

Barriers *to* *Patient Enrollment in Therapeutic Clinical Trials for Cancer*

A Landscape Report



Barriers to Patient Enrollment in Therapeutic Clinical Trials for Cancer - A Landscape Report

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Foreword



Insufficient cancer clinical trial participation rates have long been identified as a challenge facing the cancer research community, resulting in the failure of as many as one out of five cancer clinical trials. These failed trials represent thousands of patients per year who enroll on clinical trials that ultimately are unable to advance our understanding of cancer as they were intended to. In this light, it is important to note that simply focusing on the rate of trial enrollment could risk missing the primary objective of clinical research, which is to advance knowledge. In other words, simply enrolling more patients on more failing trials would not be helpful. To be beneficial, higher trial participation rates must result in more trials being completed in a timely and

efficient manner, thus translating to greater and faster knowledge generation that can lead to better outcomes for patients with cancer.

The barriers that keep patients from enrolling in clinical trials have been well studied, but often in isolation from each other. While this report relies on previous studies, it attempts to bring all the relevant evidence together in one place, synthesizing the relationships of barriers to each other and scaling each barrier's contribution to the problem as a whole. The report is organized by chapters dedicated to patient barriers, provider and institution barriers, and trial-design barriers, recognizing that barriers may fit in multiple categories.

Note: Barriers exist to patient enrollment in many types of clinical trials in many different diseases, but the focus of this report is strictly with respect to cancer and strictly on therapeutic interventional trials that actively assign treatment protocols to participants who have consented to take part. Any mention of the term “patients,” “participants,” or “trials” in this report should be narrowly interpreted to apply to these circumstances unless otherwise specified.

Executive Summary

The objective of cancer research is to generate new knowledge that can be used to improve survival and quality of life for patients with cancer. Clinical trials are the key step in advancing potential new cancer treatments from the research setting to the cancer care clinic, and patient participation in trials is crucial to this success. Most patients express a willingness to participate in clinical research, yet only a small fraction ultimately end up enrolling in a cancer clinical trial due to barriers that make participation difficult or even impossible. Consequently, approximately 20% of cancer clinical trials fail due to insufficient patient enrollment. Understanding and addressing these barriers is critical to accelerating progress in cancer research.

Enrollment in a cancer clinical trial involves a multi-step process and while participation is typically thought of in terms of a patient decision, it is notable that the patient is not presented with the option until the last step, which is only reached if previous barriers have not been encountered. Analyzing studies across a variety of settings suggests that:

- 56% of patients will not have a local trial available for their cancer
- 17% will be ineligible for a trial due to exclusion criteria
- Many eligible patients will not be asked by their provider to enroll
- Only 27% of cancer patients will have the option to enroll in a local clinical trial

Typically, greater than 50% of eligible patients asked to enroll will agree to do so, and those who decline to take part in a clinical trial cite fear of side effects, loss of control,

costs, and logistics involved with participating in trials as their primary reasons.

Healthcare providers and institutions have a significant impact on cancer clinical trial enrollment as a result of decisions regarding which and how many trials to open at a site, the quantity and type of research personnel employed, and whether and how they identify and enroll patients in trials. These decisions are heavily dependent upon adequate funding, often supplied from the National Cancer Institute or the pharmaceutical industry, to support necessary research personnel and infrastructure. Typically, high-performing sites manage their trial portfolios to match the patient population they serve, systematically pre-screen their patients for trial eligibility, and collaborate across networks.

As science propels cancer treatments forward, clinical trials are increasingly designed around very small genetically defined subsets of cancers, making finding eligible patients even more difficult. At the same time, eligibility criteria like age, HIV status and the presence of previous cancers are being reexamined to ensure that restrictions are not unnecessarily preventing willing patients from enrolling on trials. Involving patients in the design of clinical trials has also been found to improve their appeal to patients and accrual success.

This report is meant to serve as a resource to inform discussions and actions aimed at addressing the barriers preventing patient participation in clinical trials. Stakeholders ranging from cancer researchers, cancer patients, industry, as well as members of our society, will all play critical roles if these barriers are to be successfully overcome.



Background



Overview

Reducing barriers to patient participation in trials would facilitate faster, more efficient trials, and thus speed improvements in treatment outcomes for patients with cancer. Moreover, trials present patients the opportunity to access the newest developing treatments, so the option to participate in trials should be equitable and easy for patients.

Cancer research is rapidly leading to advances in cancer therapies, across a wide variety of therapeutic categories of drugs. The number of clinical trials for patients with cancer dwarfs that of any other single disease, with cancer clinical trials comprising between 40% and 50% of all trials conducted in the United States [1, 2]. Nonetheless, the vast majority of adult patients with cancer do not participate in clinical trials, despite the fact that most Americans are inclined to do so [3-6]. This gap between the willingness of patients to participate in trials

and their actual participation rates suggests there are numerous barriers to trial participation for patients. In short, clinical trials cannot be conducted unless patients are both willing and able to participate. Therefore, the identification of barriers to trial participation and efforts to remove such barriers represent critical objectives for cancer investigators, patients, trials sponsors, and all stakeholders in the research system.

History of Trials

Clinical trials have evolved over centuries. This evolution includes the identification and broad acceptance of foundational elements of trial conduct. These elements include: 1) the prospective observation of individuals receiving different interventions or treatments; 2) the need for a control group for comparison, established within the framework of an experiment; 3) an understanding of the complex science of conducting research with humans; and

Background

4) the need for an ethical framework of consent and safety principles for the individuals who participate.

Much of today's regulatory and ethical frameworks for clinical research have arisen from past abuses. One of the most prominent examples of abuse in American medical research is the Tuskegee Syphilis Study, conducted from 1932 to 1972. During the period while this study was being conducted penicillin was discovered to cure the disease, but was withheld from study participants in order to study the natural progression of the disease [7]. Internationally, Nazi experimentation on concentration camp prisoners led to the Nuremberg Code, a set of research principles that have served as the foundation of modern research ethics frameworks. In 1978, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research released the

Belmont Report, which outlined the three basic principles relevant to research involving humans. These are: 1) respect for persons; 2) maximizing possible benefits and minimizing harms (beneficence); and 3) justice [8]. From this history, modern clinical trials have arisen, with emphasis on informed patient consent and presenting patients with the option of being treated with an experimental therapy. Patients may decline participation for any reason, and may at any time drop out of trials even after they have initiated participation.

Clinical trial designs and methods are still evolving today, as evidenced most recently by the development of precision-medicine trials, which attempt to link patients' genetic and proteomic signatures to uniquely tailored treatments [9]. The evolution of patient consent and participation also continues. Patient-reported outcomes

MODEL PATHWAY OF TRIAL ENROLLMENT PROCESS

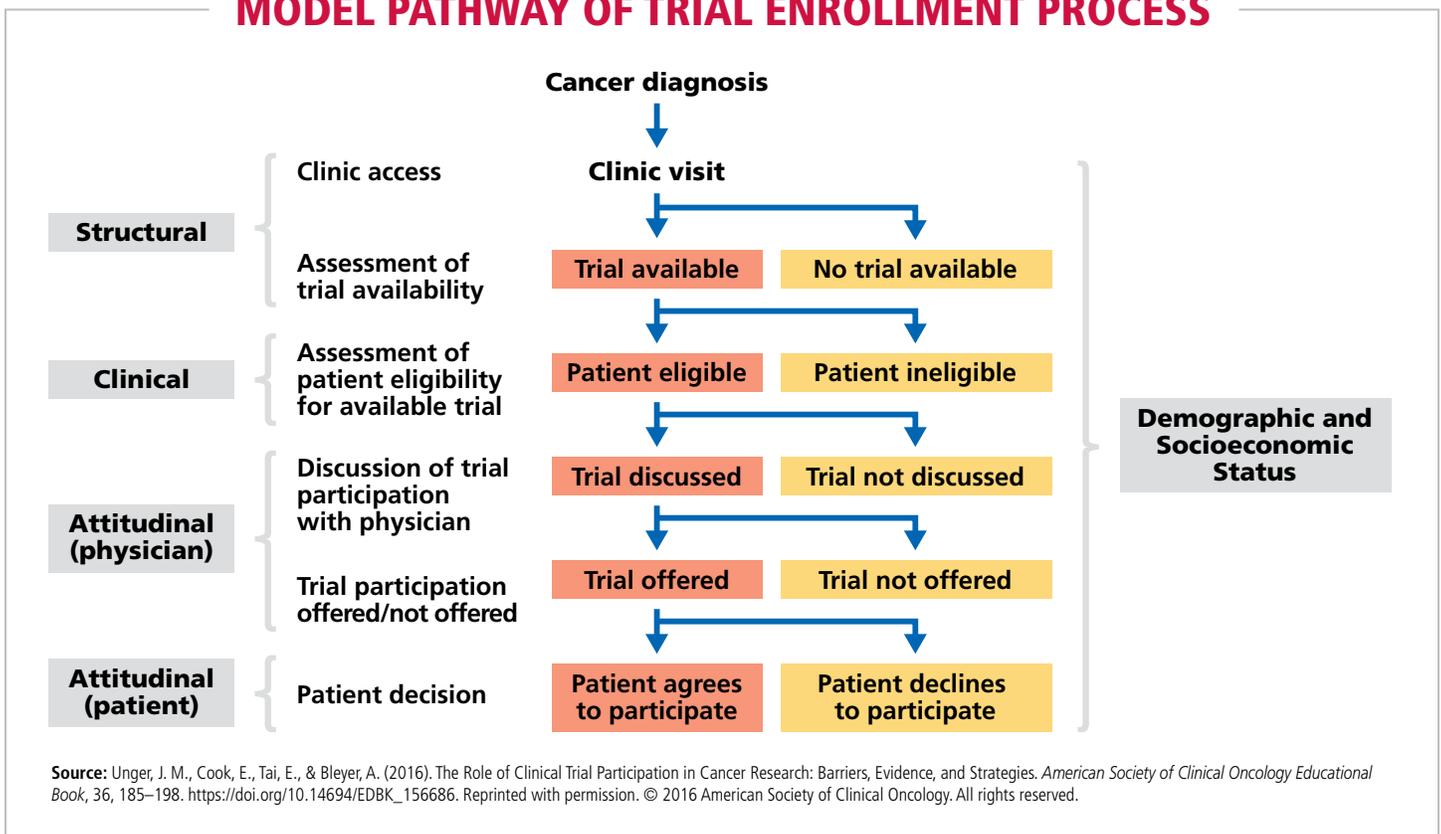


FIGURE 1: The model for patient enrollment in a clinical trial is a multi-step process with different barriers occurring at each step. Patients may experience barriers differently based on demographic and socioeconomic status.

“The centers most successful at clinical trial enrollment are those that prioritize inviting every single patient who might be eligible.”

Karen Winkfield, MD, PhD, Wake Forest Baptist Medical Center

(PROs), which are designed to give patients a voice in the evaluation of new treatments by focusing on symptoms and quality of life, are also growing in use [10, 11]. Policy-makers and clinical investigators also continue to improve ways in which to incorporate patient views during review and design of trials, and to facilitate continued refinement of patient consent procedures to account for other ways to digest information [12-15].

Types of Trial Barriers

Barriers to trial participation have been the subject of frequent study, but the rate of trial participation has not changed substantially over time. In fact, the infrastructure around the conduct of clinical trials has been designed to anticipate a low, albeit steady, trial participation rate. While only one clinical trial source among many, the National Cancer Institute’s (NCI’s) National Clinical Trial Network (NCTN) program budget recently capped enrollment for its funded network groups to 17,000 total patients per year, representing 1% of the estimated 1.7 million new cancer diagnoses in the U.S. in 2015 [16-18].

The representation in Figure 1 serves as a guide to understand how trials may become an option for patients within the process of determining their cancer treatment. After cancer diagnosis, a patient will visit a cancer clinic, at which time clinic staff may assess whether a trial is available for the patient’s histology and stage of cancer depending on the site’s infrastructure and protocols. If an initial assessment reveals that a trial is available, staff will typically further evaluate if the patient is eligible for the trial based on more specific inclusion/exclusion criteria. If the patient is eligible, the physicians will then discuss and potentially offer the patient the opportunity to participate in the trial. Ultimately the

decision about whether to participate in a trial or pursue standard of care rests with the patient. However, it is notable that the patient’s decision does not come into play if previous steps of the process are not successful. This framework suggests the numerous and varied types of barriers that may prevent patients from participating in trials, including structural barriers (especially the absence of an available clinical trial), clinical barriers (such as the patient not meeting eligibility criteria), and attitudinal barriers on the part of both patients and physicians. Each of these types of barriers may also vary depending on demographic and socioeconomic attributes.

Estimates of Structural and Clinical Barriers to Trial Participation

As suggested by Figure 1, for some patients, trial participation is simply not possible, irrespective of their willingness to participate. Numerous studies have examined the treatment-decision making process for patients in the context of clinical trial participation, following the framework outlined above. These studies show that on average, a clinical trial is not available for patients more than half the time (56.2%) (see Table 1, page 8). This rate is much higher at community sites (59.9%) than at academic sites (41.4%), since academic sites are more oriented around clinical research, may have more physicians engaged in research, and have the ability to support a greater volume of trials.

Unfortunately, many patients with a cancer and stage that matches a trial ultimately are not eligible to participate due to many specific criteria for inclusion and exclusion (17%), a pattern that is more pronounced at academic centers than community sites. Clinical trials exclude patients for many reasons related to the goals of maintaining patient safety and

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CLINICAL TRIAL ENROLLMENT PATTERNS FOR MULTIPLE STUDIES IN THE LITERATURE¹

	TRIAL UNAVAILABLE	INELIGIBLE	NOT ENROLLED	ENROLLED
Academic Centers				
Average rate²	41.4%	24.3%	19.5%	14.8%
Community Centers				
Average rate²	59.9%	15.7%	17.9%	6.3%
Combined				
Adjusted rate³ All studies	56.2%	17.4%	18.2%	8.0%

¹ Adapted from Unger et al., 2018, in press.

² Calculated using a weighted average based on study size

³ Based on multiple sources, we estimated that approximately 80% of patients receive their care in community-based cancer centers. Thus the overall average rate was weighted at a ratio of 4:1 based on average estimates from community:academic centers.

Sources: Academic [34, 118, 139, 207], Community [109, 110, 111]

TABLE 1: Studies at academic and community treatment sites have quantified barriers preventing patient enrollment in clinical trials and show that most patients will not have the opportunity to enroll in a clinical trial.

establishing a study cohort with similar patient profiles, in order to more accurately assess the response of patients to the investigational treatment [22].

These structural and clinical barriers to trial participation generate a system in which about two-thirds of patients seen at larger, generally academic cancer centers and about three-fourths of patients seen in smaller community treatment centers have no real option to participate in a clinical trial. Eighteen percent of the remaining patients do not participate in trials for reasons related to either patient-focused barriers, or barriers associated with the care provider or institution (see Figure 3, page 10). The categories of barriers are detailed in subsequent chapters of this report.

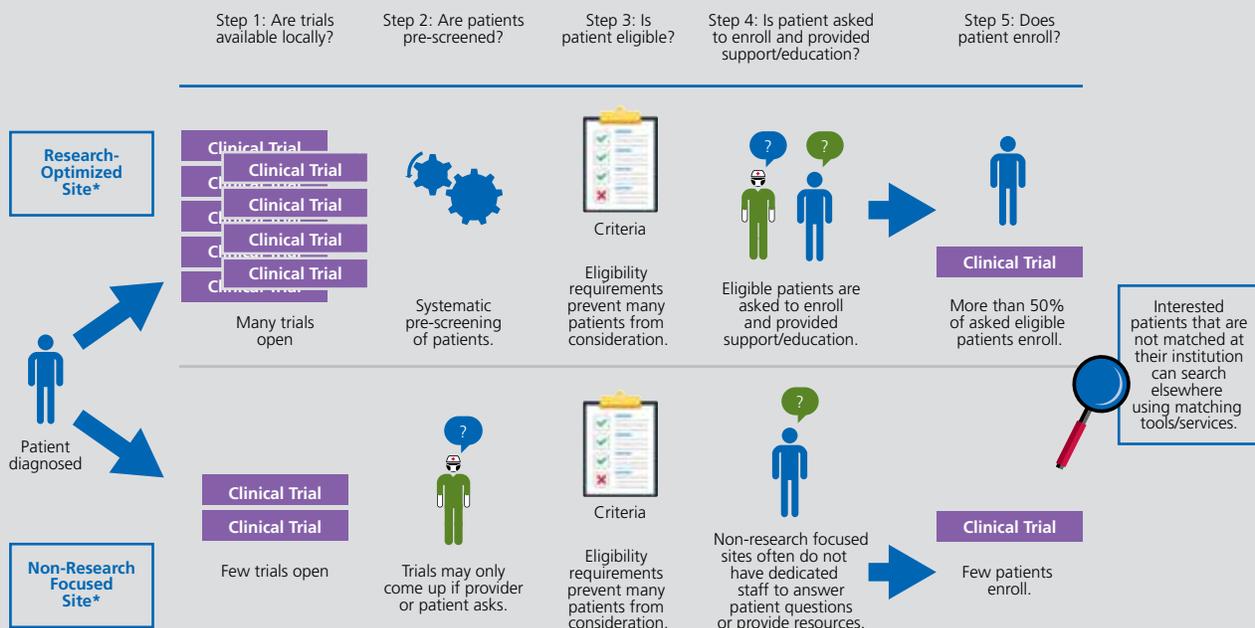
The Average Trial Participation Rate

While the common refrain is that “only” 3-5% of cancer patients enroll on clinical trials, there is little empirical data to support this statistic, and the sources usually referenced for these figures analyze only NCI-sponsored therapeutic trials [3, 23], which may account for less than 20% of all cancer trials [24]. If so, the overall rate of trial participation, including participation in industry-sponsored or other trials, may be notably higher. In an examination of the literature, the overall trial participation rate averages 14.8% at academic centers and 6.3% at community centers (see Table 1). Since more cancer patients are seen in the community than in large research institutions, the actual overall enrollment is likely closer to that of community centers and is estimated at approximately 8%, significantly higher than the oft-cited 3%-5% figures.

