted during the course of clinical research and drug development as investigational agents progress from earlier- to later-phase clinical trials. 4. Increasing the intervals between protocol-specified tests should be considered to help reduce patient burden and increase ability to rely on routine clinical testing, especially in later cycles of treatment and over the evolution of the protocol from earlier- to later-phase clinical trials.
Performance status	1. Patients with reduced PS (e.g., ECOG PS 2) should be included unless there is a scientific and/or clinical rationale for exclusion justified by established safety considerations. a. ECOG PS eligibility criteria should be based on the patient population in which the intervention is expected to be used in clinical practice. b. PS eligibility criteria should be continually reevaluated and modified throughout the clinical development process to reflect accumulated safety data of the investigational treatment. Decisions about PS eligibility criteria should be based on early clinical safety and efficacy data about the specific investigational agent or based on known data from other drugs in the same class with similar mechanism of action. Later-phase trials (e.g., phase II/III) should generally mirror the intended use population and ECOG PS 2 patients should be included, unless safety concerns have manifested in earlier-phase trials. The rationale for exclusion should be justified and stated explicitly. c. Incorporating the rationale for inclusion of a broader population into the protocol could help encourage investigators to enroll these patients. d. Performance status data should still be collected for use as a stratification factor, regardless of how it is incorporated into eligibility criteria. 2. Consider alternate trial designs, such as prespecified cohorts with lower PS that are exempt from the primary analysis, to encourage inclusion of these patients. These cohorts would generally be small in size and exploratory in nature and could be enrolled in an incremental way to enable an early stopping rule based upon safety data. Consideration of the data analysis approach for the broader eligibility cohort and subgroup analysis should be determined during the study design phase. Early discussion with FDA about enrollment of a broader population may have implications for marketing and post-marketing research requirements. 3. Additional assessments of functional status should be considered to better characterize the functional status of ECOG PS 2 patients and patients ages ≥65, such as activities of daily living (ADLs) and instrumental ADLs.

treatment. Washout/waiting time periods prior to enrollment are common for all modalities of cancer treatment. In many cases, washout periods are associated with theoretical concerns (e.g., prevention of untoward adverse events, drug interactions, and incorrect adverse event attribution) that lack scientific rationale and/or are clinically irrelevant.

Concomitant medications

On average, patients with cancer take five chronic noncancer medications, in addition to drugs that manage adverse effects of their cancer treatment (22). Exclusion of concomitant medications during trials is intended to prevent adverse drug interactions that may affect pharmacokinetic assessment or patient safety, reduce the risk of drug-related adverse events, and, rarely, prevent the use of drugs that are known or predicted to antagonize the anticancer efficacy of investigational therapies. While some medications may be necessarily prohibited early in the development of an investigational agent while knowledge is gained, persistent prohibition reduces the applicability of a therapy to a broader population of patients both in trials and following approval.

Prior therapies

Many cancer trial protocols disallow patients based upon receipt of previous cancer-directed therapies. This may take the form of blanket EC (e.g., any history of prior therapy excluded) or conditional criteria (e.g., specific treatments or a specified number or type of prior treatment lines excluded). In other situations, particularly earlier in drug development, clinical trials commonly exclude patients if they have not received a specific therapy prior to enrollment. Improved molecularly driven therapies and immunotherapies may alter the risk-benefit consideration of study participation in relation to treatment with standard therapies with low efficacy or high toxicity, and in some cases participation in a clinical trial without a requisite receipt of prior standard-of-care therapy may be warranted with appropriate informed consent. As with any other EC, clinical trial designers and sponsors should rigorously justify any restrictions based on prior therapies.

Laboratory reference ranges and test intervals

Laboratory tests that predict and assess toxicity are critical for determining whether a patient can safely enroll on a clinical trial. However, some laboratory reference ranges and test intervals that are included as trial EC are arbitrary, with minimal justification for their use, particularly for investigations of targeted therapies and immunotherapies that may have more favorable or unique toxicity profiles. Reference ranges or intervals that lack scientific rationale and/or differ from routine clinical care often result in biased clinical trial outcomes (as healthier, more homogeneous trial participants may not represent the patients actually treated with a drug once it is approved) and may hinder clinical trial accrual. In addition, nonroutine testing, requirements for central testing, and/or strict adherence to time intervals often increase trial expenses for participants, sponsors, and research sites, and may increase risks associated with certain tests and biopsies (23). Because each clinical trial has distinct therapies with differing toxicity and pharmacokinetic considerations, it is not feasible to provide specific laboratory test value thresholds for broad applicability. Nevertheless, incorporation of principles in **Table 2** may help ensure safety, while minimizing unnecessary participant exclusions.

PS

PS is one of the most common EC utilized in oncology, with many trials limited to patients with good PS [i.e., Eastern Cooperative Oncology Group (ECOG) PS 0 or 1; ref. 13]. This practice restricts therapeutic options for a significant proportion of patients (12), contributes to the pervasive age disparity observed in oncology clinical trials (24), and limits the generalizability of research results in clinical practice. PS as an eligibility criterion should be reconsidered to be more inclusive while maintaining patient safety and study integrity.

Discussion

ASCO and *Friends* are engaged in additional activities to maximize the likelihood that these recommendations are implemented and representative participant populations are accrued to trials.

