Strategies to Maximize Patient Participation in Clinical Trials

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OVERVIEW

Despite considerable interest and success in oncology drug development, the minority of patients with cancer diagnoses enroll in clinical trials. Multiple obstacles account for this low enrollment rate. An improvement in patient participation in clinical trials could increase patient access to novel and potentially promising agents, provide faster trial results, and, with implementation of rational eligibility criteria, allow for a better understanding of the drug's safety and efficacy in a heterogeneous population. We present barriers and potential solutions to maximize patient participation, including a review of the ASCO and Friends of Cancer Research (FoCR) Modernizing Eligibility Criteria Project, U.S. Food and Drug Administration (FDA) regulatory considerations, an industry perspective, and a patient perspective.

The goal of oncology clinical trials is to understand the risks and benefits of a therapy and to facilitate and expedite the development of safe and effective drugs to treat patients with cancer. Clinical trials also provide patients with access to investigational agents; however, U.S. oncology clinical trials only enroll approximately 3% of patients diagnosed with a new cancer.[1] Multiple barriers can contribute to this low rate of enrollment, including those at the patient, physician, institutional, and protocol levels.[2,3]

Patient-level barriers to enrollment in clinical trials result from the fear that clinical trials will delay initiation of antineoplastic drugs (particularly if biopsy and genomic sequencing are required), fear of undergoing additional testing and procedures, or concerns about enrolling in randomized trials that might include a placebo or perceived inferior investigational or control arm. Other patient barriers include socioeconomic issues, such as concerns over travel costs with increased frequency of follow-up visits in a clinical trial. The lack of clinical trial access and/or a decline in functional status are additional commonly reported reasons that patients are not enrolled in clinical trials.[4] Physician-level barriers such as lack of knowledge about new agents and available clinical trials may also present obstacles to enrollment. Institutional-level barriers are reflected by the number of available protocols at one institution, and the fact that for many community practices, knowledge about the potential for referral to clinical trials may be limited. Overly restrictive eligibility criteria are a major protocol-level barrier. Given these obstacles, strategies are needed to maximize patient participation in clinical trials.

MAXIMIZING CLINICAL TRIAL PARTICIPATION AND IMPLEMENTATION OF MODERN ELIGIBILITY: INDUSTRY PERSPECTIVE

From an industry perspective, key parameters in clinical trial implementation and participation are as follows: (1) speed and efficiency in evaluating the safety and efficacy of an experimental oncology agent, (2) investigator and site experience with investigational drug trials (including obtaining patient informed consent and assessing adverse events), (3) speed of trial initiation at sites, (4) site accrual rates, (5) site data quality, and (6) investigator experience with the pathway targeted by the experimental agent.

Protocols for industry-sponsored clinical trials undergo a rigorous internal review process, typically involving multiple review committees with members possessing expertise in trial design, statistics, and regulatory, safety, data management, and operational aspects of clinical trials. During protocol development, industry sponsors typically obtain investigator input and ensure that the patient perspective is understood in order to confirm feasibility and maximize accrual rates.

Single-arm, personalized treatments (e.g., trials that select among various treatments based on a biomarker evaluation of a tumor biopsy) are often attractive to patients; thus, these trials tend to accrue rapidly. Single-arm trials may be sufficient for regulatory approval in some cases, such as rare cancers and/or where initial data suggest a remarkable improvement relative to existing treatment options. However, in most cases, randomized controlled trials will be necessary to demonstrate clinical benefit. In these trials, accrual rates can vary widely depending on patient perspectives on the potential benefits of the experimental and control arms.

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Clinical Trial Designs to Improve Enrollment

Depending on the molecular target for an investigational agent, it may be preferable to use clinical trials that use enrichment designs (i.e., eligibility is dependent on having a "positive" result from a biomarker test performed on a tumor or blood specimen from the patient), particularly if the target is a mutated gene that has a low prevalence among a given tumor type. Using adaptive trials (e.g., trials that include prespecified changes based on accumulating data) may improve efficiency relative to use of multiple sequential trials, each requiring several internal and external committee reviews as well as separate site contracting and trial initiation efforts.[5-7] However, there may be tension in terms of the degree of flexibility desired by an industry sponsor versus prespecification of sample sizes based on statistical evaluations of efficacy and safety. In addition, adaptive trials increase protocol complexity, particularly if multiple amendments are required even if the adaptive changes are prespecified.