THE INFLUENCE OF THE CLINICAL SETTING

Patterns of barriers will differ depending on where patients are receiving care. Settings of care vary considerably, from those optimized around conducting clinical research, to those with little to no research infrastructure and emphasis. In general, fewer clinical trials are available in smaller non-research focused community sites than in larger, typically academic research institutions [19] (see Table 1, page 8). These differences are reflected in enrollment expectations imposed by outside organizations. For example, the Commission on Cancer has nine different categories for treatment setting, with different minimum enrollment standards that must be met for their accreditation. NCI-designated comprehensive cancer centers must enroll a minimum of 20% of patients to be accredited, but community cancer programs only need to enroll 2% of patients to meet accreditation requirements [20]. As another example, the American Society of Clinical Oncology has suggested that exemplary clinical trial sites should strive for enrollment of 10% of patients on clinical trials [21]. Industry-sponsored research, trial site identification and feasibility exercises often follow these same, or similar, expectations for the different classifications and sizes of research sites. Comprehensive cancer centers typically also have more resources and larger, more diverse patient populations to support a greater volume of trials and trials with greater complexity.

PATIENT ENROLLMENT BARRIERS VARY BY LOCATION



*Comparisons are illustrative only, and individual sites vary.

FIGURE 2: The opportunities and barriers for clinical trial participation differ depending on where a patient receives care. Large research optimized sites often have far more open clinical trials than smaller, non-research focused sites. Further, research optimized sites often have dedicated personnel and a systematic process for pre-screening patients for trial eligibility, while sites with limited or no research focus often lack methods to efficiently examine whether a patient has research opportunities. Lastly, research sites typically have dedicated staff to help with the enrollment process. Regardless of the site, patients who are not offered a clinical trial have the opportunity to seek out trials using 3rd party matching services that may identify trials available at other locations.

Background

There is not necessarily an “appropriate” enrollment rate for cancer clinical trials as a whole, or even for specific types of cancer. Rather, the goal is to rapidly and efficiently conduct clinical cancer research to generate results that are applicable to an appropriate target population. Nonetheless these findings point to the significant challenges that trial design and availability pose to enabling patients to participate. Patient education and outreach have often been the focus of initiatives to boost enrollment, but a relatively small proportion of patients even have the opportunity to consider a trial. This emphasizes the need to address structural

barriers as well as patient and physician barriers in order to meaningfully change the rate of participation by patients in clinical cancer research.

Trial Sponsors: Industry and NCI

The two largest categories of cancer clinical trial sponsors are the pharmaceutical industry and the federal government through NCI. While not universal, a significant portion of NCI-sponsored trials tend to be comparative in nature (testing one approved treatment/approach against another) or may seek to test approved therapies in other cancer types.

CLINICAL TRIAL DECISION-MAKING PATHWAY

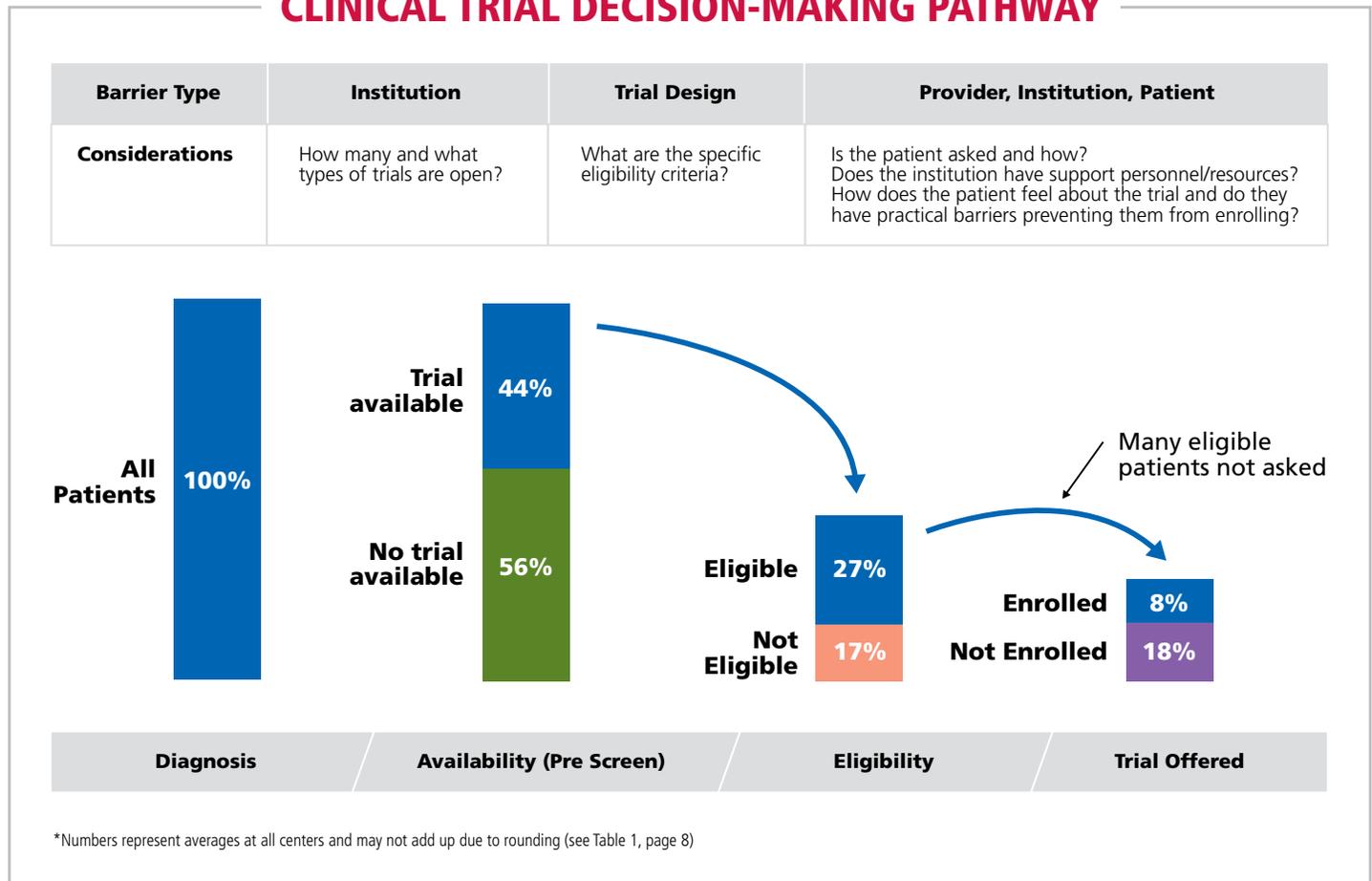


FIGURE 3: Patient attrition occurs throughout the trial-enrollment decision process. Based on numerous studies (see Table 1, page 8), over half of patients will not have a local trial available as a result of decisions about which trials an institution opens. Forty percent of patients with trials available (17% of total) will not be eligible to enroll on a trial due to eligibility requirements established during the trial’s design. Ultimately, 8% will enroll in a trial and 18% will not enroll. Multiple studies show that around 30% of eligible patients will not be asked to participate. Only a small fraction of patients overall ever have the opportunity to consent to a request to participate in a clinical trial, and when asked, over half typically agree.

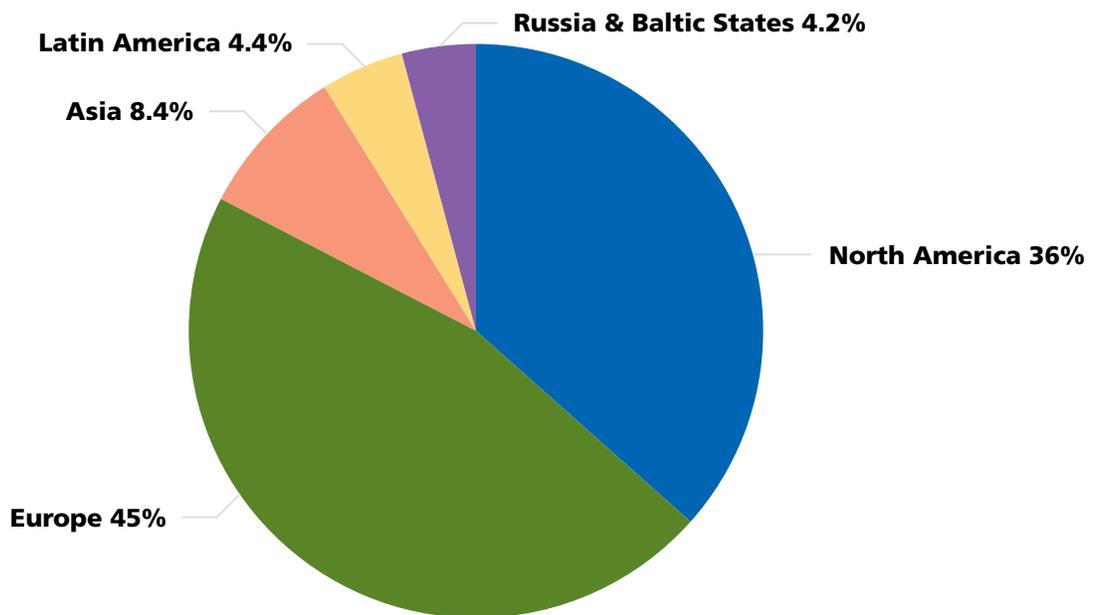
Industry trials are usually designed to generate data that can be submitted for FDA approval and product registration and often use unapproved or provisionally approved therapies or seek to expand use of approved drugs to new indications.

NCI is one of the 27 institutes that make up the National Institutes of Health (NIH). The annual NCI budget now exceeds \$5 billion; however, a significant portion of NCI research is basic, non-clinical research. NCI funds clinical research through a variety of grant mechanisms, with a significant portion of their clinical research portfolio through the National Clinical Trials Network (NCTN). NCTN trials benefit from central coordination but operate at multiple sites throughout the country through grants and infrastructure funded by NCI. NCTN trials enroll approximately 17,000 individuals in clinical trials annually and seek to advance the

standard of care [25]. In addition to NCTN trials, individual investigators can initiate clinical trials using NCI grants. Additionally, some clinical trials can be jointly funded by NCI and industry, with industry supplying the investigational drugs while NCI grants fund data collection.

Industry is by far the largest sponsor of clinical trials. In 2013, industry funded over 2,500 individual cancer trials [1]. Industry-funded trials are typically conducted to collect safety and efficacy data on unapproved drugs to support an application for marketing approval from FDA. Testing unapproved drugs requires submission of an Investigational New Drug (IND) application to FDA for approval. Such testing normally passes through several progressive phases, but fewer than 15% of drugs initially tested in phase I trials ever reach full FDA approval [26]. While industry trials often

GEOGRAPHIC ORIGINS OF PARTICIPANTS IN FDA-SUBMITTED CANCER TRIALS



Source: Kanapuru (2017), FDA analysis of patient enrollment by region in clinical trials for approved oncological indications, ASCO Annual Meeting. (Trials from 2005-2015)

FIGURE 4: Data submitted to FDA in support of a drug application does not have to come from trials conducted in the U.S., and in fact a minority of the total number of patients represented in oncology drug applications is derived from the U.S. Data is from oncology trials submitted from 2005-2010.

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use some of the same sites to enroll patients as NCI trials, the infrastructure and some of the regulatory requirements may differ. Clinical trials used to gather data for submission to FDA are not required to be conducted in the U.S., and in fact only 36% of patients in clinical trials submitted to FDA for drug approval come from North America, with the rest coming from Europe, Asia, Latin America, and Russia (see Figure 4, page 11).

Demographic and Socioeconomic Disparities in Trial Participation

Demographic and socioeconomic disparities in trial enrollment can occur anywhere along the pathway from initial clinic visit until the patient ultimately makes their treatment decision. One of the largest measured disparities in clinical trial participation in both NCI and industry trials is an age disparity. This disparity has been persistent over several decades. In 1999, investigators noted how although nearly two out of three cancer patients are 65

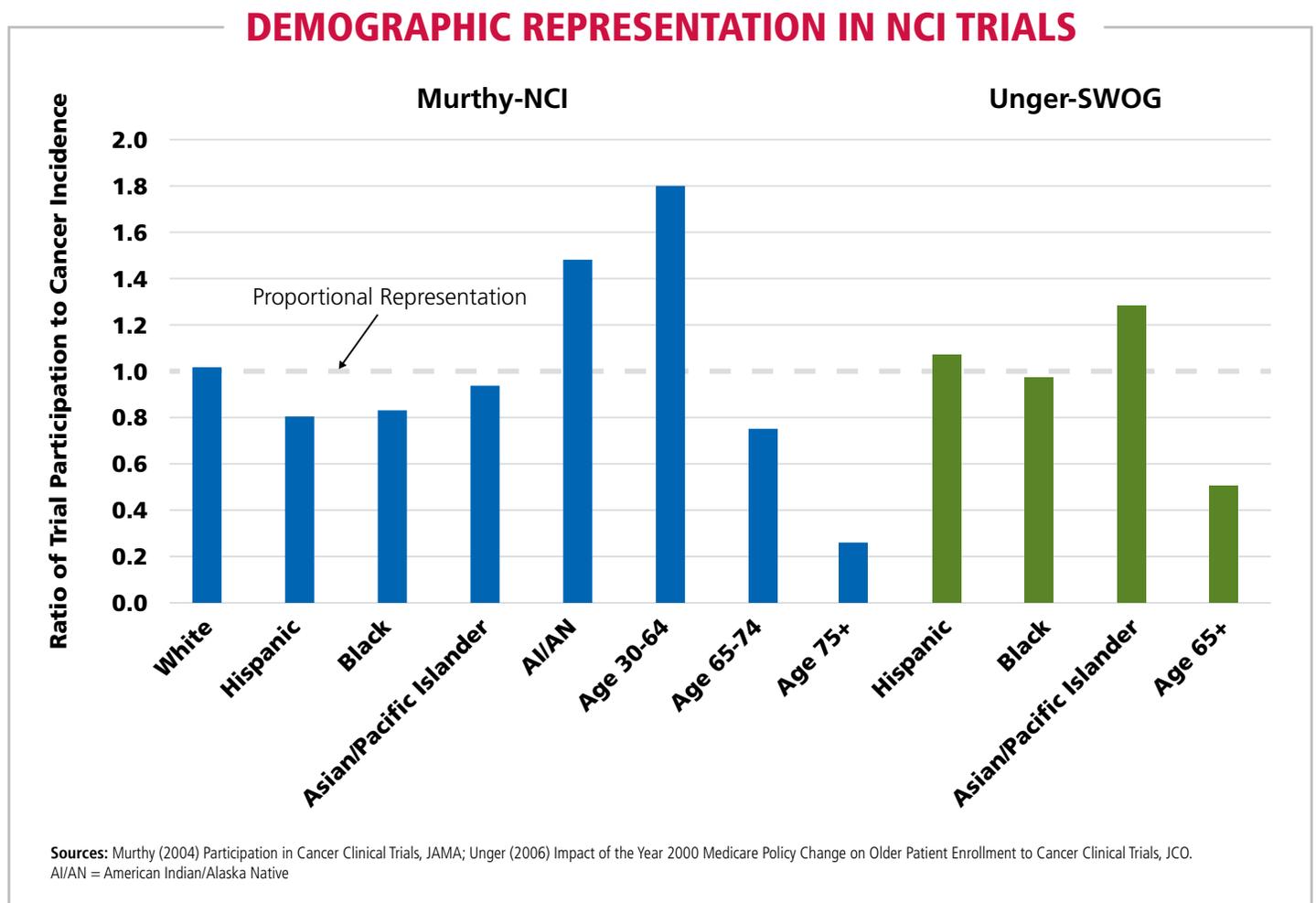


FIGURE 5: Demographic representation was evaluated in NCI cooperative group trials as well as within SWOG (Southwest Oncology Group), one of the NCTN clinical trial groups. Bars represent the ratio of the demographic representation in clinical trials versus demographic representation in the broader population diagnosed with cancer. A ratio of 1.0 indicates that the demographic make-up of a clinical trial matches the demographic make-up of the population with cancer. A number greater than 1.0 indicates over representation in clinical trials while a number less than 1.0 indicates under representation in clinical trials. AI/AN-American Indian/Alaskan Native

or older, only about 25% to 30% of participants in trials were 65 or older [27]. One likely culprit for this major discrepancy was the fact that, at the time, Medicare did not cover the routine care costs of patients enrolled in clinical trials. The enormity of this disparity was revealed and the Institute of Medicine recommended changes to this policy [28]. In the year 2000 an executive order directed the Center for Medicare and Medicaid Services to change this policy resulting in coverage [29]. Since then the participation of older patients in trials has improved, although the rate remains quite low [3, 30-33]. While older patients are equally likely to consent to trials [34], fewer trials are available to them, often because of increased comorbidities, and fewer are asked to enroll [34-36]. In 2018, NIH announced a policy that will become effective in

January 2019 requiring researchers to have plans in place to include research participants across the lifespan [37].

