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Modernizing Clinical Trial Eligibility Criteria: Recommendations of the ASCO–Friends of Cancer Research Prior Therapies Work Group

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Abstract

Purpose: Restrictive eligibility criteria induce differences between clinical trial and ‘real-world’ treatment populations. Restrictions based on prior therapies are common; minimizing them when appropriate may increase patient participation in clinical trials.

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Related Manuscripts

This manuscript is submitted as part of a six manuscript bundle. The five related manuscripts listed below are attached.

Harvey et al., “Impact of Broadening Trial Eligibility Criteria for Advanced Non-Small Cell Lung Cancer (NSCLC) Patients: Real-World Analysis of Select ASCO-Friends Recommendations”

Harvey et al., “Modernizing Clinical Trial Eligibility Criteria: Recommendations of the ASCO-Friends of Cancer Research Washout Period and Concomitant Medication Work Group”

Kim et al., “Continuing to Broaden Eligibility Criteria to Make Clinical Trials More Representative and Inclusive: ASCO-Friends of Cancer Research Joint Research Statement”

Magnuson et al., “Modernizing Clinical Trial Eligibility Criteria: Recommendations of the ASCO-Friends of Cancer Research Performance Status Work Group”

Spira et al., “Modernizing Clinical Trial Eligibility Criteria: Recommendations of the ASCO-Friends of Cancer Research Laboratory Reference Ranges and Testing Intervals Work Group”

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Methods: A multi-stakeholder working group developed a conceptual framework to guide evaluation of prevailing practices with respect to using prior treatment as selection criteria for clinical trials. The working group made recommendations to minimize restrictions based on prior therapies within the boundaries of scientific validity, patient-centeredness, distributive justice and beneficence.

Recommendations: 1) Patients are eligible for clinical trials regardless of the number or type of prior therapies and without requiring a specific therapy prior to enrollment unless a scientific or clinically-based rationale is provided as justification. 2) Prior therapy (either limits on number and type of prior therapies or requirements for specific therapies before enrollment) could be used to determine eligibility in the following cases: a) the agents being studied target a specific mechanism or pathway that could potentially interact with a prior therapy; b) 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.

Conclusion: Clinical trial sponsors and regulators should thoughtfully re-examine the use of prior therapy exposure as selection criteria to maximize clinical trial participation.

Keywords

Clinical trials; access; equity; generalizability

INTRODUCTION

An expanding number of innovative approaches to cancer treatment, such as targeted anti-cancer therapies, are reframing our approach to patient selection for the evaluation of experimental agents in clinical trials.(1) For example, targeted anti-cancer therapies are efficacious in molecularly defined patient subsets, irrespective of previous exposure to other types of treatment; they also tend to have more favorable side-effect profiles than traditional cytotoxic chemotherapeutic agents, thus patients treated with targeted agents are often physically well enough to receive subsequent therapies.(2–8) With ever-increasing understanding of drug interactions and novel toxicity profiles of innovative therapies, it is important to rethink the use of prior therapy as eligibility criteria for patient exclusion or inclusion into controlled studies.

The prior therapy selection criteria are a key aspect of clinical trial design and vary substantially, depending on the goals of the study. Updating their use would promote patient access to experimental drugs, improve patient participation, clinical trials accrual and increase the applicability of trial results to a more general population of patients. The rationale for broadening eligibility criteria to make clinical trial participants more representative of the general population has been previously described in a joint effort by the American Society of Clinical Oncology (ASCO) and Friends of Cancer Research (*Friends*). (9) Key recommendations to modernize clinical trial eligibility criteria associated with minimum age,(10) organ dysfunction, prior or concurrent malignancies,(11) brain

metastases,(12) and HIV infection(13) have been published and led to new guidance documents development by the U.S. Food and Drug Administration (14–17).

Building on the success of this initial effort, ASCO and *Friends* convened a multi-stakeholder working group of experts from multiple disciplines to evaluate the current practice of using prior therapy as entry criteria for clinical trials, and developed recommendations to support the design and conduct of clinical trials.