In some types of enrichment trials, it may be expected that that the biomarker test may identify responsive patients regardless of tumor type. In this case, "basket" trials have become increasing popular, in which eligibility is determined by the biomarker test rather than the tumor type.[8] However, this approach may create challenges in terms of selection of site principal investigators, because cancer centers are not organized by biomarkers but by tumor type. Thus, it may be difficult to identify an optimal principal investigator in terms of patient accrual to the trial.

KEY POINTS

- **Despite considerable interest and success in oncology drug development, the minority of patients with cancer diagnoses enroll in clinical trials, owing to barriers at the patient, physician, institutional, and protocol levels.**
- **An ASCO and FoCR Modernizing Eligibility Criteria Project, in collaboration with the FDA and other stakeholders, is working toward evaluating clinical trial entrance criteria that may unnecessarily restrict clinical trial access and providing recommendations for a more rational approach to determining inclusion and exclusion criteria.**
- **Working groups with representatives from ASCO, FoCR, FDA, patient advocacy programs, industry, and others have prioritized assessments on criteria for patients with brain metastases, organ dysfunction, history of prior malignancy, and HIV and for those younger than age 18 to come up with recommendations for a more nuanced approach to determining eligibility.**
- **Creative clinical trial designs such as enrichment designs, master protocols, and "basket" trials in the right clinical scenario can maximize patient participation and efficiency.**
- **Clinical trials hold the promise of providing benefit to patients/survivors and patient-level barriers to enrollment can be addressed through reasoned interventions.**

Master protocols are another trial design that has become increasingly popular as a means of improving efficiency of oncology drug development for a particular tumor type.[9] When testing multiple drugs with non-overlapping eligibility criteria (e.g., drugs targeting non-overlapping gene mutations), these designs have advantages over use of multiple two-arm randomized registration trials. First, grouping these trials under a single protocol, with a common control arm, reduces the overall screen failure rate. For example, assuming a prevalence of 20% for biomarkers A, B, C, and D in a given histologic cancer type (with no overlap among each subpopulation) and a need for 200 biomarker-positive patients each on an experimental arm and in the treatment-control arm, 8,000 patients would need to be screened in the case of four separate randomized studies, whereas only 2,163 would need to be screened in the case of a single five-arm study with four experimental arms and one control treatment arm. Second, process and operational efficiencies are improved through the ability to amend a single master protocol as needed as drugs enter and exit the trial. For example, after implementation, sponsors enrolling new drugs would benefit from the presence of a preexisting infrastructure. Although master protocols can improve the efficiency of drug development, they may not be fully endorsed by industry, particularly if trial arms include similar agents.

Implementation of Modern Eligibility

Although there are already examples of industry sponsors embracing changes in traditional eligibility criteria that have been suggested recently by various stakeholders (see section on modernizing eligibility criteria), challenges remain. Because industry typically desires to register new drugs in many different countries, registration trials usually involve sites from many different countries, and in certain countries, the view on reducing eligibility restrictions may differ from that of the United States, particularly as related to age. Furthermore, although mitigating factors have been described, allowing patients with impaired organ function or performance status may bias evaluation of safety and efficacy, potentially leading to premature discontinuation of the development of a particular agent. In some trials, accrual may be dominated by non-U.S. sites as a result of limited access of patients in some countries to investigational drugs or newly approved drugs. This can result in U.S. filing applications consisting of patient data from predominantly non-U.S. sites.

Strategies to Address Low Enrollment

Some studies enroll poorly, which may relate to several possible issues. These reasons may include lack of interest in the investigational agent or the control arm treatment, overly restrictive eligibility criteria, complex requirements (e.g., prolonged inpatient stays, uncomfortable procedures, or multiple invasive biopsies), or, in the case of enrichment trials, a low prevalence of biomarker positivity. Another possible reason for slow enrollment is the existence of similar studies competing for the same patient population,

particularly if the eligible population is uncommon (e.g., a biomarker-selected population in which the prevalence of biomarker positivity is low). Although many sites attempt to limit the number of trials competing for the same population, this does not address competition for patients between sites.