Racial and ethnic disparities are very pronounced in FDA registrational trials for oncology drugs, but in NCI trials, enrollment of different racial and ethnic groups more closely matches the US cancer population demographics (Figures 5 and 6). Barely over a third of patients in FDA registrational cancer clinical trials are from North America (see Figure 4, page 11), making it unlikely that the racial and ethnic makeup of such trials could accurately reflect the U.S. cancer population. In contrast, some studies have shown that minority patients were enrolled in NCI-sponsored clinical trials in a representative fashion over an extended period of examination [27, 33, 38]. However, others have shown certain

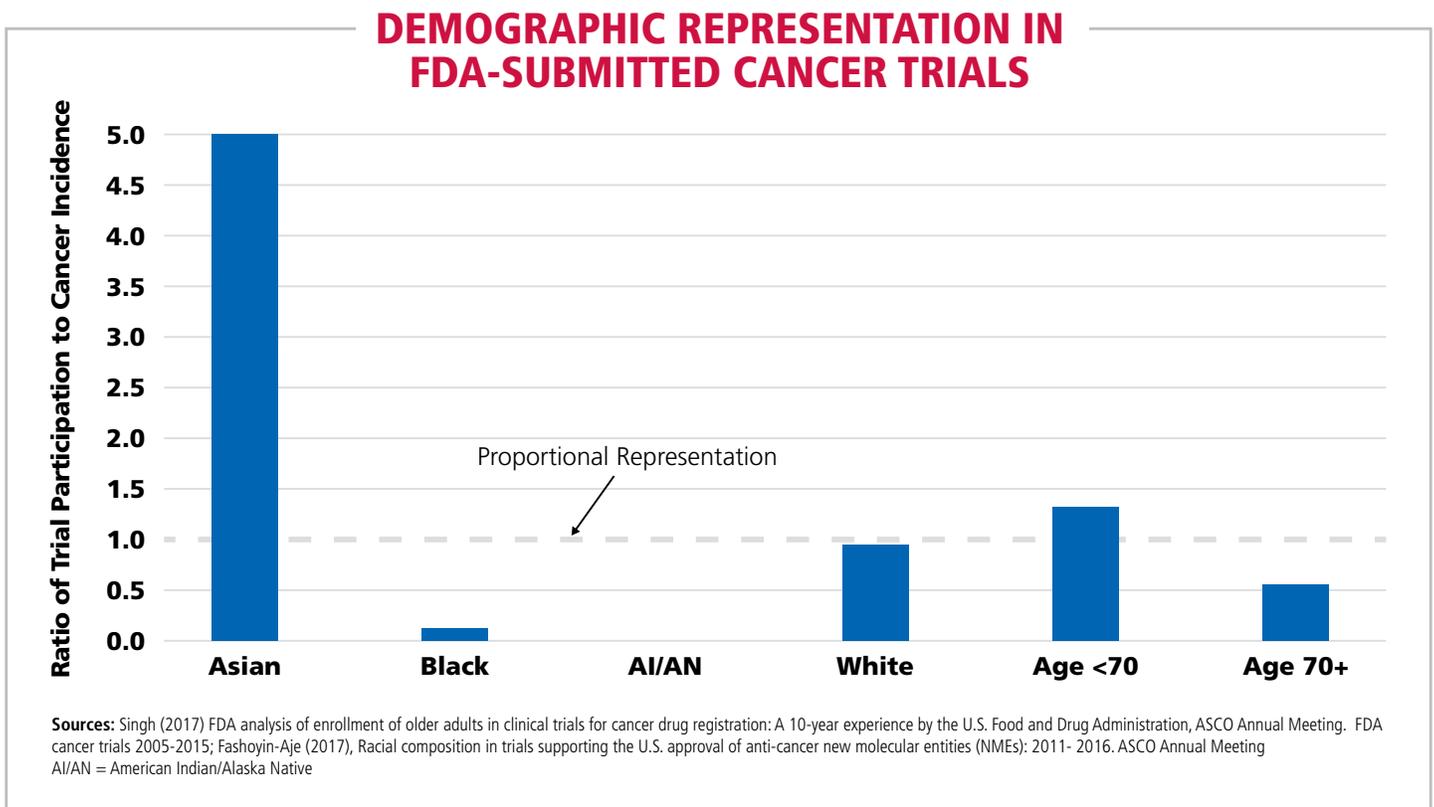


FIGURE 6: Data from a decade of FDA-submitted cancer trials shows large over representation of Asians and significant under representation of Blacks and American Indians/Alaska Natives (AI/AN). Bars represent the ratio of the demographic representation in clinical trials versus demographic representation in the broader population diagnosed with cancer. A ratio of 1.0 indicates that the demographic make-up of a clinical trial matches the demographic make-up of the population with cancer. A number greater than 1.0 indicates over representation in clinical trials while a number less than 1.0 indicates under representation in clinical trials.

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groups such as black patients to be underrepresented [3, 39]. Hispanic patients may also be underrepresented [3, 33]. To accommodate these challenges, researchers have generated well-designed outreach programs for large individual trials [40-42]. More women participate in cancer clinical trials than men, although this is due mainly to the large number of trials for breast cancer. Among cancers that are not sex-specific, females have been shown to be modestly underrepresented, although the magnitude of the disparity is fairly small [27, 33, 43].

The impact of socioeconomic status on access to resources, which has been widely discussed in many settings, has also been found to be influential in clinical trial participation. Two recent studies have found that patients with household income less than \$50,000/year were about 30% less likely to participate in trials [30, 44]. It is likely that additional cost sharing copays and coinsurance play a role for some patients. Patients with fewer financial resources may find the indirect costs of trial participation, such as travel, time off work, or daycare needs, to also be prohibitive.

In the early 1990s, Congress passed The NIH Revitalization Act of 1993, requiring NIH to establish guidelines for inclusion of women and minorities in clinical research [45]. This has led

to NIH policy requiring that researchers consider differences in responses among different subpopulations, and if data suggests that different groups will have different responses, then the clinical trial must be designed with enough patients to sufficiently analyze outcomes in each distinct group [37]. If there is no evidence for such differences then subgroups should be proportionately represented, but the trial does not need to be designed to assess differential outcomes. FDA does not require proportional representation in clinical trials, but in 2014, the agency released an action plan to enhance the collection and distribution of demographic data on trials submitted for review [47]. Included in this plan was the creation of drug snapshots that summarize demographic breakdowns of participants for newly approved drug products, including any significant differences in outcomes if there was sufficient subgroup participation to analyze such differences. Given the increasing diversity of the U.S. population, continued attention to this issue is necessary. Representative participation in cancer clinical research will help ensure that racial and ethnic minorities benefit from the improved outcomes achieved with newer cancer therapies, but because of the limited size of trials, a full understanding of disease heterogeneity may not be possible until new therapies are approved and used in larger numbers of patients.

“If the data from prior studies strongly support the existence of significant differences of clinical or public health importance in intervention effect based on sex/gender, racial/ethnic, and relevant subpopulation comparisons, the primary question(s) to be addressed by the proposed NIH-defined Phase III clinical trial and the design of that trial must specifically accommodate this. For example, if men and women are thought to respond differently to an intervention, then the Phase III clinical trial must be designed to answer two separate primary questions, one for men and the other for women, with adequate sample size for each.”

—NIH Inclusion Guidelines

Pediatric vs. Adult Differences

Unlike adults with cancer, most children with cancer participate in trials, and corresponding advances in cancer outcomes for childhood cancer have been shown to exceed those for adults. Enrollment of pediatric patients (<15 years old) in clinical trials is around 50%-60% [48, 49]. About half of these patients participate in treatment trials, and the remainder in observational cohort studies. Importantly, the structural and clinical environment for treatment of childhood cancers differs from the treatment of adult cancers, with most treatment of children occurring at a small number of specialized academic centers with a high proportion of care providers also involved in research.

The improvement in population survival rates for children with cancer exceeds that of adults with cancer. Indeed, mortality rates for children with cancer have been decreasing since the 1970s. In contrast, in adults with cancer, mortality rates have only been decreasing since the 1990s [50]. This evidence points to the value of trials in benefiting not just those patients who participate in trials but also patients in the cancer community writ large, and as Figure 7 illustrates, trial participation by age strongly correlates with improvements in survival [44, 51, 52].

Differences Between the U.S. and Other Countries

The examination of international patterns in trial enrollment and attitudes can yield important insights about trial participation in the U.S. Both similarities and differences exist between the U.S. and other countries. For instance, trials with study sites outside high-income countries (HICs) tend to recruit more participants and are more likely to be phase III or IV studies [53]. In the case of cancer specifically, a larger share (45%) of trial participants in trials submitted to the FDA for oncology drug approvals from 2005 to 2015 were enrolled in Europe, while North America was second (36%) (see Figure 4, page 11) [54]. Europe also had a much higher number of older patients enrolled in trials compared to North America. Several factors drive the regional differences in trial participation such as clinical exclusion criteria, patient attitudes and other treatment options. In particular, North

American trials – especially early phase trials – may be more likely to restrict eligibility criteria based on comorbidities including heart failure, coronary artery disease, HIV, hepatitis, and hemoglobin-related criteria [55, 56].

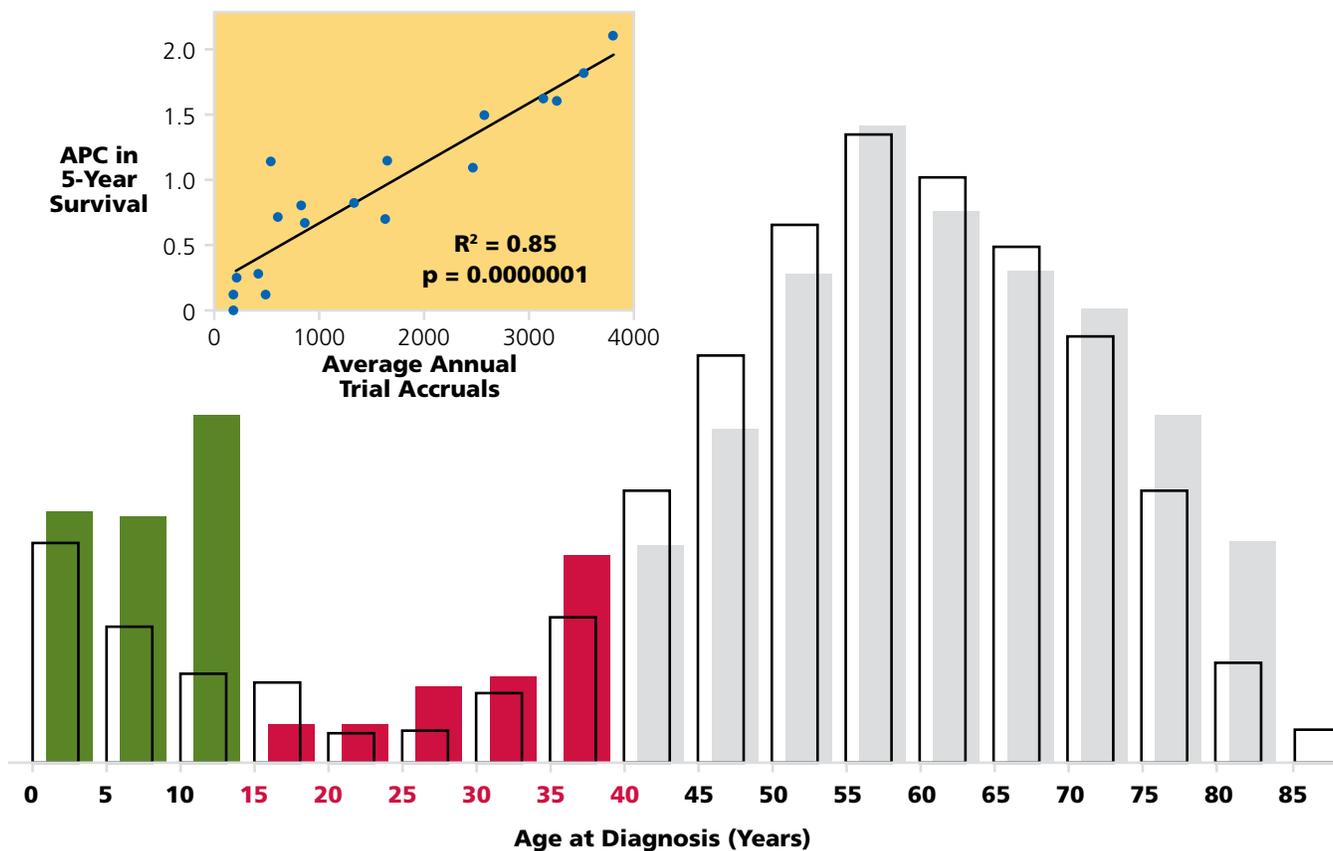
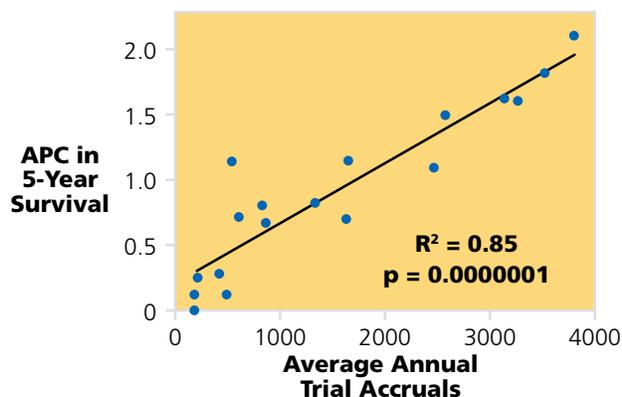
Similar to American patients, patients in the United Kingdom showed willingness to participate in trials but were concerned about randomization [57]. However, many of the patients initially concerned about randomization were more inclined to participate when provided with additional information. In Korea, cancer patients with higher income and education levels were more aware of clinical trials but not necessarily more willing to participate, a pattern that stands in contrast with the U.S., where higher income is associated with greater participation [30, 58].

Positive vs. Negative Results from Trials

Clinical trials with positive results are important because they indicate clinical advances. Multiple sources have estimated that the rate of trial positivity in the cancer setting is about 20%-30% [59-61]. This rate is consistent with the notion of equipoise; that is, that true uncertainty exists about whether a new treatment is better than standard treatment [62]. Equipoise is an essential characteristic for the ethical conduct of any clinical trial that compares two or more treatments to each other. If the likelihood of success is too high or too low, then patients and clinicians are unlikely to entrust their treatment choice to random assignment, in the case of a randomized clinical trial, and it is unethical to ask them to do so [61]. While positive clinical trials are widely hailed, trials with negative results are often interpreted as scientific failures. But it is important to note that negative trial results (i.e., worse or no significant improvement with the intervention being tested) can also provide very important information. Well-designed and conducted clinical trials with a strong scientific rationale that yield negative results can also have a sizeable scientific and medical impact by generating important scientific observations and new hypotheses for further testing, and by showing treatments that are either no better, or are worse and should not be used. It has been shown that when all of the science derived from positive and negative trials is added together, the scientific impact of negative trials on clinical

Background

COMPARISON OF AVERAGE PERCENT CHANGE IN THE 5-YEAR CANCER SURVIVAL RATE AND TREATMENT TRIAL ACCRUALS, BY 5-YEAR AGE INTERVALS



 The open columns represent trial accruals during 2001 to 2006
 The colored bars represent the average percent change (APC) in 5-year relative survival rate of all invasive cancer except Kaposi sarcoma during 1985 to 1999. Green indicates pediatrics; red adolescent and young adults; grey adults.

The inset compares to the APC in 5-year survival rate with the treatment trial accruals. Accrual data from the National Cancer Institute Cancer Therapy Evaluation Program (CTEP) were provided by Steve Friedman, Michael Montello, Troy Budd, and Samantha Finnegan via the Freedom of Information Act. Survival data were obtained from SEER 9 Regions.⁷⁵ Kaposi sarcoma is excluded from the survival statistic because the HIV/AIDS epidemic occurred during the 1980s and early 1990s, which substantially altered the overall cancer survival rate in AYAs during those years. Reprinted with permission. Unger, J. M., Cook, E., Tai, E., & Bleyer, A. (2016). The Role of Clinical Trial Participation in Cancer Research: Barriers, Evidence, and Strategies. American Society of Clinical Oncology Educational Book, 36, 185–198. https://doi.org/10.14694/EDBK_156686, © 2016 American Society of Clinical Oncology. All rights reserved.

FIGURE 7: Clinical trial participation rates closely correlate with gains in survival. Specifically, adolescents and young adults have the lowest trial participation rates and have seen the least progress in outcomes.

practice is not much different from positive trials [61]. Thus the conduct of a clinical trial serves a vital scientific, medical, and societal interest, regardless of the result of the trial. This may be an important consideration for some patients who are considering whether their participation in a trial will be of benefit to others.

Outcomes for Patients Treated in Clinical Trials

The question about whether patients participating in clinical trials, as a whole, have better outcomes than those who do not enroll in trials is of interest but has not been resolved. A few authors have attempted to review and summarize the literature on cancer clinical trials to decipher overall patterns [63, 64]. Unfortunately, the question cannot yet be answered using this approach because the conclusions drawn from these studies have varied, ranging from no evidence of a benefit for trial patients, to positive, but weak, evidence that participation in trials improves patient outcomes. In a recent comprehensive examination of trial outcomes from a large set of cancer treatment trials, participants in trials were found to have better outcomes than non-participating patients in the first year after diagnosis only; after the first year, trial and non participants had similar outcomes [61]. This finding may be due to the influence of strict trial eligibility criteria, which likely exclude cancer patients with comorbid conditions from trials, leaving a trial cohort of healthier patients with better early outcomes than patients who did not enroll in a trial.