PROCESS

The ASCO-*Friends* Prior Therapies Working Group included clinical investigators, clinical pharmacologists, patient advocates, and regulatory and industry representatives. The working group developed a framework for eliminating barriers to participation in clinical trials based on restrictive criteria on the types and timing of prior cancer therapy, in order to maximize inclusivity in clinical trials. All working group members acknowledged that the use of prior therapies as a criterion for eligibility is deeply tied to clinical trial design. For example, a trial may require patients to be treatment-naïve if investigating an agent as frontline therapy, while another trial may require patients to have received a specific prior therapy or a limited number of prior therapies if investigating an agent as a later line of therapy, or if a prior therapy is known to interact with the investigational agent.

The working group, thus, developed a conceptual framework with which to guide subsequent discussions; and reviewed a sample of the most recently registered, ongoing clinical trials in five disease areas selected from the [ClinicalTrials.gov](https://clinicaltrials.gov) website to examine how prior therapies are being used as eligibility criteria. The working group used these insights to guide subsequent discussions that led to the final proposed recommendations.

Conceptual Framework

We developed a conceptual framework for evaluating the advantages and limitations of using prior therapy as eligibility criteria in clinical trials (Figure 1). This framework considers both information about the potential or known toxicity of the experimental agent and its efficacy in relation to existing treatments, to determine the appropriateness of restricting clinical trial participation based on previous treatments. By deconstructing the decision-making process into its basic elements of safety and efficacy, the working group was able to develop recommendations within the context of patient-centeredness, keeping with the ethical principles of distributive justice and beneficence.(18,19) These considerations guided the thought process behind the [ClinicalTrials.gov](https://clinicaltrials.gov) exercise and the recommendations proposed by this working group.

Current Use of Prior Therapies as Eligibility Criteria- [ClinicalTrials.gov](https://clinicaltrials.gov) Assessment

In order to better understand the scope of the problem, we used the [ClinicalTrials.gov](https://clinicaltrials.gov) website to assess the extent to which prior therapy is currently used as eligibility criteria.(20) In July 2019, we accessed the [ClinicalTrials.gov](https://clinicaltrials.gov) website to select the 11–12 most recently registered phase I–III clinical trials in breast cancer, colon cancer, lung cancer, malignant melanoma and multiple myeloma, for close evaluation of how prior therapy requirements were being used as eligibility criteria. The working group defined inclusion and exclusion

criteria based on prior therapies as those criteria that did not have a specified washout period. Any criteria based on prior therapies that included a washout period were categorized as “washout period criteria” and not assessed in this study. Trials were categorized by cancer type, clinical trial phase (with Phase I/Phase II trials considered Phase I due to their emphasis on the exploration of safety endpoints), and by drug class (including immunotherapy—alone or in combination, chemotherapy only, and other).

The working group reviewed a total of 57 trials to assess whether there were requirements based on prior therapies, specifying whether these were inclusion or exclusion criteria (Figure 2, Supplemental Table 1). Thirty-three clinical trials corresponded to phase I (58%), fifteen trials to phase II (26%) and nine to phase III (16%). More than ninety percent of clinical trials investigated immunotherapies (91%, 52/57), either alone or in combination with other agents or treatment modalities, such as chemotherapy and radiotherapy. Of the remaining five clinical trials (9%), 4 investigated other therapies, such as retinoid X receptor and hyperbaric oxygen, and 1 investigated a chemotherapy agent only (Supplemental Table 1). The breakdown of clinical trials by cancer type was 12 trials in breast cancer, 11 in colon cancer, 11 in lung cancer, 11 in melanoma and 12 in multiple myeloma.

Two thirds (38/57) of the trials included prior therapy as an eligibility criterion; 19 trials (33%) did not specify prior therapy as an eligibility criterion. Among 38 trials, 19 (50%) specified prior therapy as an exclusion criterion only, 14 (37%) specified prior therapy as both an inclusion and exclusion criterion, and 5 (13%) specified prior therapy as an inclusion criterion only. When categorized by clinical trial phase, 58% (19/33) of phase I trials specified either an inclusion or exclusion criterion based on prior therapies, while 42% (14/33) did not. Of the 15 phase II trials, 10 (67%) specified either an inclusion or exclusion criterion based on prior therapies, compared to 5 (33%), which did not. Lastly, all 9 phase III trials specified either an inclusion or exclusion criterion based on prior therapies, with exclusion criterion only specified in 6 trials (67%), and both inclusion and exclusion criteria based on prior therapies specified in 3 trials (33%) (Figure 2).