Sponsors may evaluate several options in cases of slow enrollment. A commonly used option is to simply add additional sites. If there is a high rate of screen failures, eligibility criteria may be re-evaluated, particularly if one criterion is a predominant reason for screen failures. For example, the number and types of previous treatment allowed may be too restrictive. In addition, for randomized trials, patients and investigators may not view the control arm as an attractive treatment option. In this case, adding additional treatment options to the control arm (e.g., allowing investigators to choose among a list of treatments), or allowing crossover to the investigation arm upon disease progression, may improve accrual rates.

MODERNIZING ELIGIBILITY CRITERIA FOR CLINICAL TRIALS

Historically, eligibility criteria were appropriately put in place because of concerns over safety in selected populations but, in many cases, clinical trial protocols are copied forward between and within drug development portfolios and are not always based on a rational analysis. It is critically important for developers of clinical trials to take a more thoughtful approach to the selection of eligibility criteria, not only to provide improved access to clinical trials for patients with cancer but also to understand a drug's safety and efficacy in a more representative population. Despite years of recognition of this issue, inclusion and exclusion criteria remain prohibitive for many patients.[10-13] Certain populations in particular are frequently excluded from oncology clinical trials, including patients with HIV, brain metastases, history of prior malignancies, poor performance status, and comorbidities and those younger than age 18.[13] Of approximately 300 commercial Investigational New Drug Applications submitted to the FDA's Office of Hematology and Oncology Products in 2015, only 3.7% included pediatric patients; 60% required Eastern Cooperative Oncology Group performance status of 0–1; 77% excluded known, active, or symptomatic central nervous system or brain metastases; 47% allowed treated or stable brain metastases; and 84.2% excluded patients with known or active HIV (with only 1.7% allowing patients to enroll with adequate CD4 counts).[14] Multiple stakeholders realize that taking a more rational approach to eligibility criteria will result in improved patient benefit.

ASCO/Friends of Cancer Research/FDA Modernizing Eligibility Criteria Project and Working Groups

The ASCO and FoCR Modernizing Eligibility Criteria Project, in collaboration with the FDA and other stakeholders, is working toward evaluating clinical trial entrance criteria that may unnecessarily restrict clinical trial access and providing recommendations for a more rational approach to determining inclusion and exclusion criteria.[13,15] Working groups were formed with representatives from ASCO, FoCR, FDA, patient advocacy programs, industry, the National Cancer Institute, biostatisticians, pharmacologists, and clinical investigators to come up with recommendations for a more nuanced approach to determining eligibility. These groups have prioritized assessments on criteria for patients with brain metastases, organ dysfunction, history of prior malignancy, and HIV and those younger than age 18.

Working Group Preliminary Recommendations

Publications from these working groups are pending; however, preliminary recommendations presented at the FoCR Annual Meeting in November 2016 detail current working group thinking.[16] The brain metastases working group endorsed the routine inclusion of patients with treated or stable brain metastases in all phases of clinical trials unless there is a compelling rationale for exclusion.[16] In certain instances, patients with new, active, or progressing brain metastases may also be included, taking the history of the patient's disease, trial phase and design, drug mechanism, and potential for central nervous system interaction into account. Patients with leptomeningeal disease may also have specific situations that warrant an eligible cohort in early-phase trials. The minimum age working group proposed that pediatric-specific cohorts be included in dose-finding studies in which strong scientific rationale is present. This rationale could be based on preclinical data or an understanding of the mechanism of the disease. In later stages of drug development, the group proposed that trials in diseases that span adult and pediatric populations should enroll pediatric patients, particularly patients age 12 and older. Others, including the FDA, have also suggested the inclusion of patients age 12–17 in appropriate adult disease-specific trials.[17] The working group also proposed that HIV-related eligibility criteria be rationally developed and focus on current and past CD4 and T-cell counts, a history of AIDS-defining conditions, and status of HIV treatment.[16] The working group advised that HIV should be considered a comorbidity and antiretroviral therapy should be considered a concomitant medication. The organ dysfunction working group proposed that eligibility regarding renal function should be based on creatinine clearance rather than serum creatinine levels, and knowledge of a drug's excretion by a specific organ system could inform exclusion criteria cutoffs. In addition, it was advised that exclusions based on prior malignancy be liberalized.