However, the findings from these literature reviews should be comforting to patients considering trial participation. Little evidence suggests that patients participating in trials have worse outcomes on average than patients who are not treated in a trial. Furthermore, participants might benefit from receiving care administered according to high-quality trial protocols from a team of clinicians well-trained in the research process. Some patients also could benefit from the opportunity to access greater treatment options, including the newest experimental therapies. Therefore, patients participating in a trial are likely to receive care that is at least as good as treatment administered outside of a trial, and, if the investigational treatment works, perhaps even better.





Rob

Rob credits his wife, a nurse, for helping to catch his cancer. She noticed that his eyes were taking on a yellow tint. Scans ordered after a visit to the doctor led to a diagnosis of pancreatic cancer, which was blocking his bile duct and causing his jaundiced eyes. While getting his initial workup in the hospital in Rhode Island his doctors began talking to him about participating in a clinical trial. "They found me, rather than me finding them," said Rob about how he found his clinical trial. Eager to explore all his options, Rob engaged his extensive network of friends and family in the medical professions, and explored options in Boston, a hub of clinical trials only 90 minutes away. In the end, however, he felt the trial his initial care team offered him was the best option. "Unless it was clear cut that other sites had better options, I wanted to stay close to home and this offered the possibility of getting a new drug, so I jumped on the opportunity," said Rob about how he came to take part in a clinical trial. Rob recognizes how fortunate he is to have an engaged network of friends to rely on, and found the whole process smooth, but worries that not everyone is so lucky. "You have got to have someone besides yourself in the field advocate for you and help with the process."

Provider / Institutional Barriers

Overview

Providers and institutions have a significant impact on cancer clinical trial enrollment as a result of control over a variety of factors including decisions regarding which and how many trials to open at a site, the quantity and type of research personnel employed, whether and how they identify and enroll patients to trials, as well as investment in research infrastructure. Together, these factors account for the largest influence on whether patients are able to enroll in a clinical trial. The availability of trials varies depending on the type of institution, with on average 41% of patients receiving treatment at academic research centers without local trial options, and 60% similarly without local options at community sites (as referenced in more detail in the Background chapter). More detailed trial eligibility criteria, which are typically outside of an institution's control, result in an additional 24% and 16% of patients being ineligible at academic and community sites respectively, leaving between one third and one quarter of patients eligible to enroll on trials. While between 50% and 75% of eligible patients who are asked to enroll in a trial will typically agree to enroll [30, 65-68], not all eligible patients are asked. Through attrition at each step of this phase, studies show ultimately around 15% of cancer patients enroll at academic sites and just over 6% at community sites (see Table 1, page 8). This chapter further examines what role institutions and providers play in barriers patients face when trying to enroll in clinical trials.

Research Resources—Staffing

Clinical research is an activity distinct from clinical care. Many providers may both conduct research and engage in clinical practice, but research requires significant additional specialized personnel, training and resources. Specialized, dedicated, in-house research personnel, often made possible either through NCI grant mechanisms or industry-sponsored research contracts (described below), have been shown to significantly increase site enrollment [69-71], and providers have reported lack of staffing as a leading barrier to enrolling patients in cancer clinical trials [72]. Smaller practices or institutions that do not have funding for dedicated recruitment and enrollment personnel often rely on existing clinical personnel to perform research pre-screening and enrollment functions in addition to their clinical day-to-day practice activities. Oncologists have to also be investigators, nurses have to also be clinical research coordinators, pharmacists have to be specialized in the handling and management of investigational agents, and practice/institution finance experts have to also specialize in the billing and reconciliation of research funds for staffing, facilities, and equipment. As a result, providers at practices that lack specialized staff and protected time for research face challenges enrolling patients in clinical trials [73]. Technology, such as patient matching/eligibility algorithms built into electronic medical record systems, has the potential to reduce the human workload associated with identifying



Provider / Institutional Barriers

RESEARCH (CLINICAL TRIAL) STAFF SPECIFIC TRAINING NEEDS

TITLE	ROLE IN ENROLLMENT AND / OR RETENTION	RESEARCH EXPERTISE / TRAINING REQUIREMENTS
Physician Investigator	Ongoing patient care and advise on care choices. May refer patients to clinical trials or may also care for the patient during the trial; conduct informed consent process. If a principal investigator, then responsible for oversight of trial at the site.	International Conference on Harmonization Good Clinical Practice (ICH-GCP) and human subject protection training at a minimum; confidentiality and conflict of interest requirements. NIH / NCI and FDA if trial is funded or regulated by these agencies.
Clinical Research Nurse / Clinical Research Coordinator <i>(May have dedicated research responsibilities or be split with clinical care)</i>	Screen and enroll patients to trials, coordinate research care, educate study participants and clinical staff, collect research data, administer study drugs, report serious and non-serious events, may supervise, study coordinators, data managers or other research staff. Works under the supervision of the PI or co-investigator.	ICH-GCP and human subject protection training at a minimum. American Nurses Association (ANA) code of ethics
Navigators, Patient Advocates	Expose patients to the possibility of clinical trials, answer questions and connect patients with resources.	May be lay or clinical staff. Would require familiarity to research processes (e.g. informed consent, subject rights, types / sources of trials)
Regulatory	Responsible for initial and ongoing submissions to and approvals from regulatory authorities (e.g. FDA, IRB) for study conduct, for approval of patient-facing educational materials, and maintaining and updating regulatory documentation throughout study.	GCP / ICH and human subject protection training at a minimum; knowledge of relevant regulatory requirements (e.g. FDA, NIH / NCI, state agencies); IRB policies and requirements
Data Manager	Abstracts data from patient primary medical record as dictated in the research protocol and enter on to paper or electronic case report forms (CRF) or directly into clinical trials data management system.	GCP / ICH and human subject protection training at a minimum
Budget Analyst	Prepare a trial budget for review by the PI to include trial expenses.	N/A
Contract Analyst	Facilitates the negotiation of the trial legal agreement between the sponsor and trial site, including budget and invoicing terms.	N/A
Trial Coverage Analyst	Develops Local Coverage Determination (LCD) to ensure the provider billing compliance as per relevant payer requirements.	Billing compliance training. Knowledge of payer billing rules.

TABLE 2: A wide variety of research staff is needed to support the conduct of clinical trials at a site. While staff is sometimes wholly dedicated to research duties, often staff will also have concurrent clinical duties.

eligible patients [74-76], but even with technology, staff time is required to find and enroll patients in clinical trials. Examples of other specialized research personnel include data collection and management, contracts management, and billing and federal regulations compliance. More about the research roles and their responsibilities with clinical trials is found in the table to the left.

For industry-sponsored trials and NCI studies alike, all investigators must complete FDA documents, agreeing to follow many complex, but relevant regulations. Investigators also need to complete financial disclosure forms, provide documentation of credentials and experience (e.g. CV/ Biosketch, publications, certifications), and receive initial approval and annual review from an Institutional Review Board (IRB) for study conduct and ongoing monitoring of human subject protection. These steps are completed for every clinical research study their institution/site conducts. Almost universally, primary research staff who have direct contact with a clinical trial patient also require at least minimal, often annual, completion of International Conference on Harmonization Good Clinical Practice (ICH-GCP) and human subject protection (HSP) training. It is also worth mentioning that, although NCI studies have consistency, there are hundreds of potential biopharma industry clinical trial sponsors, all of whom may require varying levels of research training, work with specific IRBs, or mandate specific contract details. Independent professional organizations such as the Association of Clinical Research Professionals (ACRP) or the Society of Clinical Research Associates (SoCRA) provide training and accreditation for research professionals. Similarly, the Society for Clinical Research Sites (SCRS) provides support and a community dedicated to research site sustainability. This training provides critical skills for personnel involved in research, but also represents staffing requirements on a site in addition to what is involved for any non-research practice activities.

Finding qualified candidates for research staff positions, such as clinical research coordinators (CRC), can be challenging. According to one study, it takes an average of three to six months to fill open CRC positions [78]. Many

factors figure into this recruitment issue but can include a lack of awareness of the role by potential candidates and unrealistic expectations by the research site about the skill set most candidates bring as well as competition for high-quality candidates [79]. For instance, most academic nursing programs have little to no content related to clinical research and the potential roles nurses can play [80].

Given these challenges, retention of quality research staff is imperative. Frequent turnover of staff can lead to greater numbers of inexperienced study coordinators, which can impact the data quality and timeliness of completing a trial [81]. Study sites wishing to retain quality research staff should consider factors that improve job satisfaction, such as opportunities for trial participant interaction, diversity in responsibilities, protected research time, the opportunity to contribute to medical advances, and autonomy. Sites should also address factors that can decrease job satisfaction and increase turnover such as lack of attention to workload, equitable pay for experience lack of career advancement opportunities, and not providing training and resources when new responsibilities are added [78].

Research Resources—Financing

Although payers may cover portions of some services in a research trial considered standard of care, insurance does not pay for research-related services or personnel. So, compensation for research personnel (whether dedicated to research full-time or part-time), like those detailed earlier, must be funded via means other than through insurance or revenue from treatment, although cross-subsidization of research activities is generally acknowledged to occur [73]. These staff are typically funded from either government or industry research revenue, through fixed or variable funding streams (see Figure 8).

For sites that participate in industry-sponsored clinical trials, research revenue comes from budgets and contracts (Clinical Trial Agreements-CTAs) between the site and the company or companies sponsoring the research. Industry CTAs attempt to pay or reimburse for patients enrolled, based on the efforts and resources necessary for their specific trial or program –

Provider / Institutional Barriers

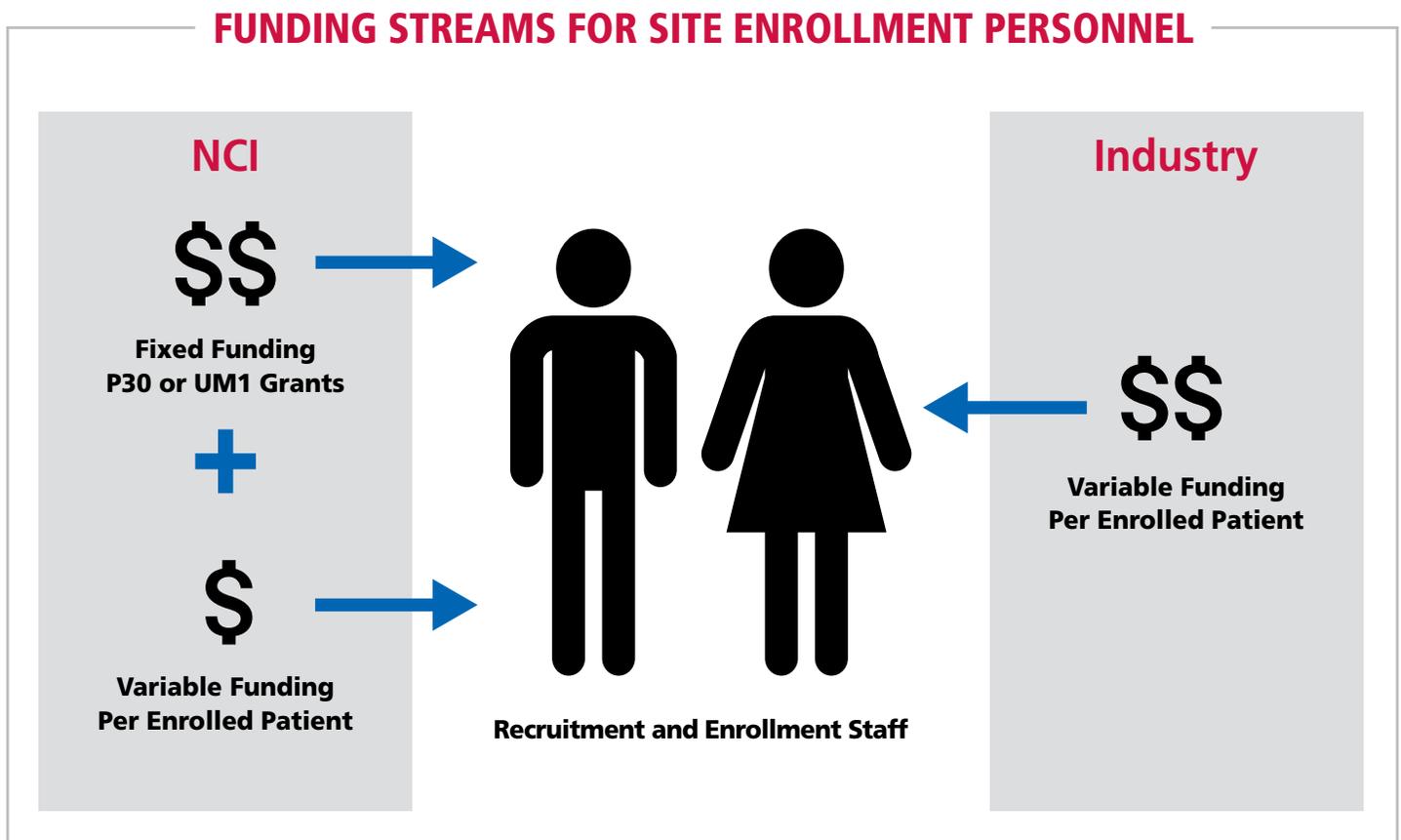


FIGURE 8: Dedicated personnel are critical to identifying/pre-screening potential trial candidate patients and recruiting and screening patients in cancer clinical trials. Federal funding can pay for these personnel through grants that fund such positions directly as well as indirectly through per-enrolled patient payments. Industry typically pays for these staff indirectly through per-enrolled patient payments that are larger than similar NCI per-enrolled patient payments. Low-volume sites without grants that provide fixed funding are wholly reliant on variable funding and may not have personnel dedicated solely to enrollment of patients onto clinical trials, but will often rely on clinical personnel (e.g. physicians, PAs, nurses) to perform these duties in addition to their normal clinical responsibilities.

largely based on the complexity of the trial. These CTAs are most often from a single pharmaceutical company seeking to gather clinical safety and efficacy data on their compound or proposed combination therapy. Clinical trials, can also be sponsored by multiple companies working in collaboration on a specific therapy or combination of therapies. After therapies are approved by the FDA and become part of clinical practice, post-approval observational and/or outcomes research studies are conducted. These “Real World” and “Late Phase” (phase IV) trials can also be an ongoing source of revenue for research sites willing and able to follow specific patients long term and collect safety, efficacy, and clinical outcomes data.

NCI Grants and Infrastructure

Sixty-nine clinical cancer centers across the U.S. have achieved designation by the NCI as either a “Cancer Center” or a “Comprehensive Cancer Center.” These designations are in part based on the type, volume, and quality of clinical cancer research conducted at these locations, and the designation comes with receipt of an associated grant (P-30) [82]. Smaller community sites/practices were also given the opportunity to apply for NCI Community Oncology Research Program (NCORP) designation and grants (UM1) [83]. Both grant types can include money to directly fund staff who navigate and enroll patients. Institutions not aligned with a cancer center

or NCORP grantee can participate in NCTN-sponsored trials as an affiliate member of an NCI-recognized cancer center or in some cases as an independent research site. They would also receive variable funding for these positions through per-patient enrollment reimbursements when patients are enrolled on NCTN-sponsored trials. This variable funding ranges from a few hundred dollars up to a few thousand dollars per enrolled patient. Per-enrolled-patient payments, however, can include funds for activities in addition to screening and enrollment, and may include funds for tissue banking or data collection as well. High enrollment sites known as Lead Academic Participating Sites (LAPS) and High-Performance NCI Community Oncology Research Programs (NCORPs) receive more funding than lower-volume sites [84]. It should be noted that NCI funding for research has historically been less than the actual cost to conduct such research [85].

Research sites use their ability to enroll patients onto a clinical trial as a service to attract patients as well as trial sponsors looking for investigational sites to work with. Whether a patient ultimately decides to pursue treatment options inside or outside of a clinical trial, larger research-enabled sites are typically able to provide more options within the institution. Smaller sites, or those with few or no clinical trials, can still help patients consider and find clinical trials, but these sites typically lack the staff and infrastructure to do so. For example, research-oriented sites may have more systematic pre-screening of patients for matching them to eligible trials, but in a site not equipped with such a system, screening for individual patients may be done in a more manual and ad hoc fashion. Referring the patient to another site that is conducting more trials may also result in lost revenue for the practice or institution if the patient does not return for care. As a result, physicians and institutions without significant research programs and infrastructure may be limited in their ability and desire to promote trials elsewhere.

Non-Monetary Incentives to Conduct Research

Conducting research can also provide a level of prestige and indirect validation of overall quality cancer care. Other

organizations (e.g. Joint Commission) directly accredit institutions based on their non-research medical practice, but even these often include measures of participation in clinical research as part of their quality metrics. The American College of Surgeon's Commission on Cancer (CoC) program accredits over 1200 cancer programs throughout the U.S., ranging from small community practices to large academic research networks. To achieve CoC accreditation, institutions must meet minimum clinical research enrollment thresholds, which are tiered based on the type and size of the institution [20]. The threshold ranges from a low of 2% for community or freestanding cancer programs to as high as 30% for pediatric cancer programs. Notably, recruitment onto disease registries or collection of tissue for biobanking count toward these thresholds, but may involve significantly less effort, for example obtaining consent to store and analyze a vial of blood.