The pattern of use of prior therapies as eligibility criteria in trials categorized by drug class and tumor type is shown in Figure 2. Use was most prevalent in lung cancer trials (82%, 9/11) and least prevalent in melanoma trials (45%, 5/11). The predominance of immunotherapy trials in the survey, which may be indicative of the predominance of immunotherapy trials in recent [ClinicalTrials.gov](https://www.clinicaltrials.gov) registrations, may limit the extrapolation of our findings to non-immunotherapy trials.

RECOMMENDATIONS

Taking all available evidence into consideration, the working group proposed the recommendations outlined in Table 1, based on the key principles of preserving patient safety, facilitating the assessment of drug efficacy, and promoting patient-centeredness. The recommendations reflect the general position that as a default, minimal eligibility restrictions based on prior therapy should be implemented. The working group encourages critical thinking about the appropriate use of eligibility criteria based on prior therapies by

considering the need to balance the goals of scientific rigor, and trial efficiency, with the goal of broader clinical trial inclusivity.

DISCUSSION

Traditionally, clinical trials specify prior therapies that are either required for inclusion or exclusion of patients from participation. Tightly controlled eligibility criteria are thought to optimize conditions to test the safety and efficacy of an investigational therapy.(21,22) The working group characterized scenarios under which the use of prior therapies as exclusion criteria (i.e., no prior therapy or no prior therapy of a certain type allowed) or as inclusion criteria (i.e., a defined number and/or type of prior therapies required for eligibility), may be appropriate. We further outlined the rationale for, and the pros and cons of, these scenarios (Table 2). We avoided scenarios in which prior therapies might be specified to exclude overlapping exposure to prior and new therapy (i.e., washout periods), deferring to the ASCO-*Friends* working group on Washout Periods and Concomitant Medications, which was charged with the task of addressing this important topic ().

For example, to ‘optimize for safety’ prevailing practice may be to specify a maximum number of prior therapy exposures, in order to minimize the risk that heavily pre-treated patients may be more likely to experience excessive toxicity. Another common practice may be to limit prior exposure to specific types of prior therapies whose toxicities potentially overlap those of the experimental therapy, such as would be the case for potentially irreversible toxicities like bone marrow toxicity, neuropathy, or cardiotoxicity. However, the concerns for excess toxicity may be more appropriately addressed by requiring resolution or improvement in the toxicities of concern, rather than by implementing broad exclusions based upon exposure to prior therapies.

Eligibility criteria may also be designed to ‘optimize for efficacy’ by defining a study population that is comparable to historical trials to permit an evaluation of improvements in outcomes with the new therapeutic in non-comparative trials. Trial designers may seek to define a study population that is most likely to respond to the treatment being studied. For example positioning a second-generation agent targeting resistance mutations where either relapse after a first-generation compound has selected for the acquired resistance mutation or designing upfront treatment for an *ab origin* mutation,(23,24) or limiting the number of prior treatments to minimize the risk that heavily pre-treated patients with refractory disease will bias trial results against treatment response.(25,26) This raises the fundamental question whether restricting patients from enrollment in a clinical trial solely based on prior therapy is justifiable to show the best outcome of the trial treatment for a specified patient population or whether it is more advantageous to open up patient eligibility in order to enable quantification of outcomes across the spectrum of potential clinical use scenarios.(22,27)

In addition to safety and efficacy considerations, the intent of the trial is an important consideration. A trial designed to evaluate safety and effectiveness of an investigational agent for the purposes of gaining marketing licensure may seek to enroll patients with an unmet medical need, for example patients with advanced refractory disease who have exhausted currently available treatment options, for whom clinical trials may be the only

potential treatment option.(28,29) A trial may be designed to compare a new investigational agent against a standard of care treatment in a particular treatment setting, such as a specific line of therapy or treatment with a particular class of drugs.(30,31) In this case, trial designers often insist that a study population be naïve to any treatment or restricted to a population that has received a minimum or maximum number, or certain specific types, of prior therapies.

