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Modernization of Eligibility Criteria

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Summary

Eligibility criteria are a critical component of clinical trials and serve to define the patient population under study. They can be inclusionary, perhaps by specifying a tumor type or molecular alteration needed for study entry, or exclusionary by specifying certain characteristics such as comorbidities that would render a patient ineligible for enrollment. While restricting trial eligibility to a homogenous patient group improves the ability of a trial to detect a treatment effect, should one exist, a primary purpose of eligibility criteria is to protect the safety of those patients who are thought to be at increased risk of experiencing a treatment-related adverse effect. However, excessive or overly restrictive eligibility criteria can impair clinical trial accrual and the applicability of trial results to heterogeneous "real-world" patients who ultimately may receive the drug in the post-market setting. It also delays access to investigational agents for patients who may in fact stand to benefit. In 2016, the American Society of Clinical Oncology (ASCO), Food and Drug Administration (FDA), and Friends of Cancer Research (Friends), launched an initiative to re-assess the current approach to determining clinical trial eligibility. We will build on these and other efforts and provide recommendations for how sponsors, investigators, and regulators can work together to implement expanded clinical trial eligibility where appropriate.

Background

Common exclusion/inclusion criteria have developed over time, primarily through experience with cytotoxic chemotherapeutics. Many of these are grandfathered from prior trial protocols, with little consideration as to whether they are truly appropriate for the specific clinical question being asked. Given the increase in complexity of cancer treatment, and the advent of novel therapeutic modalities, many have called for simplified, rational eligibility criteria.[1,2] Newer, molecularly targeted agents generally do not have the same safety profiles as chemotherapies and often require additional biomarker-driven patient selection parameters that may severely limit the number of patients eligible for a trial; therefore, identifying opportunities to safely broaden eligibility has been recognized as a priority.[3]

Recent cooperative group studies of the impact of different eligibility criteria on trial and patient outcomes support the need for a re-evaluation of clinical trial eligibility. Gerber *et al* reviewed lung cancer trials sponsored by the Eastern Cooperative Oncology Group (ECOG) between 1986 and 2013 and determined that patients with prior malignancies were excluded from 94% of trials that used survival as a primary endpoint and 73% of trials that used other primary endpoints.[4] This study also analyzed the SEER-Medicare database and determined that up to 18% of lung cancer patients have prior cancer diagnoses, and therefore a substantial portion of patients are potentially excluded from trials for this reason alone. Subsequent work by this group showed that prior malignancies did not impact survival outcomes in patients with stage IV lung cancer or locally advanced lung cancer, suggesting that clinical trial outcomes would not be adversely impacted by inclusion of patients with a history of prior cancer.[5,6] A similar case-by-case, evidence-based approach to assessing other common eligibility criteria will be useful to determine when they can be safely relaxed.

[1] George SL. "Reducing patient eligibility criteria in cancer clinical trials." J Clin Oncol. 1996 Apr;14(4):1364-70."

[2] Fuks A, Weijer C, Freedman B, Shapiro S, Skrutkowska M, Riaz A." A study in contrasts: eligibility criteria in a twenty-year sample of NSABP and POG clinical trials. National Surgical Adjuvant Breast and Bowel Program. Pediatric Oncology Group." J Clin Epidemiol. 1998 Feb;51(2):69-79.

[3] Kim ES, Bernstein D, Hilsenbeck SG, Chung CH, Dicker AP, Ersek JL, et al. "Modernizing Eligibility Criteria for Molecularly Driven Trials." J Clin Oncol. 2015 Sep 1;33(25):2815-20.

[4] Gerber DE, Laccetti AL, Xuan L, Halm EA, Pruitt SL. "Impact of prior cancer on eligibility for lung cancer clinical trials." J Natl Cancer Inst. 2014 Sep 24;106(11).

[5] Laccetti AL, Pruitt SL, Xuan L, Halm EA, Gerber DE. "Effect of prior cancer on outcomes in advanced lung cancer: implications for clinical trial eligibility and accrual." J Natl Cancer Inst. 2015 Feb 9;107(4).

[6] Laccetti AL, Pruitt SL, Xuan L, Halm EA, Gerber DE. "Prior cancer does not adversely affect survival in locally advanced lung cancer: A national SEER-medicare analysis." Lung Cancer. 2016 Aug;98:106-13.