Although industry does not formally certify a research site or honor them with specific, public, prestigious designations, pharmaceutical companies and Contract Research Organizations (CROs) keep and share extremely detailed metrics on research site's past enrollment performance, speed in startup, trial type and indication experience, data quality, and protocol adherence. Research sites that establish collaborative relationships with industry and CRO companies often gain access to shared datasets, which can help them plan and strategize their research trial portfolios and help provide metrics to guide operational improvements while working with their industry partners. There are a number of pharmaceutical and CRO companies that have very public and robust investigative site relationship programs [86, 87], and the aforementioned Society for Clinical Research Sites is dedicated to supporting sites in research planning and conduct, including identifying research patients from a broad spectrum of sources. Some of these programs are beginning to publicly recognize certain high performing and highly collaborative investigative sites with commensurate designations. Both NCI designations and these newer industry designations will allow consistently well performing research sites to be more recognized and more visible to others seeking the same opportunities.

Provider / Institutional Barriers

“The only way to recruit patients on a trial reliably is if the treating clinician believes in the trial and talks to the patient about the trial.”

—Monica M. Bertagnolli, MD, Chief of the Division of Surgical Oncology at Dana-Farber / Brigham and Women's Cancer Center

Role of Provider

Most clinical trial investigators are physicians but very few physicians are clinical trial investigators. One study reported that up to 50% of researchers who register with FDA as a principal investigator (PI) only conduct one study [88]. Over 40% of those that ceased to serve as a PI would like to continue, but felt they lacked opportunities. Of the surveyed investigators that voluntarily decided to no longer conduct clinical research, the top reasons cited were workload balance, time requirements, reporting requirements, and unsatisfactory financial outcomes. Research staff typically assume some of these duties, suggesting that increased staff support could alleviate some of the negative aspects reported by providers and enhance investigator retention. While providers who are not investigators themselves can refer patients to trials and counsel them to consider trials, non-PIs have been shown to enroll fewer patients than PIs [67]. Physicians may lack the appropriate incentives for participating in clinical research, whether with respect to the amount of time required for enrolling patients into a trial, conducting potentially more frequent services or visits, conducting additional data collection, or, importantly, being adequately compensated for their and their staff's time [89-92].

Surveys consistently show that patients with cancer who have enrolled on trials first heard of a trial from their physician [5, 93, 94], and provider recommendation is a leading factor in enrolling on a trial [6, 94, 95]. Physicians are consistently rated as the most trusted source of information by patients [94]. In one study, women advised by their provider to enroll on a breast cancer prevention trial were 13 times more likely to enroll than those who were advised not to enroll [96].

Studies have shown that the quality of the discussion around clinical trials as a treatment option is highly variable [97]; however, training can improve this conversation [98].

Physicians' clinical trial referral behavior has not only the ability to affect overall accrual, but it can also affect disparities in accrual. In studies of breast cancer patients, the rate at which women under the age of 65 were offered clinical trials was up to twice that of older women (68% vs 34%) [36, 99] and a similar two-fold referral difference was seen between black and white women [99].

Access to Trials

Improving cancer clinical trial enrollment requires not only personnel, but also available trials. Institutions can develop their own site-specific trials, or, more often, they can activate an existing multi-site trial locally. Trials range from those that apply to broad categories of patients to those that seek small, genetically defined, subsets of patients (see more detailed discussion in Trials section). If locally available trials are not well matched to the needs of the patient population that the site serves, then robust accrual is unlikely. Opening a research study at a site without determining in advance that a sufficient number of eligible patients are seen at the site is a poor strategy. While contract research organizations (CROs) can employ sophisticated analytics, manual effort, and connections to match trials to sites, sites themselves may not use a systemized process for trial selection, instead relying on individual physician interest. This can lead to poor local patient / trial match, inconsistent organizational commitment to a study and lower accrual rates [100]. Most large academic cancer centers have a variety of support committees to help manage and organize their trial portfolio, but the majority of

EXAMPLES OF SITE NETWORKS

INSTITUTION / NETWORK	TYPE	NUMBER OF MEMBER SITES IN THE USA	SUPPORT SERVICES
Academic and Community Cancer Research United (ACCRU)	Academic Research Organization (Mayo Clinic Affiliate)	>100	Trial placement support, contracting / budgeting, protocol development, patient enrollment
Translational Oncology Research International (TORI)	Academic Research Organization (UCLA Affiliate)	>90	Trial placement support, contracting / budgeting,
Sarah Cannon Research Institute (SCRI)	Site Management Organization (SMO)	>70	Full service support from trial placement, regulatory, contracting / budgeting, recruitment, staffing, etc.
US Oncology Research (USOR)	Site Management Organization (SMO)	>100	Full service support from trial placement, regulatory, contracting / budgeting, recruitment, staffing, etc.
Multiple Myeloma Research Foundation (MMRF)	Patient advocacy driven research network and foundation	22	Tissue bank, IT support, trial portfolio
Partners Healthcare	Healthcare system hospital group with research support infrastructure	>30	Full service support from trial placement, regulatory, contracting / budgeting, recruitment, staffing, etc.

TABLE 3: Institutions often rely on networks to support aspects of conducting clinical trials.

patients with cancer in the U.S. are treated in the community setting. Community practices often lack such clinical trial portfolio management support. Site-trial mismatches can also occur because of competition from similar trials looking at the same patient population, especially in trials looking for small subsets of patients, at specific small-window times during their disease. Many trials fail due to the inability to find the right patients, at the right time, in the right locations.

In both government and industry-sponsored research, there are a number of networks that develop and sponsor clinical trials. Membership or affiliations with such groups can play a significant role in a site's research study portfolio. NCI's

NCTN is comprised of four adult groups and one pediatric cancer group [25]. An institution may be a part of one or several of these groups, and each group has funding not only to conduct clinical trials, but also for shared infrastructure. This infrastructure allows an NCTN trial sponsored by one of the member groups to be available at any other NCTN member institution regardless of group affiliation. There is, therefore, a lower effort required by an institution to offer an NCTN trial than for a site to host its own unique clinical trial. The difference in site-specific burden and ability to enroll a sufficient number of patients for a trial at limited sites can make trial networks an appealing way to efficiently open trials at multiple locations.

Provider / Institutional Barriers

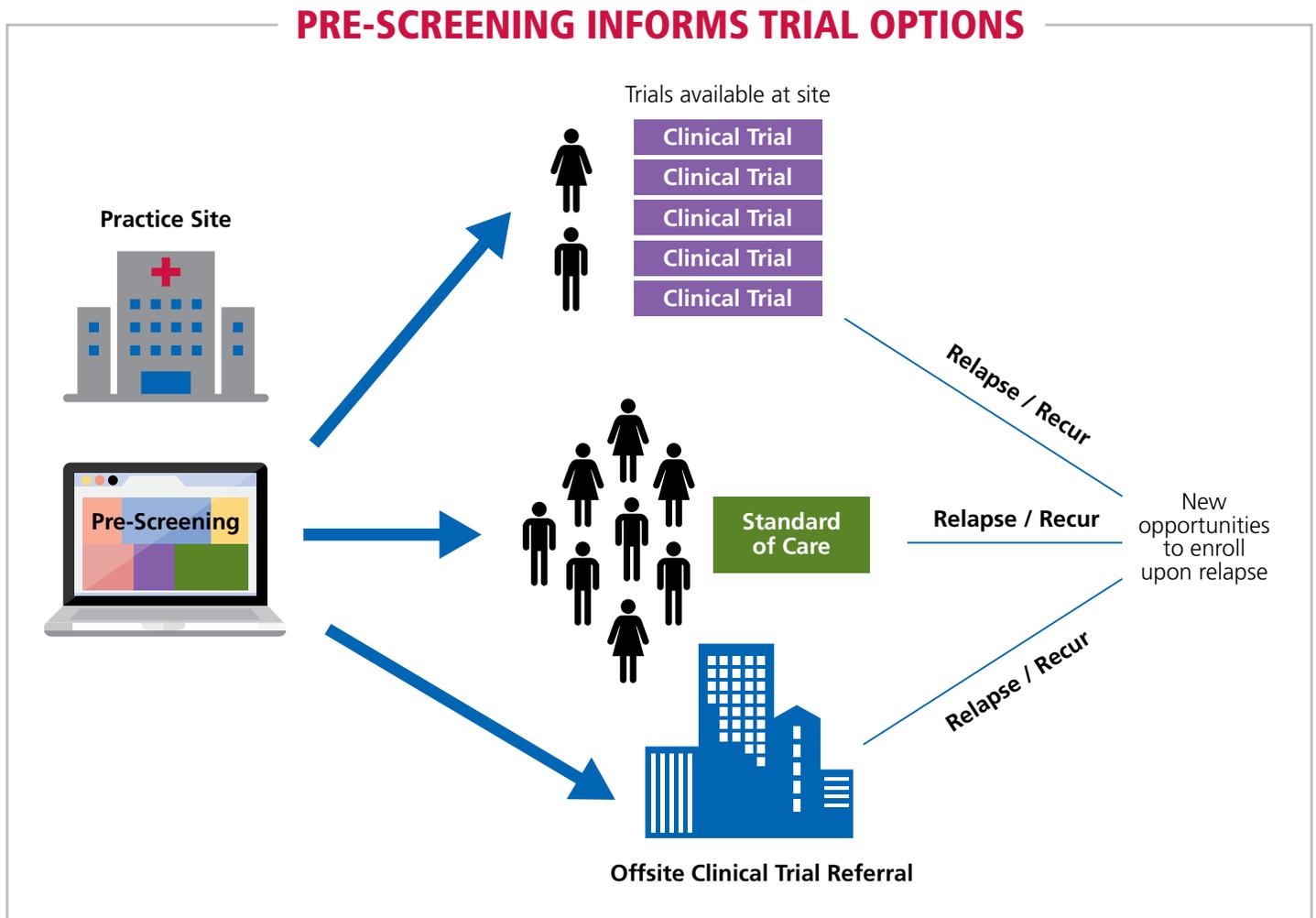


FIGURE 9: Practice sites with pre-screening can place patients on a clinical trial at the site, refer them to a trial located at another site, or provide standard care. Reevaluation of patient options can occur with cancer relapse or recurrence.

“The primary driver for why physicians do not refer is not being aware of what studies are available, either because at their own institution they don’t have easy access to that information, or it is not easy to quickly find out about trials and eligibility criteria at institutions they may refer to.”

—Jennie Crews, MD, MMM, FACP, Medical Director and Medical Director of Research Integration, Seattle Cancer Care Alliance Network

While the NCTN is a government-sponsored network, other private networks exist that serve similar functions (see Table 3). Large academic medical centers with large cancer centers sometimes collaborate in a group. Smaller groups of cancer centers might collaborate on portfolio management or investigators at several sites may collaborate on a specific cancer type, for example multiple myeloma [101]. Site Management Organizations (SMOs) are a commercial form of a clinical trial network. SMOs either own and operate a network of investigational research sites, provide a la carte or full-service support to a network of investigational research sites, or some combination of these services. SMOs also enable access to patients at community sites, where most cancer patients are cared for in the U.S. Regardless of the network type, these support systems are set up to provide the specialized staff, the expertise, and the infrastructure needed to conduct clinical research trials at a site.

Similar to the way that SMOs assume responsibilities of research sites for industry-sponsored trials, CROs contractually assume some of the industry trial sponsor's responsibilities by providing a range of a la carte to full-service support services to plan, operate, analyze, and report their clinical trials [102]. CROs and SMOs / site networks often work in collaboration to assess trial placement and predict trial outcomes for better planning and implementation. All SMO or CRO services include the option for some manner of support for, or consultation on, patient identification and recruitment.

Patient Identification and Enrollment

Providers or institutions with a strong clinical research focus often have some form of systematic pre-screening of all patients to determine eligibility for trials (see Figure 9). Systematic patient pre-screening has been shown to increase clinical trials enrollment, reduce the opportunity for bias [66, 103, 104] and minimize burdens to accruing research physicians. Pre-screening requires a systematic

STUDIES REPORTING PROVIDER ENQUIRY ABOUT TRIALS

STUDY	ELIGIBLE PATIENTS NOT OFFERED TRIAL
Go, 2006 [109]	30%
Guarino, 2005 [110]	19%
Klabunde, 1999 [111]	17%
St. Germain, 2014 [65]	32%
Albrecht, 2008 [68]	76%

TABLE 4: Studies show that many eligible patients are are not asked about clinical trial participation.

and consistent process for documenting (and reflecting upon) the identification of all patients who appear to be eligible to participate in a study. Such processes can be manual [104] or increasingly electronic [75, 76]. With more targeted drugs in development, prescreening may involve advanced molecular testing in order to identify rare subsets of cancers (molecular testing discussed further in Trial-Design chapter). Even with pre-screening, however, studies indicate that a significant portion of otherwise eligible patients will not be approached by their provider about trial opportunities (see Table 4).

Summary

Institutions and providers are responsible for most of the variables that affect patients' ability to enroll in clinical trials. No one factor has been found to be a determinant of high-performing sites [105], but rather a multi-faceted approach is needed that combines funding, personnel, processes, open trials, and the right culture [69].



Sheila

When Sheila was diagnosed with melanoma, she decided to investigate her clinical trial options by searching on clinicaltrials.gov. She soon found that she did not have the proper information about her cancer to identify trials that she would be eligible for. To find the answers she needed, Sheila approached her doctor, who worked with her to get the tests required to determine her eligibility for trials. After communicating her interest in clinical trials, Sheila's doctor referred her to the institution's clinical nurse navigator to help her identify an appropriate trial. Throughout the process, Sheila discovered that there was a lack of a systematic process for navigating the clinical trials arena at her institution and that she needed to be the driving force behind collecting the necessary information and identifying potential trials.

Patient Barriers

Overview

Treatment decisions for cancer patients are intensely personal and significant and are typically made after consultation with providers, families and trusted friends [106]. Clinical trial participation can be one of the options considered; however, only a minority of patients (between a quarter and a third) will typically have a trial for which they could enroll available at their treatment location (see Table 1, page 8). Availability varies greatly by cancer type and the institution where a patient is seen, with larger research-focused sites typically offering more trial opportunities than smaller non-research focused sites (see Provider / Institution chapter for further discussion). While availability of a trial is a minimum prerequisite for enrollment, a patient must also be aware of the opportunity, have interest, and be able to overcome any practical challenges to participation. An interest in seeking the best care possible is cited as a primary reason for taking part in clinical trials [5, 30, 93, 107] followed by an altruistic impulse to advance the science of cancer research so as to improve future treatments for others [5, 108]. When fully eligible and asked to enroll in a clinical trial, patients typically agree to enroll over half the time [30, 65-68]. The most common reasons they decline involve fear of side effects, loss of control, costs, and logistics involved with participating in trials. The patient barriers to enrollment are discussed further in the following sections.

Awareness

The majority of the public expects their healthcare providers to be aware of clinical trial opportunities, offer trusted advice, and be the primary source of information about research in general, and more specifically about clinical trials for which the patient might be eligible [5,6]. While the public professes a high level of understanding of clinical research, most cancer patients who have participated in clinical trials (66%) learned of their trial either through one of their personal providers, or one of the study staff [123]. Only 6% had learned about their trial through a patient advocacy group, and a similar share found their trial through registries like ClinicalTrials.gov. These results closely mirror previous surveys of trial participants [4], and show that while patients may proactively seek out trials, they are at a disadvantage

compared to clinical staff in terms of familiarity with trial-related resources and information.

Prescreening can facilitate more efficient enrollment; however, the process for follow-up with patients flagged as eligible is critical to maximally benefiting from such screening. If providers do not use this process or act on these results, eligible patients may still be left unaware of the opportunity to take part in a clinical trial. Studies have documented the prevalence of providers failing to discuss trial options with between 17 to 76% of their trial-eligible patients [68, 109-112] (see Table 4, page 27). This is especially true for patients from minority groups or who are 65 or older [99, 113-115] and comes from assumptions about treatment preferences (i.e., standard care) [99, 113] made before clinical trials are discussed. The timing of a patient's awareness about trial opportunities is critical, as certain trial opportunities relate to very specific windows within the course of treatment [116]. Prior therapy choices can make a patient ineligible for certain trials, so early awareness is critical for a patient to consider the full breadth of clinical trial opportunities.