Advances in the understanding of the biological underpinnings of cancer have facilitated the development of therapies that are based on key tumor characteristics such as gene and protein expression profiles, have relatively well-understood mechanisms of action, are often effective irrespective of prior drug exposures, and have a wider therapeutic index.(2–5,32–38) This has mostly rendered obsolete the clinical rationale for eligibility criteria that specify requirements for prior therapy, simultaneously raising the ethical dilemma of the opportunity cost to the patient, of arbitrary patient selection criteria based on prior therapy.(18,19,39) Patients increasingly seek access to promising drugs in development, particularly those that treat rare or clinically aggressive cancers. Mandating prior exposure to marginally effective or excessively toxic treatments, in theory, may delay or prevent access to potentially more beneficial novel treatment. Conversely, blanket exclusion of patients who have received any prior treatment may prevent otherwise healthy patients with disease progression from gaining access to potentially health-preserving new treatments.

Lastly, the implementation of prior therapy criteria in the absence of scientific or clinical rationale may unnecessarily restrict the post-approval target population and delay evaluation of a new drug's efficacy and safety in the wider population that may ultimately receive the drug once it is approved.(40) Limiting patient access to clinical trials based either on exposure to prior therapies or the requirement for patients to have progressed after specific therapies limits patient access to clinical trials and may significantly slow trial accrual or compromise completion of these trials.

CONCLUSION

The discovery of highly effective anti-cancer treatments, and the technologies that enable the selection of patients with targetable genomic alterations, has resulted in the traditional line-of-treatment demarcations becoming increasingly blurred. Ultimately, the inclination to conduct clinical trials in homogeneous populations for more robust comparisons (internal validity) must be finely balanced against the pragmatic need to test novel therapies in the 'real-world' populations that will eventually be exposed to approved treatments (external validity),(40) as well as the concept of patient-centeredness, and the ethical principles of distributive justice and beneficence. The Institute of Medicine, now National Academy of Medicine, defined patient-centeredness as 'responsiveness to the needs, values, and expressed preferences of the individual patient.'(41) In 2010, the same body recommended that the National Cancer Institute, Cooperative Groups and physicians should take steps to increase the speed, volume and diversity of patient accrual and to ensure high-quality performance at all sites participating in cooperative group trials. As an example, they recommended that they should "encourage patient eligibility criteria that allow the broadest participation possible."(42)

Clinical trial designers and sponsors should clearly justify any restrictions based on prior therapies. The working group's overarching consideration in making these recommendations was to promote patient-centered clinical trials with the minimum entry criteria needed to ensure participant safety and broad access. We hope these recommendations will be widely adopted by key stakeholders, especially designers, sponsors, and regulators of clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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STATEMENT OF TRANSLATIONAL RELEVANCE

With rapid-cycle discovery of new drugs with well-characterized targets and mechanisms of action, the therapeutic index and efficacy of new candidate cancer drugs are significantly better than in the past, reconfiguring the safety and efficacy calculus in using prior therapy exposure to select patients for clinical trials. Concurrently, there is growing awareness that cancer drugs approved in restrictive clinical trials are often used in real world practice for groups of patients ineligible for such trials, even without evidence for their safety or efficacy. Using a patient-centered conceptual model that considers safety, efficacy and the ethical principles of distributive justice and beneficence, a multi-stakeholder working group has proposed three recommendations to promote more thoughtful consideration of the use of prior therapy as a selection criterion for oncology trials. The overarching objective is to minimize this potential barrier to clinical trials access for willing patients.

Figure 1. Conceptual framework to guide the use of prior therapy as selection criteria in clinical trials.