Regulatory Considerations of Eligibility

Regulatory incentives that might encourage a thoughtful approach to eligibility are also possible. For example, an expanded marketing claim could be granted if an adequately studied patient cohort included a previously excluded population such as patients with brain metastases. In addition, postmarketing requirements or commitments, such as the study of organ impairment, might be unnecessary if these

populations were included previously. Pediatric incentives include the ability to address requirements from the Pediatric Research Equity Act to study the effects of drugs on children. So that efficacy is not compromised in trials intended to support registration, a broader clinical trial population could include a prespecified, more narrowly defined population for the primary efficacy evaluation.

ASCO/FoCR/FDA Eligibility Criteria Future Directions

Appropriate eligibility criteria define a patient population that will result in patient protection, but strict eligibility criteria can negatively affect patient participation and result in failure to understand a drug's safety and efficacy in a representative population. Future endeavors of the ASCO/FoCR/FDA project will focus on approaches to appropriately defining drug washout periods, exclusion of concomitant medications, and inclusion of elderly patients.[16,18] The Modernizing Eligibility Criteria Project advocates for a culture shift in the approach to inclusion and exclusion criteria and will continue to pursue a broad implementation of this rational approach to eligibility.

IMPROVING ACCESS TO CLINICAL TRIALS: A PATIENT PERSPECTIVE

Although it is important to acknowledge that there is no single patient or patient advocate perspective or consensus on clinical trials. The views and suggestions offered here are those of an individual advocate informed and enriched by more than 20 years of active engagement across numerous advocacy groups.

A Goal of Patient Benefit

Simply put, clinical trials hold the promise—the enormously hopeful potential—of providing benefit to patients/survivors. Patient advocates, some as research advocates, support the clinical trial enterprise in numerous ways and participate in clinical trials for many reasons—one being the hope of personal benefit and another being the desire to contribute to the likelihood of benefit to future generations. Low trial enrollment decreases the speed and likelihood of trial progress and thus ultimate patient benefit (practice changing or incremental), wastes precious human and funding resources, and compromises confidence in the entire enterprise (thus becoming an additional barrier to enrollment).

Overview of Patient Barriers

Barriers to participation in clinical trials vary widely across institutions, professions, and populations. Low trial enrollment, relative to the available pool of participants, is a recurring topic or theme at nearly all conferences, meetings, and other gatherings of individuals involved in the clinical trial enterprise, seeking access to trials, or hoping to benefit from them. The long list of often-overlapping barriers includes (1) a history of unethical trials, (2) lack of understanding of clinical trials or the availability of specific trials, (3) lack of trust in the medical system, (4) uneven or unequal recruitment (including physician conscious and unconscious bias), (5) patient-physician communication (or the lack thereof), (6) access and logistical considerations (including financial, geographic, and educational considerations), and (7) the fear factor (e.g., of being randomized or of randomization not being so random and of being the object of unfettered experimentation).

These barriers and others combine to create limited and unequal participation in clinical trials, with differing effects on various populations, partially depending on their experience with the health care system. For example, "history" is often cited as a barrier to participation by populations described as vulnerable or "special" (a misnomer); however, history can be a barrier for any population and any individual who understands the medical misconduct and infamous studies that litter the research landscape. When known and understood, events such as the Nazi experiments (1940s), the Willowbrook studies (1956–1972), the Jewish Chronic Disease Hospital studies (1963), the AIDS trials (1980s), and the Tuskegee syphilis study (1932–1972), which is perhaps the most often cited example, prompt or exacerbate distrust in the system and increase reluctance to participate even with the potential of benefit to the participant or to others.

Distinguishing Myth From Reality

Important overarching concerns related to clinical trial participation include limited understanding of clinical trial terminology, standards, and protections. These concerns support the rise and maintenance of myths, such as those described in Table 1.