In addition to making patients aware of specific trial opportunities, efforts have been made to create awareness of clinical trials in general as a treatment option. The goal of this more general awareness is to encourage patients to proactively ask their provider about trials as an option, or to normalize trials in order to increase the likelihood that patients asked to participate would be more willing to consent to take part. Past efforts to increase general public awareness of cancer clinical trials appear to have had little differential effect on clinical trial enrollment by themselves. A statewide public awareness campaign in Florida increased traffic to a state-specific cancer trial registry that was also created for the initiative, but this increased traffic was transient and quickly returned to baseline after each media push, and the effort ultimately did not affect enrollment rates in the state [117]. Another state-based public awareness campaign in California similarly failed to increase trial enrollment, but it did appear to increase the public's awareness of trials [118]. Community awareness efforts that are integrated into more multifaceted systems changes are more likely to succeed [69,

Patient Barriers

A CLOSER LOOK AT CLINICAL TRIAL MATCHING SERVICES FOR PATIENTS

Clinical trial matching services are designed to help pair engaged patients and their proxies (e.g., caregivers) with potential trials. While all such services collect patient data and compare it against the eligibility criteria of open trials, in a database to produce a list of potential trials, their goals vary and exist across a spectrum. At one end of the spectrum are services that seek to simply introduce patients to their trial options. These services produce a long list of trials that the patient may not be able to participate in. At the other end of the spectrum are more advanced services that are aimed at helping patients find and enroll in trials for which they are fully eligible and interested in, resulting in a narrower list of trials. Services vary across four key attributes depending on their goal:

1. The amount and type of patient data collected. Simple services may only ask for the type of cancer, age and zip code, while more advanced services may request dozens of data points including staging, treatment history, lab results, and information about the patient's other health conditions (see figure below).
2. The robustness of information contained in the clinical trials database. All matching services utilize clinical trials databases to run their searches. While most start with publicly available databases, more advanced services augment publicly available information, resulting in a more highly curated and accurate database.
3. The amount of resources dedicated to ensuring that good matches are identified. Simple services may only search using the few data fields in databases that are in standardized formats. Advanced matching services leverage a variety of human and technological resources to improve the search, narrowing the list of potential trials to those that are a good fit for patients. These resources can exist on the front end to help patients enter the correct information or the back end to help patients understand and prioritize search results.
4. The degree to which the service has invested in improving the user experience. Every service varies in how they engage patients and the degree to which they help patients take next steps to enrollment. Advanced services often invest heavily in patient education and follow up to ensure patients are able to enroll in trials. In contrast, simpler services tend to offer little beyond a list of potential trials.

PATIENT-FACING CLINICAL TRIAL MATCHING

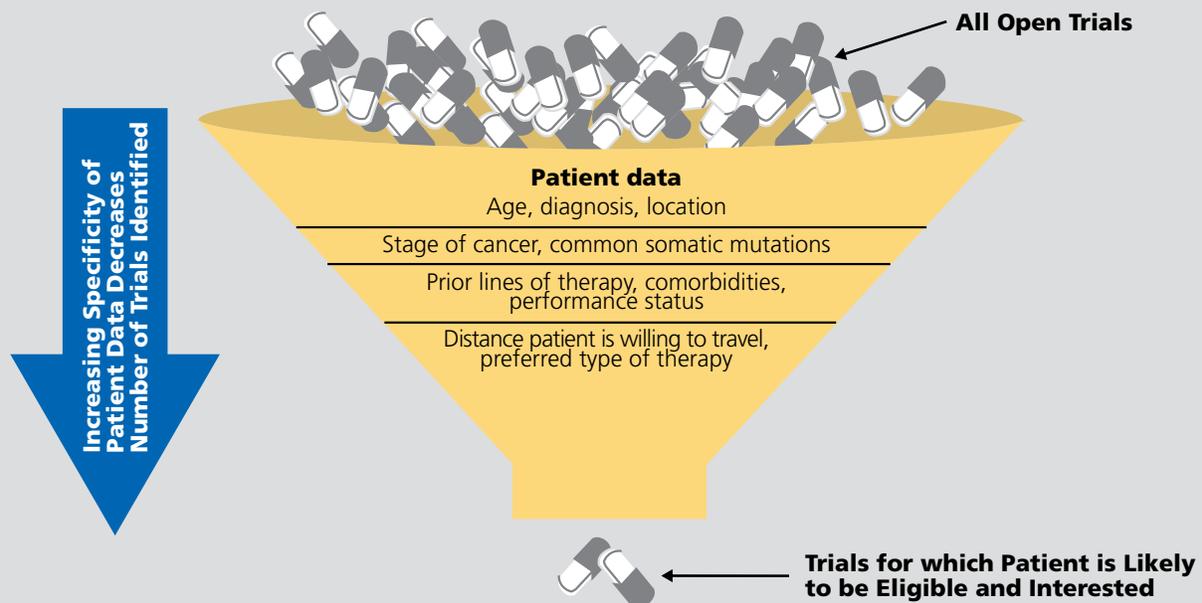


FIGURE 10: Consideration of additional patient data further refines the clinical trials considered for a patient and makes a match more accurate. Data may include clinical characteristics like genetic mutations, but may also include patient preference data such as location of the trial or type of therapy.

119]. More targeted awareness campaigns focused on newly diagnosed cancer patients and their families, rather than the general public, showed an increase in patients' comfort with a decision to enroll in a trial, but insignificant improvements in overall trial enrollment rates [120-122].

Patients' knowledge about their disease typically increases over time, and patients can become extremely knowledgeable about their own type of cancer. With this can come increased interest in clinical trial opportunities. Numerous patient-facing trial matching services exist to help motivated patients find trials that they may be eligible for and willing to participate in. Surveys have shown that around 6% of patients enrolled on clinical trials found their trials through such services [123]. These services vary in design and intent, with some services simply intended to introduce patients to the idea of clinical trials by providing example clinical trials open for their condition, while other services are designed to assist patients in identifying detailed trial matches and facilitate enrollment. Regardless of their goal, all services collect patient data and compare it against eligibility criteria of open clinical trials to produce a list of trials that the patient and his / her proxies can use as a starting point for conversations with their health care providers. Matching services may make their services available to patients via a web platform, a call center, or a combination of both. In one follow-up study of patients who had accessed a matching service, 11% reported eventually enrolling in a clinical trial. However, of those who reported enrolling in a trial, fewer than a quarter enrolled in one identified by the matching service [124]. A more detailed description of matching services can be found on page 30.

Patient Interest

Clinical trials are one of many opportunities available to eligible cancer patients who are considering treatment options, but before a patient chooses to participate in a clinical trial they must be interested in the research. This interest is a result of a combination of factors that include general understanding and beliefs about research, how the option of research participation is presented to the patient, as well as specific interest in one or more potential clinical

research opportunities. An interest in seeking the best care possible is cited as a primary reason for taking part in clinical trials [5].

Polling shows up to of 80% of the public is theoretically willing to participate in clinical trials, especially when trials are recommended by a person's healthcare provider [6]. Nevertheless, a number of cross-cutting issues affect actual willingness of a patient to participate in a clinical trial (see Table 5, page 32). The four reasons patients most often cite for why they decline to enroll in clinical trials include:

- **Fear of side effects** This category encompasses a number of specific concerns such as a feeling that research is too risky or fear of adverse outcomes, toxicity, or side effects.
- **Loss of control** Patients have expressed discomfort with the idea of a placebo, randomization, or have a desire to retain the ability to select their own treatment.
- **Logistical challenges** Patients perceive that trials will require additional time, are not conveniently located, or require too distant travel.
- **Costs** Concerns about keeping insurance coverage and additional costs prevent many patients from considering clinical trials.

Patient Education

Clinical trial awareness and education vary slightly in their goals, but programmatic efforts often overlap. While awareness campaigns are meant to introduce patients to trials as a treatment option, education initiatives are more targeted toward answering patients' questions and increasing their understanding of clinical trials in support of their decision making. Education may also help patients feel more inclined to participate in clinical research [122].

The delivery of clinical care is focused on restoring or improving health and/or quality of life for a patient. Clinical research has a primary goal of generating evidence to answer uncertainties

Patient Barriers

PATIENT-REPORTED REASONS FOR DECLINING TRIALS

STUDY	Rank of Response			
	1ST	2ND	3RD	4TH
Cancer Patients				
Meropol, (2007) [72]	Fear of side effects "I fear side effects that might come with treatment on a clinical trial"	Control "I am uncomfortable with being randomly assigned (for example, a coin toss) to a treatment"	Control "I fear receiving a placebo (for example a sugar pill) on a clinical trial."	Logistics "I would be unable to fulfill trial requirements due to logistical barriers such as transportation."
Unger, (2013) [30]	Control "Random treatment, and protocol would determine care"	"Did not want treatment"	Fear of side effects "Treatment side effects"	"No personal benefit"
Lara, (2001) [139]	Control "Desire for other treatment"	Logistics "Distance from clinic"	"Unknown"	Costs "Insurance denial"
Klabunde, (1999) [111]	"Concerns about experimentation"	"Unspecified"	Costs "Concern about cost" and "Insurance refusal"	Fear of side effects "Concerns about toxicity"
Zaleta, (2017) [206] (Minorities)	Control "Feeling uncomfortable with being randomly assigned to a treatment"	Control "Fearing receiving a placebo"	Fear of side effects "Fearing side effects that may come with treatment."	Costs "Believing that health insurance would not cover a clinical trial."
Javid, (2012) [34]	Control "Did not like that protocol dictated treatment"	Fear of side effects "Concerned that offered treatment had too many side effects"	Lack of personal benefit "Did not want treatment offered on clinical trial"	Logistics "Test and procedures and getting to/from required too much effort"
Public				
CISCRP, (2017) [5] (International)	Fear of side effects "Side effects scared me"	Logistics "Too many study visits"	"Medical procedures too invasive"	Control "Afraid of receiving placebo and too many medical procedures"
Memorial Sloan Kettering, (2016) [95]	Fear of side effects "Worried about side effects/safety"	Costs "Uncertain about insurance coverage, out-of-pocket costs"	Logistics The CT location is inconvenient"	Control "Worried about getting a placebo"
Research America, (2017) [6]	Fear of side effects "Too risky" & "Adverse outcomes"	"Lack of trust"	Costs "Little or no monetary compensation"	"Lack of access"

TABLE 5: Studies were performed either in cancer patients, or in the general public, as noted.

“Randomization is a huge issue. If you think about it from the standpoint of the patient who has just found out the cells in their body are out of control, you have lost the normalcy of your life. You want to grab a hold of something that is going to give you control. Then you talk about randomization—we have done focus groups and patients hate randomization and don’t really see the need for it.”

—Mary Lou Smith, JD, MBA, Research Advocacy Network Co-Founder

about new or existing treatments; involvement in a trial may result in clinical benefit for the trial participant, but this is not certain. The classic example is the development of a new drug, where a clinical trial attempts to answer the question of whether that new drug can safely and effectively treat a disease. To do this, that drug must be tested in humans and it is typically compared against an established treatment. While a clinical trial inherently involves some uncertainty, regulatory and ethical design considerations ensure that no treatment choice within the trial is likely to be worse than the other (e.g. the experimental drug versus the standard treatment). This concept is known as “ equipoise ” and is a key requirement for clinical trials. Understanding how equipoise limits the use of placebos, or informs randomization can help patients better understand clinical trials. Educating patients on these and other concepts to better inform their decisions, however, requires time and resources. Models for this education include using videos [120, 121] brochures [122], in-person navigators [125], advocacy organizations [126], nurses [127], or physicians. Such education can also be provided proactively to communities in addition to specific patients [119]. The clinical investigator is ultimately responsible for ensuring that a patient choosing to enroll in a trial is providing informed consent, although the physician often also enlists nurses and other research staff in patient education.

While education can help patients understand general research principles, regulatory requirements ensure that patients are informed about the potential risks and benefits

of the specific clinical trial that they are considering before agreeing to take part through informed consent. Informed consent often refers to legal, ethical, and regulatory requirements to ensure a patient is aware that they are enrolling in research that will involve potential risks and benefits. The patient must also be informed of alternate treatment options to the trial, research, or procedure and that they are able to discontinue participation at any time. [128]. While this goal is widely embraced in principle, in practice the informed consent document is often lengthy with complex language and concepts, and is often not understood by patients [15, 129-131]. Individual site informed consent processes vary, with research showing that more interactive processes involving videos, questions and answers, and more human interaction can result in greater understanding [132, 133]. Importantly, recently proposed changes to the federal regulations that govern research involving humans (the so-called Common Rule) will require simplification of informed consent documents [134].

External Patient Barriers

Patients who are aware and otherwise interested in clinical trials still often face external barriers to participating. Understanding the healthcare system can be challenging, and clinical trials can present additional complexities. Increasingly, healthcare systems provide designated patient navigators who serve as advocates for patients. These navigators provide expertise and a broad set of services that are designed to provide education, information and

Patient Barriers

resources to patients to empower them as they interact with the healthcare system [135]. While patient navigation was originally developed to help patients through clinical care, navigators have been identified as a possible resource to provide similar education, empowerment and resources related to clinical trial enrollment.

Studies on the impact of patient navigation on clinical trial enrollment have shown that navigation services can increase patients' awareness of clinical trials [117], comfort with their clinical trial decisions [125], and, in some cases, can increase adherence to trial procedures [136], but thus far have not shown increases in trial enrollment in broad populations. Several studies examining clinical trial navigation specifically targeted toward minority populations have demonstrated increased enrollment in these communities [137, 138].

Logistical Challenges

Logistical challenges are often an important barrier to patient participation in clinical trials. Patients cite factors like additional time needed to take part in trials, and trial sites that are inconveniently located or require too much travel [6, 34, 72, 93, 95, 139, 140]. This can be especially pronounced in more rural areas where switching to a different treatment site in order to access clinical trials may require significant travel. One study suggests that for men with prostate cancer, a distance of more than 30 miles is considered a burden and discourages clinical trial participation [141].

Efforts to reduce patient travel burdens have included the use of digital health tools. Digital health is the intersection of technology, health, and society for the enhancement of

healthcare delivery. It refers to a broad array of technologies, including mobile health, wearable devices, and telehealth [142]. Such tools can be leveraged to improve patient convenience and reduce the need for patients to travel to study sites, making it more likely that patients will enroll and remain in a clinical trial. While the idea of a completely virtual clinical trial (otherwise known as a “site-less” clinical trial where everything is conducted remotely) has not been widely adopted yet, there are still many ways that digital health has been leveraged to reduce cancer patient travel to clinic sites. Examples of tools that have been utilized in cancer clinical trials to reduce travel time include acquiring patient consent virtually [143, 144], remote monitoring devices and wearables that collect patient data and monitor changes in key indicators (e.g., weight, blood pressure) [145], and telehealth visits for routine checkups [146]. Recently, there has been increased interest among technology companies and drug sponsors to provide end-to-end virtual clinical trials, but no such cancer therapeutic trials have been reported to date.

Costs

Participating in clinical trials involves both direct medical costs and indirect costs like transportation and lodging. Costs of participating in a clinical trial are a major concern and negatively affect participation [6, 30, 61, 95, 111, 139]. Trial design—particularly the frequency and array of services and tests required—plays an important role in the costs patients may incur, with studies showing that overall direct medical costs within a clinical trial can range from being cheaper than care outside of a trial to up to 10% higher in trials than outside of trials [30, 147-150]. While direct medical patient costs within any given trial may or may not

“I’m not sure we have reached the balance in that the informed consent continue to be long and it may be that the best informed-consent comes from discussion rather than the patient reading the informed consent document.”

—Worta McCaskill-Stevens, MD, MS Chief, NCI Community Oncology and Prevention Trials Research Group

differ from the patient's cost if they were treated outside of a trial, the perception can nonetheless serve as a disincentive. Even nominally increased treatment costs have been demonstrated outside of the trial setting to cause patients to abandon their cancer treatments [151].

Most medical care costs in the United States are paid for through some form of health insurance, either public or private; however, insurers have often denied payment for experimental treatments. Historically, any patient care that occurred while that patient was taking part of a clinical trial was not covered by insurance, and this served as a deterrent for patients to enroll in clinical trials. The design of most cancer clinical trials, however, includes what is known as the "standard-of-care" treatment. This is the treatment that would routinely be administered outside of a clinical trial. In most NCI-sponsored cancer trials, a new drug or agent is simply used *in addition* to the usual course of care and compared to the standard to see how it works. In recognition of the role that standard of care plays both inside and outside of clinical trials, many states had instituted requirements for private insurance to cover any portion of cancer clinical trial treatment that represent standard of care. Since insurers would be responsible for routine care costs for the patient if they did not enroll in a trial, this did not represent an additional cost for the insurers. It also reduced a disincentive for patients, who may have otherwise feared being denied insurance coverage of care during participation in a clinical trial. While a national law has now superseded most of these state laws (discussed further below), awareness of these state policies was not uniform among socioeconomic and demographic subgroups. For example, three years after California implemented a state mandate that private insurers cover routine care costs in cancer clinical trials, awareness of the policy change was lower among minorities and lower-income individuals [152], raising the concern that despite broader coverage of trials, underrepresented groups may not take advantage of such coverage.

In 2000, triggered partly by the observation that Medicare patients were underrepresented in cancer clinical trials, the Clinton administration issued an executive order requiring

the Centers for Medicare and Medicaid Services (CMS) to provide Medicare coverage for routine care costs within therapeutic clinical trials [29]. This includes any medical complications that may occur during the trial, which can be a major concern for patients. This coverage is important, as two-thirds of cancer patients are age 65 or older, and are typically covered by Medicare. Subsequent to this policy change, enrollment of patients who had Medicare along with supplemental insurance increased in cancer trials, while those with Medicare alone did not [33]. This implies that copays and deductibles experienced by those without supplemental insurance still represent a significant barrier for trial participation.

By the early 2000s Medicare covered routine care costs in cancer clinical trials, but the coverage landscape for private insurance still varied greatly by state depending on each state's laws. Analyses comparing trial enrollment between states based on trial coverage mandates yielded different results, including a finding of no difference in enrollment [153], to significant differences in enrollment and an insurance denial rate of 13% [154]. In addition, many employers offering coverage to employees across state lines were subject to federal rather than state insurance product laws.

In 2010, as part of the Affordable Care Act (ACA), a national policy change occurred that required private insurance plans to cover routine care costs within clinical trials for cancer or other life-threatening diseases. The policy took effect in January of 2014; however, grandfathered plans (that were in existence at the time the law was signed in March 2010) were exempted from the requirement. A grandfathered plan jeopardizes its exemption if it reduces benefits or raises costs beyond those in effect in March 2010 [155]. The effect of the new policy on overall cancer clinical trial enrollment is unclear. In one analysis, insurance approvals for early phase cancer trials increased and delays of longer than two weeks by insurance carriers in their approval of expenses dropped after the policy's implementation [156]. Other studies have shown ongoing challenges with private insurance plans adhering to the requirements, with over half of 252 surveyed cancer sites continuing to experience insurance denial in 2014 [157].