ASCO-FDA-Friends Eligibility Criteria Initiative

In an effort to modernize clinical trial eligibility criteria to better reflect intended-to-treat populations and allow broader and more representative enrollment of patients in trials, four working groups composed of multiple stakeholders, including sponsors, investigators, biostatisticians, pharmacologists, regulators, and patient representatives, developed detailed consensus-driven recommendations regarding where it is scientifically and clinically appropriate to expand eligibility criteria. The four working groups considered: 1) patients who have brain metastases, 2) the minimum age of patients eligible for enrollment, 3) patients who are HIV positive, and 4) patients with organ dysfunction. In developing these recommendations, the working groups reviewed the state of the science, any existing case studies, and attempted to balance the needs of protecting patient safety, facilitating access to investigational therapies, and protecting trial integrity (including safety, efficacy, and statistical considerations). To maximize the generalizability of results, clinical trial enrollment criteria should strive for inclusiveness and provide justification for the selected inclusion and exclusion criteria if compelling safety or efficacy concerns mandate the exclusion of specific populations. Recommendations were presented at a public workshop on May 12th, 2016, and are summarized below.

Brain Metastases[7]

Broad exclusion of patients with brain metastases is common despite the very high incidence of brain metastases in some tumor types. Although life expectancy may be reduced for some patients with brain metastases, and there may be greater risk of neurological toxicity, existing literature does not indicate that these patients experience higher rates of serious adverse events. This working group developed recommendations specific to: 1) patients with treated or stable brain metastases, 2) patients with new/active/progressive brain metastases, and 3) patients with leptomeningeal disease. For patients with treated or stable brain metastases, the working group concluded that, without a compelling rationale for exclusion, these patients should be routinely included in prospective clinical trials of all phases. If there are specific safety concerns, then tailoring specific criteria to the concern is preferable to blanket exclusion of all brain metastasis patients. For patients with active brain metastases, the working group concluded that a one-size-fits-all approach is not appropriate, and factors such as natural history of the disease, trial phase and design, and the drug mechanism and potential for CNS penetration should determine whether such patients are included in a trial. If patients with active brain metastases are included, additional prospective planning may be required to better define safety and response. Early stopping rules may be appropriate should excessive toxicity be observed. Finally, the working group concluded that in most trials, it remains appropriate to exclude patients with leptomeningeal disease due to their poor prognosis, although there may be situations that warrant a cohort of such patients in early phase trials – for example, when CNS activity is anticipated.

Minimum Age[8]

Children and adolescents under the age of 18 years are often excluded from participating in clinical trials with novel agents until extensive adult data are available, sometimes many years after the introduction of an agent. Because pediatric patients have historically been considered

[7] Recommendations of the 2016 ASCO-Friends Brain Metastases Eligibility Criteria Working Group (N Lin, E Kim, A Tan, K Beal, J White, J Sul, T Prowell, LA Kordestani, L Perkins, O Rosen). In preparation for publication.

[8] Recommendations of the 2016 ASCO-Friends Minimum Age Eligibility Criteria Working Group (L Gore, F Balis, M Donoghue, N Goodman, P Ivy, G Reaman, E Rubin, K Thornton). In preparation for publication.

a vulnerable population, there is concern that a high profile adverse event in a child could endanger the entire drug development program. However, there is no evidence to support this concern. The main scientific barriers that preclude enrollment of pediatric patients in most "adult" clinical trials are the lack of overlap between some types of cancers that adult and pediatric patients develop, the potential for developmental toxicity, as well as differences in metabolism between the age groups. The working group developed recommendations for inclusion of pediatric patients in early and late phase trials. In initial dose-finding trials, the group recommended the inclusion of pediatric-specific cohorts when there is a strong scientific rationale, based on molecular pathways or histology as well as preclinical data, to believe that a specific pediatric population could benefit from a drug under study. These cohorts would assess dose and pharmacokinetics separately in the pediatric population. Staggered enrollment starting with older children followed by younger children could be considered to address potential concerns specific to younger pediatric patients, including not only metabolic differences but also challenges related to the availability of appropriate formulations for young children. The working group also recommended that later phase trials in diseases which span adult and pediatric populations include pediatric patients with the specific disease under study. Based on the similarity in metabolism between adults and adolescents, the working group recommended that patients aged 12 years and above be enrolled in such trials.