We encourage the use of this conceptual framework early in the process of clinical trial design, in order to minimize the barrier to entry. We encourage shared decision-making between the patient and the healthcare provider in selecting treatment options including treatment within a clinical trial. In general, clinical trials should be designed with the aim of achieving greater inclusivity with minimal restrictions placed on trial entry. Decisions regarding whether exposure to existing therapy should be required prior to administering an investigational therapy should consider the risks (i.e., known or unknown safety profile) and the efficacy of the therapy, and the availability of alternative treatments. In a clinical setting wherein the standard of care treatment provides a high likelihood of cure such as may be the case for some in an adjuvant setting or for some advanced lymphomas or pediatric cancers, it may be appropriate to restrict access to experimental therapy until after disease progression, relapse or intolerance of such existing treatments. However, in the non-curative setting a requirement for receipt of such ‘standard’ options is not recommended unless there is sound scientific or clinical rationale to support the restriction.

Figure 2. Frequency of the use of prior therapies as inclusion and/or exclusion criteria in clinical trials as part of the ClinicalTrials.gov exercise categorized by phase, drug class and tumor type. ClinicalTrials.gov was accessed on July 23, 2019. Trials with any component of Phase I trials (e.g. Phase I/II) were categorized as Phase I trials. The working group defined inclusion and exclusion criteria based on prior therapies as those criteria that did not have a specified washout period. Any criteria based on prior therapies that included a washout period was categorized as “washout period criteria” and not evaluated in this assessment.

Table 1.

Recommendations for the modernization of eligibility criteria based on prior therapies

Recommendation	Comment
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 clinical rationale is provided as justification.	There needs to be a balance between the desire to conduct a tightly controlled experiment with high internal validity, and the reality that patients with much broader demographic and disease characteristics than those patients evaluated in clinical trials, are prescribed the approved drugs.(22) Clinical trials are the most controlled mechanism for evaluation of the safety and efficacy of investigational agents in a carefully selected patient population. However, arbitrary exclusion of populations of patients who may desire access to clinical trials, and may derive benefit from them, runs counter to the principles of patient autonomy and beneficence. The opportunity cost of such arbitrary restrictions to sponsors and designers of clinical trials may also be largely under-recognized. Overly complex eligibility criteria may in part increase the burden on research staff, slow down clinical trial accrual, increase the risk of failure to complete clinical trials, and raise the audit and regulatory stakes for enrolling sites and their staff. Indeed, the Pharmaceutical Research and Manufacturers Association reported that 80% of clinical trials do not finish on time, 20% are delayed 6 months or more and up to two-thirds of clinical trials fail to meet their original patient enrollment goals.(39) Reducing barriers that hinder recruitment, such as broadening eligibility criteria, would be beneficial.
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:	To promote greater clinical trial inclusivity in trials, minimally restrictive criteria should be used, with patient safety and autonomy as the primary considerations. However, there may be some specific scenarios in which these criteria may be justifiable and necessary to maintain patient safety and ensure treatment efficacy. In these cases, when entry into a trial is contingent upon exposure to a prior therapy (or lack thereof), scientific and/or clinically sound rationale should be provided. The working group identified three cases in which prior therapy could be used to determine patient eligibility, and additional specific scenarios are found in Table 2. With evolving evidence that investigational agents with known mechanisms of action, which effectively target specific biologic pathways, are highly effective irrespective of the point in the disease trajectory, (2–5,32–36,38,43) trial designers are encouraged to continuously re-evaluate the use of prior therapies as eligibility criteria.
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.	There may be concerns that enrolling a subset of patients who may be considered higher-risk due to their exposure or lack of exposure to prior therapies might jeopardize drug development by reducing apparent treatment efficacy and/or increasing the risk of severe adverse events in such high-risk patients. To preserve methodologic rigor in clinical trials while maintaining the desire for minimal barriers to entry, multiple strategies can be considered for data analysis and interpretation. Some of these approaches have been suggested in prior publications in this series.(9,22) These concerns can be addressed at the time of trial design by pre-specifying how data from this subset of higher-risk patients will be handled in executing the trial and the statistical analyses. For example, in early-phase trials, an expanded cohort with perceived high-risk due to prior therapy history can be recruited and closely monitored for safety signals which can be used to prompt closure of that subset without jeopardizing the whole program.(9–12) The information generated from this expansion cohort can then be used to inform the criteria for later-phase trials. Additionally, patient enrollment into the arms of randomized clinical trials can be stratified on the basis of prior therapy history, with all patients included in the intention-to-treat analysis, but with pre-specified analyses restricted to a 'modified intention-to-treatment' subset. As suggested by Jin et al, in hierarchical testing, the primary analysis could be restricted to the lower-risk modified intention-to-treat population, with subsequent analyses to include the whole population.(22) Another alternative would be to enroll a parallel cohort of patients who do not meet the prior therapy restriction, which would not be part of the intention-to-treat population, but whose data, analyzed separately, would still provide descriptive safety and efficacy information. This alternative, however, might be considered less desirable because toxicity data from such a trial design would be difficult to interpret due to the absence of a control group(22) and because of the time still required to accrue the intention-to-treat population. The rapidly evolving development of adaptive clinical trial designs and statistical analysis methodologies may accommodate the goal of expanding clinical trials participation irrespective of prior therapy history.