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Importantly, states have been given extensions to allow non-ACA compliant plans to stay on the market, meaning not all plans are required to offer clinical trial coverage [158]. A more recent executive order signed in October 2017 has opened the insurance market to additional types of insurance plans that are not compliant with ACA requirements [159]. These rules have not been finalized, and, depending on plan offerings and enrollment, this may affect the number of cancer patients that have coverage for clinical trial participation.

Medicaid, the public insurance program for low-income children and adults that is jointly sponsored by the federal government and individual states, does not have a federal requirement to cover routine care costs associated with cancer clinical trials. Medicaid clinical trial coverage requirements vary by state, with few states having statutory requirements and far more operating under voluntary agreements to cover cancer clinical trials [160]. Inconsistent or unclear coverage of cancer clinical trials in the low-income population potentially

widens the disparity in who takes part in clinical trials. For uninsured patients, the patient or provider would have to find ways to seek financial support for routine care costs, perhaps through local or national charities.

Beyond medical expenses, patients also incur indirect expenses associated with travel, parking, or lodging when participating in a clinical trial. One study examining indirect costs incurred as part of clinical trial participation found an average of \$600 in indirect costs per month for participants [161]. Offering to reimburse patients for those costs significantly increased overall enrollment [162] and may also increase minority participation [163]. A survey of lung cancer patients showed that reimbursement for travel and lodging was a basic expectation as a condition of trial participation [164].

While providing financial reimbursement to research participants for expenses can improve recruitment, it is not without controversy because of the potential to unduly influence participation decisions [165]. The Belmont Report, which serves as the basis for research ethics, states that agreement to participate in research is only valid if it is given voluntarily, which is defined as free of coercion or undue influence. Undue influence can be through an “excessive, unwarranted, inappropriate or improper” reward, but the report does not quantify what is considered excessive [8]. It further notes that normally acceptable incentives could be seen as undue influences if the participant is vulnerable. The Common Rule, which is the regulation governing most federally funded or regulated research, codifies the Belmont report, but does not add much clarity on compensation. It directs researchers and institutional review boards to ensure that undue influence is not exerted to obtain participation of research participants, calling special attention to avoiding undue influence in economically disadvantaged populations [134]. Studies have shown, however, that while money is more of an incentive for those with lower incomes, the ratio of increased participation to increased incentive is the same regardless of income [166].

Outright payment of patients for trial participation is possible, and has been proposed as a way to boost trial enrollment, but this model is typically never applied in cancer, although it is more common among healthy trial participants. Importantly, because of Medicare policy, which prohibits the offer or payment of remuneration to induce a person to buy an item or service that will be reimbursed by a federal health care program, sponsors cannot pay a Medicare patient to be on a clinical trial and still charge that patient’s routine care costs to Medicare [167].

Taken together, the regulations allow financial payments for research participation, but encourage caution about how much influence that payment should play. A survey of IRB members found that nearly all thought it was appropriate to “reimburse” for expenses, but just over half felt it was appropriate to pay simply as an “incentive” for participation [168]. FDA has also clarified that it does not consider reimbursement for patient costs like parking and lodging as problematic [169, 170]. Nonetheless, ambiguity and concern of running afoul of research participant protections seems to still be present, as reimbursement of patient ancillary costs is still rare in cancer clinical trials.

With sponsor reimbursement of ancillary costs still relatively rare, many patient support organizations offer services that can help offset some of these costs. Examples include the American Cancer Society’s Road to Recovery program that offers free rides to appointments [126], and their network of Hope Lodges that provide free lodging for cancer patients and their families during treatment [171]. The Lazarex Cancer Foundation provides direct reimbursement of ancillary costs to qualifying patients enrolled in clinical trials [172], and patients seen at the NIH clinical center in Bethesda MD can obtain support from the Friends of the Clinical Center [173]. Some state Medicaid programs also include non-emergency medical transport (NEMT) benefits, recognizing that for poorer patients, providing transportation to and from appointments is critical to patients receiving care. Patient navigation services can help connect interested patients with services like those listed above in order to support patients interested in clinical trials [137].



Mary Clare

Mary Clare had just started a new job and found that she was not feeling well, leading her to go to her doctor for a check up. Her doctor ordered a blood test, which revealed that Mary Clare had acute myeloid leukemia (AML). Upon her diagnosis, she received the standard treatment at a teaching hospital. From the beginning, her oncologist provided ongoing education about clinical trials so that when she was approached about joining a trial after completing her treatment, Mary Clare already possessed a good understanding of clinical trials. Knowing that the likelihood of recurrence for her cancer was high and that she could help contribute to society with her participation, Mary Clare decided to enroll in the trial, which was testing a vaccine against recurrence.

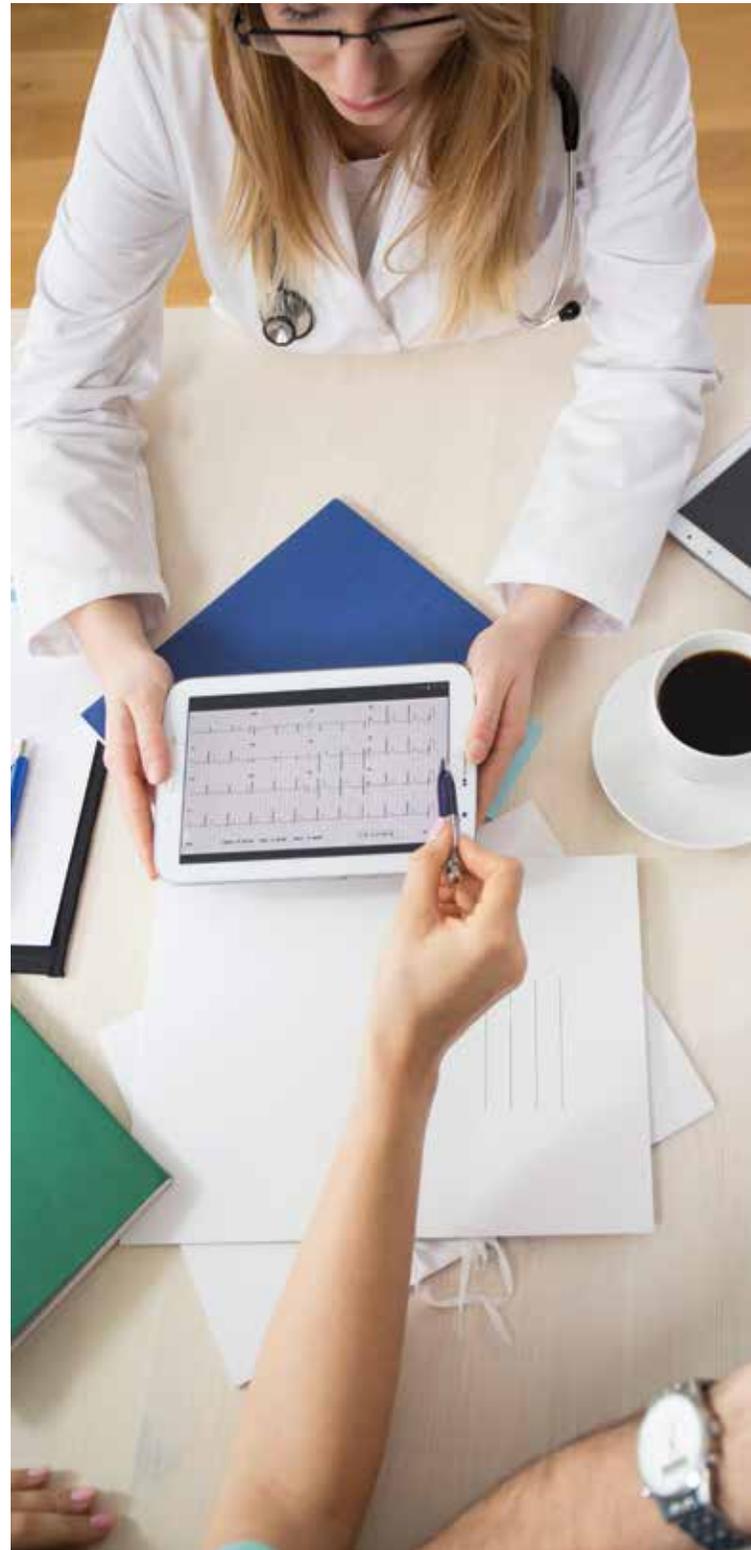
Trial-Design Barriers

Overview

When someone is diagnosed with cancer, the portfolio of open clinical trials locally and nationally determines whether or not a trial is available for them to enroll in. While a patient could enroll in a matching trial if it is open somewhere in the country other than the region in which they live, such travel can pose a significant, and sometimes insurmountable, barrier. Studies have found that for between 41% and 60% of patients seeking treatment, no clinical trial exists at their treatment location for their cancer (see Table 1, page 8). Even for those patients with trials locally available for their type of cancer, many will not be able to enroll due to more detailed eligibility criteria. In total, only around a quarter to a third of cancer patients have the ability to enroll in a therapeutic cancer clinical trial. At the same, up to one in five cancer clinical trials fails to enroll sufficient patients to meet the study objectives, painting a landscape where many patients have no trial options, while simultaneously many trials fail because of a lack of patients. This chapter examines how the design of trials can affect both patient trial enrollment opportunities and trial success.

Trial Design—Supply and Demand of Trial Openings to Eligible Patients

Clinical trials are designed to collect data in a clinical setting in order to answer a specific research question. The questions can range from assessing whether a novel therapy that may have had little or no prior use in humans will be safe and effective, to determining if there are differences in outcomes between well-established therapies. For each research question, the specifics of the question will dictate the overall design of the trial, as well as the number of patients needed to demonstrate the safety and efficacy of the therapy under investigation. Historically, cancer therapeutics have been developed for organ-specific cancers (e.g. breast, lung, or kidney cancers). Further, therapies are also typically targeted to a certain stage of cancer and increasingly focused on a certain molecular biomarker that may be present in one or more cancers (e.g. HER2). Specific clinical trials, therefore, typically limit participation to individuals with specific cancer types, stages and biomarkers; however, exceptions do occur, with some clinical trials offering broad eligibility



Trial-Design Barriers

across cancer types. Trials are also typically designed to enroll a minimum number of patients in order to collect enough data to reliably answer the scientific question around which they are designed.

In order to be successful, therefore, clinical trials must enroll a minimum number of patients with very specific attributes. Once a trial is designed and opened, accrual occurs by screening patients at one or more sites and enrolling those that meet the eligibility criteria and consent to be part of the trial. This, however, depends on eligible patients being available at the trial sites. If the trial is designed to accrue

patients that either do not exist at the sites where the trial is open, are extremely rare, or if there are other trials competing for the same patients, a trial is more likely to fail to accrue sufficient patients.

When a trial fails to accrue, not only is the opportunity to advance patient treatment through the knowledge generated by a trial lost, but the efforts of the patients who volunteered to be part of the failed clinical trial are also lost. These failed trials also consume limited financial resources and staff time that could have been used on successful trials. Studies indicate that between 18% and 40% of centrally sponsored



“It is rational to try to enroll a population that is more representative of the actual population that will benefit from the treatment and so we try to think carefully about the inclusion/exclusion criteria. That also has the added benefit for us of reducing cost because we are reducing the number of patients we have to screen.”

— Joanne Lager, MD, Head, Oncology Development, Sanofi

NCI trials fail to meet sufficient accrual goals to answer the study question [174-176], with somewhere between several hundred to a thousand patients per year enrolled in these trials. A broader study looking at cancer trials across all sponsors similarly found a rate of failure due to low accrual of 20%, with more than 6,800 patients per year enrolled in these failing trials [177].

An inadequate number of patients meeting a trial’s design requirements is only one reason that a trial might fail to accrue. Other barriers may prevent potential participants from enrolling, including high levels of competition among trials for a limited pool of patients. An analysis of NCI trial accrual failures found that poor accruing trials had twice the number of competing trials per diagnosed patient and also required enrollment of a greater fraction of the overall diagnosed population than non-failed trials [176]. In other words, these trials were by design much more difficult to accrue patients to. Such an analysis can be conducted on a more local level as well. A group at the Kimmel Cancer Center developed a model that could successfully predict which trials would fail at their location due to a lack of eligible patients [178]. The model evaluated the number of medically eligible patients based on the trial requirements, allowing a user to vary assumed willingness of the eligible population to participate (e.g. 50% of eligible patients would be willing to enroll) to determine if the necessary annual recruitment needs could be met. While this model was able to predict failure of a trial with 95% accuracy, it had no power to predict success. Such analyses may be especially important in drug development areas with high

research activity, such as in the field of immuno oncology (IO). A 2017 global assessment of IO trials found that 940 IO agents were in clinical development with 3,042 clinical trials testing these agents that would require over half a million patients to satisfy the clinical trial openings [179]. The authors of the study concluded that it is unrealistic to expect most of the investigator-initiated trials in this evaluation to ever achieve the designated enrollment targets.

Trials sponsored through the NCI Experimental Therapeutics Clinical Trials Network (ETCTN) must undergo a feasibility analysis for phase I or II clinical trials that asks investigators to project enrollment based on comparison to “...similar completed and ongoing trials in the same or similar patient population.” The analysis requests that already open NCI trials that might compete with such trials be factored into such analyses [180, 181]. Importantly, NCI does not require investigator-initiated trials it funds to conduct such feasibility requirements, although individual institutions where the trial is initiated may.

NCI is one of the largest single sponsors of cancer clinical trials, and annual enrollment into NCTN trials ranged from a low of just over 8,000 patients in 1996, increasing over three-fold to a peak of 29,000 before settling at its current limit of 17,000 openings (12,000 adults) [3, 182]. While this represents 1% of the number of individuals annually diagnosed with cancer, these enrollment figures do not include NCI-sponsored, investigator-initiated trials or industry trials. A broader analysis of cancer clinical trial openings in the U.S. across all

Trial-Design Barriers

sponsors using data from ClinicalTrials.gov has estimated that in 2017 there were just over 134,000 openings in cancer treatment clinical trials in the U.S. that patients with cancer could enroll in, representing just under 8% of the annual diagnoses of cancer. When compared with the calculated enrollment rate of 8% found in Table 1, this suggests that on a macro scale, enrollment opportunities are closely matched with current enrollment rates [183].

There are very few analyses of how available cancer clinical trial openings nationwide for specific cancers compare with the number of available patients. The Pancreatic Cancer Action Network (PanCAN) conducted one such study looking at how available pancreatic clinical trial openings in the U.S. compared with the incidence of four specific subtypes of pancreatic cancer in 2011 [116]. The model assumed that only 20% of patients would ultimately be eligible for clinical trials, and that if the full 20% enrolled, three of the four subtypes of pancreatic cancer would take multiple years to meet overall accrual goals, ranging from 1.3 to 4.2 years. The fourth subtype of cancer had a significant excess of patients available relative to trial openings, and even with

the 20% assumption those trials could enroll in less than a year. Importantly, actual enrollment was calculated to be just under 4.6% of pancreatic cancer patients.

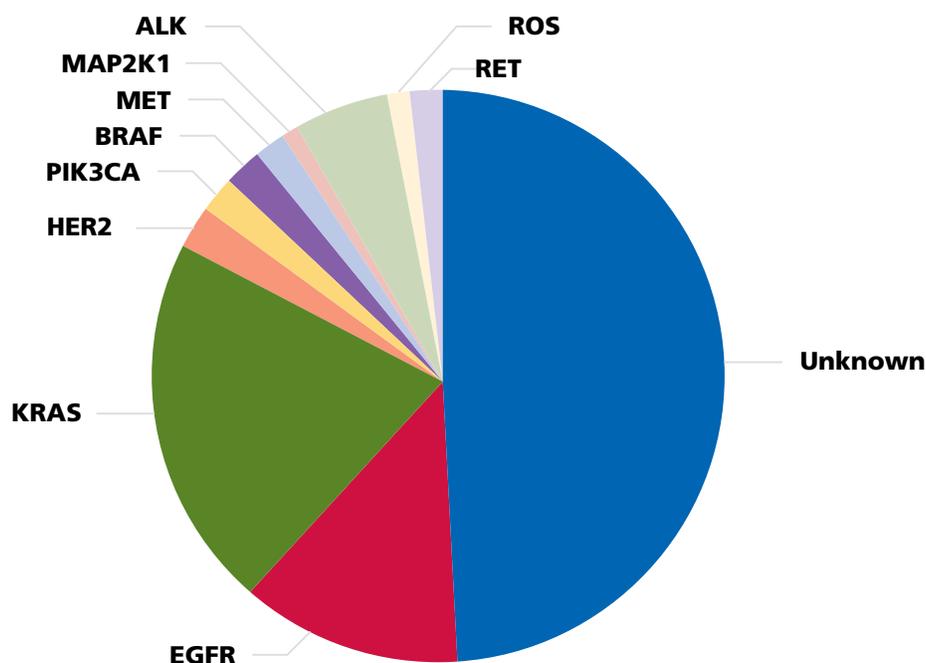
Inclusion/Exclusion Criteria

In addition to major characteristics like cancer type, stage, and biomarker status, clinical trials also have additional requirements on potential participants that further limit the patients who can take part. These exclusions can serve important reasons related to the desire to maintain patient safety and to establish a study cohort with a similar patient profile, in order to more accurately assess the response of patients to the investigational treatment [22]. Common exclusion criteria include overall performance status, prior therapies, age, presence of comorbidities, history of prior malignancies, HIV status, organ function, and brain metastases. It is also common to include criteria for organ function (i.e., serum creatinine, liver enzymes, cardiac ejection fraction or ECG) independent of relevance to the compound being studied or the patient population under evaluation. These criteria are often copied and pasted from prior protocols to new ones without evaluation regarding their

Recognizing the opportunity to lessen a barrier to trial participation, ASCO, FDA and Friends of Cancer Research have proposed changing what are often considered “default” inclusion/exclusion criteria [185], building off of previous IOM recommendations [85]. Specifically, they made the following recommendations.