HIV/AIDS[9]

Many people infected with HIV have a near normal life expectancy due to substantial improvements in HIV therapeutics over the past 20 years. Cancer is now a leading cause of mortality in people with HIV, however most oncology studies exclude this population. This working group recommended that HIV-infected patients who are healthy and have a low risk of AIDS-related outcomes should be included in cancer clinical trials unless there is a specific rationale to exclude such patients – for example, if there is reason to believe that the investigational drug might interfere with control of HIV infection, which may be the case with some immunomodulating agents. In the absence of a rationale for exclusion, HIV-related eligibility criteria should be straight-forward and focus on current and past CD4 and T-cell counts, history (if any) of AIDS-defining conditions such as opportunistic infections other than historically low CD4 and T cell counts, and status of HIV treatment. Healthy HIV-positive patients that are included in cancer clinical trials should be treated using the same standards as other patients with co-morbidities, and anti-retroviral therapy should be considered a concomitant medication.

Organ Dysfunction[10]

This working group began by discussing the types of organ dysfunction that were likely to drive most clinical trial exclusion criteria. They decided to focus on kidney, heart, and liver dysfunction, as well as exclusion based on a prior, alternate cancer history. The group conducted analysis of these criteria from a large, representative dataset that included a cohort of nearly 13,000 patients newly diagnosed with breast, colon, lung, and bladder cancers from 2013-2014. The analysis, as well as review of the literature, helped the group determine which of the organ dysfunction criteria to prioritize for development of recommendations. Because the dataset included only newly diagnosed patients, it is possible that other exclusionary criteria should also be considered,

[9] Recommendations of the 2016 ASCO-Friends HIV/AIDS Eligibility Criteria Working Group (K Dunleavy, G Ison, RF Little, BW Miller, A Noy, M Rudek, K Schwartz, TS Uldrick, J Wang, J Zeldis,). In preparation for publication.

[10] Recommendations of the 2016 ASCO-Friends Organ Dysfunction Eligibility Criteria Working Group (SM Lichtman, P Cortazar, L Fehrenbacher, RD Harvey, NA Rahman, N Roach, D Smit, M Thompson, D Walker). In preparation for publication.

but the group decided to focus on the organ performance status that raised the most challenge for patient participation. The group prioritized a focus on renal function because the rates of exclusion based on typical hepatic and cardiac function tests would not have raised a problem with participation in the newly diagnosed patients. The group concluded that renal function criteria should be based on creatinine clearance rather than serum creatinine levels. The group also proposed liberal creatinine clearance criteria in situations where renal excretion is not a significant component of a drug's pharmacokinetics or when known dose modification strategies can allow safe and effective administration. Conservative criteria remain appropriate for nephrotoxic drugs. Although the group did not recommend changes to the current criteria for hepatic or cardiac function, they did propose that future studies include cohorts of patients with organ dysfunction as well as geriatric patients when appropriate to better define the spectrum of toxicity. This would aid clinicians in decision-making and allow a more realistic description of patient outcomes. The group agreed that exclusions based on prior malignancies should be liberalized – both in terms of the timing and types of prior malignancies, as well as current malignancies that are not life-threatening in the short term.

Implementation

Through the course of working group discussions, potential benefits and risks of expanding eligibility criteria were identified (Table 1). As previously stated, the primary purpose of eligibility criteria is to protect the safety of patients presumed to be at a higher risk of experiencing an adverse event. Thus, significant concerns are that use of broader criteria may put some patients at risk, and that the development of an effective drug could be jeopardized if a serious adverse event occurs in a patient population that is inherently sicker. Inclusion of some patients may require additional screening/monitoring or the engagement of additional expertise to manage safety issues specific to that patient population. This would help to mitigate risk in these patients but would also increase trial cost and complexity. In some cases, working groups concluded that it would be appropriate to include a traditionally excluded patient population as a part of the general trial population, while in other situations, working groups recommended that certain patient groups be included as a separate cohort within a trial or analyzed separately from the general trial population. Either of these options would again present additional operational considerations and cost to drug sponsors; however, they may also provide data in an underrepresented population that could potentially be included in a drug label and used to differentiate a drug from others in its class. Potential study design options that can be considered to address these concerns and potentially mitigate risk are provided in Table 2. Some options are similar to biomarker-based stratification designs that have been used to evaluate efficacy and toxicity in biomarker-positive and -negative patients. These designs may facilitate label inclusion of safety or efficacy information in the expanded population if sufficient data is collected to draw meaningful conclusions; however, discussion with regulators will be necessary to determine the best approach for each situation. We anticipate that current efforts to expand eligibility in several clinical trials will help to demonstrate the feasibility and that future FDA guidance, particularly with regards to safety reporting, will assist sponsors in designing more representative trials.