Trial Participation in the Age of Personalized Medicine

Clinical trial participation is the primary route through which biospecimens are obtained and banked, thus serving as a gateway for individual access to personalized medicine and health care. As such, it is increasingly important for all populations to be represented in the clinical trial enterprise. Because they are not equally represented, it is not surprising that banked biospecimens do not represent the diversity of the general population and that the findings derived from these biospecimens are not widely generalizable to segments of the population. Without trial participation across populations, underrepresented populations will have little or no "skin in the game." An unintended consequence is likely to be an increase in cancer health disparities. Therefore, with a substantial share of research efforts and research dollars focused on personalized medicine and health care, representative trial participation is a must.

Potential Strategies and Interventions

Like the barriers to clinical trial participation and low enrollment, potential solutions are frequently offered, if not implemented. The following potential solutions are offered as doable, feasible, and measurable:

1. Acting on what we know and have researched (including using best practices),

TABLE 1. Myths and Realities of Clinical Trial Participation

Myth	Reality
The Tuskegee syphilis study is the reason for low enrollment of black patients and perhaps other vulnerable populations.	The Tuskegee syphilis study or what it represents is a reason (i.e., one among many others), not the reason. In fact, it can become an excuse for the opportunity to participate not being offered.
Black and Hispanic patients are less likely to participate in clinical trials than white patients.	Although both groups are less likely to be invited to participate in trials than white patients, when asked, they are slightly more likely to enroll.
Trial participants are guinea pigs and may be experimented on in ways beyond their consent.	Numerous regulations and safeguards, including 45CFR46, ensure that human participants are protected and that research is ethical. All U.S. research involving human participants is reviewed and monitored by an institutional review board, whose focus is to protect participants.
Clinical trials are or should be an option only when potential participants have no other treatment options.	Clinical trial participation can and should be an option for any patient who meets specific trial eligibility requirements and wants to participate. Not all patients will choose to participate, but all should be given the option to do so when appropriate.
Some clinical trial participants will receive treatment inferior to standard of care, perhaps through randomization or placebo use.	All clinical trial participants will receive at least standard of care. Randomization and placebo strike fear in the hearts of potential participants. This fear can be educated away.

2. Focusing on recruitment of—as opposed to continuously studying—vulnerable and special populations (as a largely untapped resource and as a matter of good conscience and good science),
3. Funding and implementing bidirectional clinical trial education and awareness (to include a sustained public awareness campaign, communications skills, and cultural sensitivity training for the public, patients and survivors, health care providers, and researchers),
4. Developing trial-specific educational material (as well as trial-general material with substantial meaningful patient advocate involvement),
5. Instituting accountability relative to uneven/unequal recruitment and unmet goals (to include the requirement for rigorously reviewed population-specific recruitment goals and the implementation of consequences where warranted),
6. Reviewing and modernizing eligibility requirements (understanding, for example, that exclusion of potential participants with comorbidities—unless scientifically warranted—has a profound effect on eligibility by population and that trial participants should more closely align with the general population that might benefit from the trial),
7. Formalizing engagement of patient advocates beyond recruitment and throughout and beyond protocol development and review, and
8. Requiring an informed consent process as well as a signed informed consent document.

This may seem a smorgasbord or data dump of possibilities. It is not. Instead, it is a listing of potential solutions that can and should often be combined and fashioned into interventions that move from discussing low enrollment and the concomitant barriers to overcoming them.

In Summary—A Patient Advocate's Perspective

This cancer survivor and patient advocate's perspective focuses on the implementation of interventions old and new, alone and in combination. The breadth and depth of research on clinical trial participation have been extensive and the conversation is ongoing; however, to effect measurable change, we must move from conversation to research-based and best practice–informed action, that is, reasoned interventions.

CONCLUSION

Although restrictions on clinical trial entry for the protection of patients are appropriate and supported by all stakeholders, an examination of more nuanced eligibility is appropriate in many cases. This rational approach to defining eligibility will benefit patients by providing clinical trial access and ultimately resulting in a greater knowledge of a drug upon approval. Additional barriers can also be approached with similar efforts to expand and maximize patient participation in clinical trials. Through collaborative efforts across academia, government, industry, and advocacy, there is great promise and potential for maximizing patient participation in oncology clinical trials.

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