Our strategies involve four primary elements:

(i) Dissemination—Stakeholders are aware of the EC recommendations and endorse the new cancer clinical trial paradigm outlined above.
(ii) Implementation—More inclusive EC are incorporated into cancer clinical trial protocols.
(iii) Equity—Investigators discuss clinical trial participation with all patients who would qualify and seek to enroll all eligible participants.
(iv) Evaluation—Clinical trial sponsors and investigators monitor the impact of implementing the recommendations, continuously assess accrual during clinical trial conduct to address any challenges that may delay efficient enrollment and completion, and identify additional opportunities to broaden EC to ensure that cancer clinical trial populations mirror the entire population who will be prescribed the treatment.

In efforts to broaden EC, ASCO and *Friends* gathered feedback, reviewed evidence, and conducted analysis of the most common and restrictive criteria. An analysis of 21 Southwest Oncology Group studies showed that 60% of EC are related to comorbidities (including prior treatment exclusions, prior malignancy exclusions, PS, organ function status, HIV status, and brain metastases, among other criteria; ref. 25). Recommendations in this statement and the previous ASCO-*Friends* statement address all of these EC (13).

Research suggests that adoption of the 2017 ASCO-*Friends* recommendations could lead to more inclusive protocols. Data presented at the 2019 ASCO annual meeting demonstrated in a cohort of 10,500 patients with advanced non–small cell lung cancer that implementation of ASCO-*Friends* recommendations could avoid exclusion of nearly half the cohort due to broadened inclusion criteria for brain metastases, prior/concurrent malignancies, and/or reduced kidney function (26).

Publication of these recommendations and analysis of their potential impact will accomplish little if protocols are not updated and investigators do not enroll representative participant populations. Support from trial sponsors, physician investigators, institutional review boards, contract research organizations, and research staff is essential to ensuring that broadened EC are applied appropriately. Eligibility for clinical trials should be recognized as a distributive justice issue for individual patients and for vulnerable populations (27). To the fullest extent possible, FDA, NCI, NIH, and other regulatory bodies, and sponsors should leverage the incentives for broader enrollment that they can offer.

ASCO and *Friends* have partnered with various stakeholders to disseminate and encourage implementation, including working closely with FDA, NCI, and NCI Network Groups. FDA finalized four guidance documents in July 2020 to encourage sponsors to apply the 2017 ASCO-*Friends* recommendations (28–31). NCI revised its protocol template to incorporate the recommendations, including implementation in active protocols and future NCI-funded trials (32).

The general EC in ASCO's TAPUR (Targeted Agent and Profiling Utilization Registry) study mirrors ASCO-*Friends* recommendations by not excluding patients who: are 12 years and older; have new or progressive brain metastases or previously treated or untreated brain metastases, if they are clinically stable; have a prior malignancy; are HIV+; and/or are ECOG PS 0–2. For biomarker-selected therapies, the biomarker driving the cancer should be the primary inclusion criteria, as these therapies often do not pose the same risks as cytotoxic chemotherapy.

Conclusions

EC for washout periods, concomitant medications, prior therapies, laboratory references ranges and test intervals, and PS can and should be modernized to be inclusive of broader, more representative patient populations. These considerations, along with previously proposed

Table 2. Benefits and risks/challenges of expanded eligibility criteria (Adapted from Kim and colleagues, 2017).

Benefit and risk/challenge	Patients	Physicians	Sponsors and investigators
Benefits	Earlier access to investigational agents and expanded trial and treatment options	More complete safety data, which can inform clinical use and enable safe delivery if investigational agent becomes commercially available	Ability to generalize to real-world patients and potentially reduce postmarketing requirements; efficacy in traditionally understudied population(s) could potentially result in expanded marketing claims and provide a differentiating factor between drugs of same class
	Increased confidence in treatment decision-making due to availability of efficacy and safety (i.e., side effect) data from a representative group of trial participants	Availability of efficacy and safety data informs weighing of available treatment options across a broader array of patients and increases confidence in therapy selection	Quicker accrual, fewer trial delays and failures, and more patients may be eligible at each site. All these factors may also reduce cost and time of clinical trial conduct.
	If early trial data in expanded populations demonstrates concerns with efficacy or safety, future patients will have better information to avoid more toxic or less efficacious therapies or know how to modify therapy delivery to avoid toxicities.	Earlier identification of drugs that may not be efficacious in a specific patient population or that may cause more harm than good or earlier knowledge about dose modification of an investigational therapy to improve efficacy or safety/tolerability	Identification of potential safety issues earlier during closely monitored clinical trials may facilitate earlier development of mitigation strategies, enabling broader uptake after approval, and avoidance of post-marketing harms in a larger number of patients due to length of time required for the passive, postmarketing safety surveillance system to identify safety concerns
Risks/challenges	Patients with comorbidities may have a potentially higher risk of experiencing an adverse event as a result of the investigational drug or their disease	Limited data from small cohorts enrolled with broadened criteria may not be adequate for clinical decision-making	More variability in outcomes may require larger sample sizes and inferences may not be as precise
	Additional procedures for increased safety monitoring in some situations may incur additional costs to patients	Additional procedures for increased safety monitoring in some situations may incur additional costs and increased complexity of patient care	Potential safety concerns may require separate cohorts or analysis plans and early stopping rules for excess toxicity
		Additional resources may be required to ensure staff are able to manage safety monitoring	May complicate attribution of adverse events
			Increased costs associated with additional cohorts, statistical requirements, additional testing, additional data for analysis, or special expertise to manage specific patient needs

modifications, may result in greater efficiency of trial conduct and faster clinical trial accrual. Implementation will increase opportunities for patient participation and generation of generalizable evidence to better inform use of new therapies in populations encountered in clinical practice.

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Disclaimer

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