Following publication of the current working group recommendations, future efforts will include data-driven efforts to identify other opportunities to safely broaden clinical trials, including evaluation of potential opportunities to adjust requirements around drug washout periods, use of concomitant medications, and inclusion of geriatric patients. One goal will be to create

standardized and consistent language for trial protocols to facilitate electronic data collection and searches of clinical trials. Another goal will be to develop metrics to monitor uptake of these recommendations. Outreach to institutional review boards will be critical to ensure that patient safety is appropriately balanced with access to investigational therapies. Ultimately, the goal of this initiative is to change the culture such that sponsors and investigators include patients unless there is a compelling rationale not to, rather than the current default to exclusion. Given the significant interest in and enthusiasm for this effort from many in the cancer community, we believe this goal can be achieved for the benefit of all stakeholders.

Table 1: Benefits and Risks of Expanded Eligibility Criteria

	Patients and Physicians	Sponsors/Investigators
Benefits	Earlier access to investigational agents, expanded trial and treatment options	Ability to generalize to "real-world" patients, and may reduce post-marketing requirements.
	More complete safety data, which can inform clinical use and enable safe delivery if/once investigational agent becomes commercially available	Faster accrual
		Identification of potential safety issues during clinical trials may facilitate early development of mitigation strategies, enabling broader uptake after approval
	Availability of efficacy data can inform weighing of commercially available treatment options	Efficacy in traditionally understudied population could potentially be included in drug label and provide a differentiating factor between drugs of same class
Risks	Limited data from small cohorts may not be adequate for clinical decision-making	More variability in outcomes – may require larger sample sizes and inferences may not be as precise
	Patients that are inherently sicker may have higher risk of experiencing an adverse event due to the drug or disease	Potential safety concerns – may require separate cohorts or analysis plans and early stopping rules for excess toxicity
		May complicate attribution of adverse events - consider randomization and data from other drugs in class
	Additional screening or imaging needs in some situations may incur additional costs to patients	Increased costs associated with additional cohorts, statistical requirements, additional testing or special expertise to manage specific patient needs

Table 2: Potential Trial Designs and Considerations

Early Phase Trials

Add an expansion cohort restricted to a specific patient population (e.g., a pediatric population, patients with poor performance status, or patients with active brain metastases).

- Maximum tolerated dose, dose-limiting toxicities, pharmacokinetics may be assessed separately in that population
- Serious safety issues could prompt the cohort to be closed without compromising the entire drug development program.
- Results in early phase can inform the decision as to whether and how to include (or not) the patient population in later phase trials

Later Phase Trials

Expand eligibility criteria to include a specific patient population (may be appropriate for prior malignancies or patients with HIV) and include these patients in primary analysis

Allow broad enrollment while restricting primary analysis to narrower patient population

- Protects integrity of trial while enabling data collection in broader populations
- Data may be helpful to inform safe clinical use in "real-world" patients

Expand trial eligibility to include a specific patient group but stratify randomization where one strata includes patients who would not meet traditional eligibility to ensure balance of these patients across treatment arms.

- May be appropriate when early-phase data shows that special subset can tolerate drug but only at a lower dose, or when life expectancy is shorter in special subset

Consider adaptive designs where trial is expanded or restricted based on data collection early in the trial and recommendations from a Data Safety Monitoring Board

Initiate a separate cohort or companion protocol restricted to a specific patient population

- Similar to expanded access protocols and may only include safety monitoring