Table 2. Scenarios in which selection criteria based on prior exposure to therapy may be applied, rationale, pros and cons.

Scenario	Rationale	Pros	Cons
Limitation to treatment-naïve patients (i.e. first-line treatment trials)	Comparison to standard first-line treatment. Typically, drug registration trials.	<ul style="list-style-type: none"> Need clearly defined target treatment population High risk of poor efficacy or greater toxicity when pre-treated patients included Minimize expense of including patients deemed higher risk for failure Need to establish a market niche 	<ul style="list-style-type: none"> Exclusion of healthy individuals, often long-term beneficiaries of prior therapy with recent disease progression. (e.g. long-term cancer survivors with subsequent disease) Progression to metastatic disease after prior systemic adjuvant therapy is a common scenario with arbitrary time-interval rules for inclusion/exclusion.
Limitation to previously treated patients ('salvage therapy' trials).	Assurance of prior exposure to standard of care. Possibly, drug registration trial.	<ul style="list-style-type: none"> Secure means of testing promising new agents in the face of existing, highly curative standard treatments Establishment of market niche Potentially enable comparison to historically treated population outcomes 	<ul style="list-style-type: none"> Risks of requiring prior therapy in the face of potentially more effective or safer novel treatment, especially in rare or clinically aggressive disease, when available standard treatment is modestly effective or highly toxic. Violation of patient autonomy/threat to principle of beneficence Comparisons across clinical trials and over different time frames and populations, even of ostensibly similar groups, is rife with unknown bias, statistically unsound and should be discouraged. Furthermore, restricting access to clinical trials in relatively uncommon diseases is particularly wasteful.
Strict limitation of the number of allowed prior therapies (typically one or two).	Assurance of prior exposure to standard of care. Often, drug registration trials.	<ul style="list-style-type: none"> Patients typically still good candidates for treatment despite prior therapy. Clearly defined population with relative homogeneity in terms of disease refractoriness and susceptibility to toxicity Establishment of market niche for registration. Enable comparison of outcomes in a non-comparative trial to historically treated populations 	<ul style="list-style-type: none"> 'Indication creep' occurs in real-world practice, creating exposures with unknown safety or efficacy Optimal time to identify adverse safety and/or efficacy signals is under the auspices of a clinical trial with greater standardized data collection and evaluation than in routine practice Potential missed opportunity to detect new efficacy signals that can expand market share Expansion of eligible cohorts promotes accrual, timely trial completion, with associated cost savings Given greater success rates and less toxicity of drugs with well-defined mechanisms of action, ethical dilemma created with potential loss of opportunity for access to beneficial treatment, in violation of patient autonomy and the principle of beneficence. Comparisons to historical populations spurious and invalid.
Exclusion based on prior exposures to specific treatments	Concerns about interference with action of trial agent (effectiveness and/or toxicity)	<ul style="list-style-type: none"> Typically, exclusion of exposure to drugs of the same class, with similar mechanism of action and therefore likelihood of adverse interaction with effectiveness or safety of trial agent 	<ul style="list-style-type: none"> Potential missed opportunity for detection of differential activity Increasing population of long-term survivors who have had remote prior exposure and no residual effects from prior therapy.