- **Brain Metastases:** The systematic exclusion of treated and/or stable brain metastases should be eliminated [186]. An evaluation of commercial cancer INDs in 2015 showed that 77.4% of protocols had excluded known or active brain metastases, while 47.1% allowed treated or stable metastases [187].
- **Minimum Age:** Where a disease spans pediatric and adult populations, the minimum age of enrollment should go down to age 12. Where there is scientific rationale for likelihood of benefit from targeting the same molecular pathway in pediatric as adult patients, pediatric-specific cohorts should be included [188].
- **Organ dysfunction:** Liberal creatinine clearance should be used to measure renal function. If renal excretion is not significant. Cardiac ejection fraction tests should not be used for exclusionary criteria where there is no known cardiac risk, and cardiac function should be determined by investigator use of clinical classification system [189].
- **HIV/AIDS:** Default exclusion of HIV+ patients should no longer occur, but rather HIV+ patients who are relatively healthy and at low risk for AIDS-related outcomes should be able to participate on cancer trials. [190]. In 2015 84.2% of commercial cancer INDs had excluded known or active HIV / AIDs.
- **Prior and concurrent malignancies:** Prior malignancies should exclude patients if treatment was completed two years prior and no evidence of disease. Patients with a concurrent malignancy should also be included if they are clinically stable, and the concurrent cancer is not in need of tumor-directed therapy [189].

GENETIC SUBSETS OF LUNG CANCER (ADENOCARCINOMA)



Reproduced from: Pikor, (2013). Genetic alterations defining NSCLC subtypes and their therapeutic implications. *Lung Cancer (Amsterdam, Netherlands)*, 82(2), 179–189. © 2013 The Authors

FIGURE 11: Relatively common cancers, like lung cancer, may be made up of many rare genetic subsets as indicated here. Clinical trials targeted toward a single subset require molecular screening of a large number of patients to identify the few patients with a given genetic alteration.

scientific relevance to the therapy under investigation [184]. While they can provide a more uniform pool of participants, these requirements can also create a trial population that isn't representative of the population with the given disease, often resulting in a trial population that is younger and healthier than most patients with the disease being studied. In addition to calling into question the generalizability of trial results, these restrictions also exclude otherwise willing participants from taking part in clinical trials making accrual more difficult. It is estimated that on average just over 17% of cancer patients are excluded on the basis of these criteria (see Table 1, page 8).

Trial Design - Targeted Therapies

At one time, cancer was thought to be one disease, but over time scientific advances have led the better characterization of

different types of cancer. Cancers were first subdivided into the organs where they occurred (e.g. lung, brain, colon), and then as diagnostic techniques improved even these site-specific diagnoses were further refined by tissue characterization (e.g. small-cell versus non small-cell lung cancer). Even more recently, the advent of genetic testing techniques has allowed further differentiation of cancers based on specific genetic alterations. The result of this detailed characterization has been the development of targeted therapies that have shown increased activity in genetic subsets, and can save patients from receiving treatment that they are unlikely to benefit from, but this sub categorization introduces significant challenges to conducting clinical trials. Specifically, many of these cancer subsets may only represent less than 10% of patients affected by the cancer and makes finding and enrolling these relatively rare patients more difficult.

Trial-Design Barriers

The ALK mutation in lung cancer, for example, occurs in approximately 5% of diagnosed patients, meaning that a screening protocol of prospective lung cancer patients for a trial of an ALK-targeted drug would involve 19 patients found to be ineligible for every patient identified with an ALK mutation. Drugs targeting other lung cancer mutations would have similar failure rates, and if diagnostic tests were for single mutations, a patient could conceivably have to undergo multiple screenings in an attempt to find a matching trial. In addition to the delay and inconvenience involved for patients to undergo such sequential tests, often there is not enough tissue available to conduct multiple separate tests.

Testing tissue for a wide array of genetic mutations or molecular markers at once is an approach that can address some of the limitation of multiple single-gene tests; however, if different trials require their own diagnostic test, the use of a common diagnostic panel can be difficult. So-called “Master protocols” have been developed to address this challenge [144] and include Lung-MAP [191] in lung cancer and NCI’s Molecular Analysis for Therapy Choice (MATCH) trial [192]. Such trials allow greater coordination of what would otherwise be separate clinical trials.

While genetic testing of tumors can provide a patient with critical information for finding clinical trials for which he / she is eligible, such screening is not always performed during routine clinical care. Historically, such tests have not always been paid for by insurers, leaving patients to either pay for such tests themselves or find a clinical trial that would provide the testing as part of trial prescreening. In November 2017, the Centers for Medicare and Medicaid Services (CMS) proposed to provide Medicare coverage of next-generation sequencing of broad panels of genes in tumor samples. This coverage applies to specific situations, but included in this proposed coverage are tests administered as part of NCI-sponsored clinical trials [193].

Patient-Focused Trial Design

The design and development of clinical trials has traditionally been dominated by scientists and clinicians; however, patients and patient advocates are increasingly taking greater roles in this process. This involvement has been shown to lead to new patient-reported outcomes measures [194-196], trial designs more attractive to patients (e.g. reducing frequency or types of testing and number of procedures), more ethically sound (e.g., allowing crossover if a patient progresses), and more likely to succeed [64, 197-201]. Recent modeling has even predicted that patient engagement can reduce trial costs by tens of millions of dollars due to the avoidance of post-initiation protocol amendments that might otherwise occur to address accrual challenges [202]. Patient advocates also might help modify frequency or types of testing, reduce time off-therapy prior to enrollment, decrease number of visits, or make risky procedures optional.

Some of the earliest examples of engaging patients and their advocates include community based participatory research (CBPR), which is an approach to health services research that partners with communities in selecting research topics and designing research. More recently, patient engagement in research has grown rapidly through concerted policy and programmatic efforts. The Patient Centered Outcomes Research Institute (PCORI) was created in 2010 as part of the Affordable Care Act, with a mission to “...promot[e] high-integrity, evidence-based information that comes from research guided by patients, caregivers, and the broader healthcare community,” and has funded over \$1.6 billion in research that both requires patient engagement and advances the methodology for doing so [203, 204]. In 2012 the fifth renewal of the Prescription Drug User Fee Act (PDUFAV) was passed, which funds FDA operations, but importantly it also formally introduced greater patient engagement at the agency through the creation of a patient-focused drug development program [47]. The 21st Century Cures Act, passed in 2017, continued to promote patient engagement, requiring the agency to produce a series of detailed guidance documents on how to engage patients in the drug development process [205] and providing clarity on how FDA will view such activities in the context of drug development.



Glen

In 2011, Glen was diagnosed with stage III prostate cancer. Upon receiving his diagnosis, Glen researched his treatment options. Of the five oncologists that Glen spoke with while exploring his options, he was most impressed by the fifth at the University of Chicago, who suggested a clinical trial comparing hormone therapy that could be taken orally instead of through an injection. Glen liked that the doctor was open and easy to talk to - he explained the clinical trial in depth, how it was designed, and potential benefits of being on the trial.

While Glen liked the oncologist at the University of Chicago, he was still unsure about what treatment would be best for him. There were many treatment options open to him that were already approved by the FDA and proven to work. To help him decide which treatment option to pursue and whether to enroll in the clinical trial, Glen spoke with two prostate cancer survivors who had undergone conventional therapies and experienced negative side effects. He also carefully weighed the clinical trial design, ensuring that he would know which treatment he received. In the end, the doctor's openness, the potential for improved quality of life with oral hormone therapy, and the transparency with which the trial was designed and communicated to him, convinced Glen to enroll in the clinical trial.

Today, Glen is in remission for his prostate cancer. During the latter half of the trial when his treatment was completed, Glen saw his doctor every six months for ongoing monitoring until 2017. Glen believes that participating in the clinical trial has given him access to many benefits, including a better treatment option with fewer side effects and ongoing care and monitoring beyond the initial treatment stage from an attentive team of health care providers.

Despite the many benefits of a clinical trial, Glen believes that transparent trial design is key to earning patients' trust and encouraging enrollment. In 2015, after he was in remission for his prostate cancer, Glen was diagnosed with stage III Merkel cell carcinoma. Glen participated in a focus group seeking patient input about an upcoming clinical trial. Despite having few treatment options for his cancer, Glen expressed that he would not participate in the trial because it was a double-blind study, meaning he would not know whether he received standard of care or the experimental therapy.

Bibliography

1. Pharmaceutical Research and Manufacturers of America. *Biopharmaceutical Industry-Sponsored Clinical Trials: Impact on State Economies*. 2015. <http://phrma-docs.phrma.org/sites/default/files/pdf/biopharmaceutical-industry-sponsored-clinical-trials-impact-on-state-economies.pdf>. Accessed March 13, 2018.
2. Krall RL. State of the Controlled Clinical Trial Enterprise in the United States. *Clin Pharmacol Ther*. 2011;89(2):225-228. doi:10.1038/clpt.2010.292
3. Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: Race-, sex-, and age-based disparities. *J Am Med Assoc*. 2004;291(22):2720-2726. doi:10.1001/jama.291.22.2720
4. Comis RL, Miller JD, Aldigé CR, Krebs L, Stoval E. Public attitudes toward participation in cancer clinical trials. *J Clin Oncol*. 2003;21(5):830-835. doi:10.1200/JCO.2003.02.105
5. Center for Information and Study on Clinical Research Participation. *Report on General Perceptions and Knowledge on Clinical Research*; 2017. <https://www.cisrcp.org/download/2017-perceptions-insights-study-general-perceptions-and-knowledge-on-clinical-research/?wpdmml=8773>. Accessed March 13, 2018.
6. Research!America. *Public Perception of Clinical Trials*; 2017. https://www.researchamerica.org/sites/default/files/July2017ClinicalResearchSurveyPressReleaseDeck_0.pdf. Accessed March 13, 2018.
7. Baker SM, Brawley OW, Marks LS. Effects of untreated syphilis in the Negro Male, 1932 to 1972: A closure comes to the Tuskegee study, 2004. *Urology*. 2005;67(6):1259-1262. doi:10.1016/j.urology.2005.08.025
8. Department of Health, Education, and Welfare. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research-the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research*; 1978. <https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html>. Accessed October 4, 2017.
9. Division of Cancer Treatment and Diagnosis NCI. NCI-Sponsored Trials in Precision Medicine. https://dctd.cancer.gov/majorinitiatives/NCI-sponsored_trials_in_precision_medicine.htm. Accessed March 13.
10. Cella D, Yount S, Rothrock N, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS): progress of an NIH Roadmap cooperative group during its first two years. *Med Care*. 2007;45(5 Supplement 1):S3-S11. doi:10.1097/01.mlr.0000258615.42478.55.The
11. Lipscomb J, Gotay CC, Snyder CF. Patient-reported Outcomes in Cancer: A Review of Recent Research and Policy Initiatives. *CA Cancer J Clin*. 2007;57(5):278-300. doi:10.3322/CA.57.5.278
12. Perlmutter J, Roach N, Smith M Lou. Involving advocates in cancer research. *Semin Oncol*. 2015;42(5):681-685. doi:10.1053/j.seminoncol.2015.07.008
13. Katz ML, Archer LE, Peppercorn JM, et al. Patient advocates' role in clinical trials: Perspectives from Cancer and Leukemia Group B investigators and advocates. *Cancer*. 2012;118(19):4801-4805. doi:10.1002/cncr.27485
14. Baer AR, Good M, Schapira L. A New Look at Informed Consent for Cancer Clinical Trials. *J Oncol Pract*. 2011;7(4):267-270. doi:10.1200/JOP.2011.000347
15. Schumacher A, Sikov WM, Quesenberry MI, et al. Informed consent in oncology clinical trials: A Brown University Oncology Research Group prospective cross-sectional pilot study. *PLoS One*. 2017;12(2):1-14. doi:10.1371/journal.pone.0172957
16. Ledford H. Budget woes hinder clinical-trials network. *Nature*. 2014;507(6):2014.
17. National Cancer Institute. The NCTN Budget. <http://www.cancer.gov/research/areas/clinical-trials/nctn/budget#1>. Accessed March 13, 2018.
18. Howlader N, Noone AM, Krapcho M, et al. *SEER Cancer Statistics Review, 1975-2012*; 2016. https://seer.cancer.gov/archive/csr/1975_2012/#contents. Accessed March 13, 2018.
19. Gerber DE, Lakoduk AM, Priddy LL, Yan J, Xie X-J. Temporal Trends and Predictors for Cancer Clinical Trial Availability for Medically Underserved Populations. *Oncologist*. 2015;20(6):674-682. doi:10.1634/theoncologist.2015-0083
20. Commission on Cancer. *Cancer Program Standards: Ensuring Patient-Centered Care*; 2016. <https://www.facs.org/quality-programs/cancer/coc/standards>. Accessed March 13, 2018.
21. Zon R, Meropol NJ, Catalano RB, Schilsky RL. American Society of Clinical Oncology Statement on Minimum Standards and Exemplary Attributes of Clinical Trial Sites. *J Clin Oncol*. 2008;26(15):2562-2567. doi:10.1200/JCO.2007.15.6398
22. Green S, Smith A, Benedetti K, Crowley J. *Clinical Trials in Oncology*. 3rd ed. Boca Raton, FL: CRC Press; 2012.
23. Tejeda HA, Green SB, Trimble EL, et al. Representation of African-Americans, Hispanics, and whites in National Cancer Institute cancer treatment trials. *J Natl Cancer Inst*. 1996;88(12):812-816. <http://www.ncbi.nlm.nih.gov/pubmed/8637047>. Accessed October 4, 2017.
24. Hirsch BR, Califf RM, Cheng SK, et al. Characteristics of Oncology Clinical Trials. *JAMA Intern Med*. 2013;173(11):972. doi:10.1001/jamainternmed.2013.627
25. Mooney M. Implementation of NCTN External Evaluational Working Group & CTAC Recommendations. 2017. <https://deainfo.nci.nih.gov/advisory/ctac/0717/8-Mooney.pdf>.
26. Hay M, Thomas DW, Craighead JL, Economides C, Rosenthal J. Clinical development success rates for investigational drugs. *Nat Biotechnol*. 2014;32:40-51. doi:10.1038/nbt.2786

27. Hutchins LF, Unger JM, Crowley JJ, Coltman CA, Albain KS. Underrepresentation of Patients 65 Years of Age or Older in Cancer-Treatment Trials. *N Engl J Med*. 1999;341(27):2061-2067. doi:10.1056/NEJM199912303412706
28. Institute of Medicine. *Extending Medicare Reimbursement in Clinical Trials*.; Washington DC: National Academies Press; 2000.
29. CMS. *Medicare Coverage - Clinical Trials*.; 2000. <https://www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/Downloads/R126CIM.pdf>. Accessed March 13, 2018.
30. Unger JM, Hershman DL, Albain KS, et al. Patient Income Level and Cancer Clinical Trial Participation. *J Clin Oncol*. 2013;31(5):536-542. doi:10.1200/JCO.2012.45.4553
31. Lewis JH, Kilgore ML, Goldman DP, et al. Participation of Patients 65 Years of Age or Older in Cancer Clinical Trials. *J Clin Oncol*. 2003;21(7):1383-1389. doi:10.1200/JCO.2003.08.010
32. Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. *J Clin Oncol*. 2004;22(22):4626-4631. doi:10.1200/JCO.2004.02.175
33. Unger JM, Coltman CA, Crowley JJ, et al. Impact of the Year 2000 Medicare Policy Change on Older Patient Enrollment to Cancer Clinical Trials. *J Clin Oncol*. 2006;24(1):141-144. doi:10.1200/JCO.2005.02.8928
34. Javid SH, Unger JM, Gralow JR, et al. A Prospective Analysis of the Influence of Older Age on Physician and Patient Decision-Making When Considering Enrollment in Breast Cancer Clinical Trials (SWOG S0316). *Oncologist*. 2012;17(9):1180-1190. doi:10.1634/theoncologist.2011-0220
35. Brooks SE, Carter RL, Plaxe SC, et al. Patient and physician factors associated with participation in cervical and uterine cancer trials: An NRG/GOG247 study. In: *Gynecologic Oncology*. Vol 138. ; 2015:101-108. doi:10.1016/j.ygyno.2015.04.033
36. Kemeny MM, Peterson B, Kornblith AB, et al. Barriers to clinical trial participation by older women with breast cancer. *J Clin Oncol*. 2003;21(12):2268-2275. doi:10.1200/JCO.2003.09.124.
37. National Institutes of Health. Revision: NIH Policy and Guidelines on the Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects. NOT OD 18 116. <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-116.html>. Accessed March 13, 2018.
38. Gross CP, Filardo G, Mayne ST, Krumholz HM. The impact of socioeconomic status and race on trial participation for older women with breast cancer. *Cancer*. 2005;103(3):483-491. doi:10.1002/cncr.20792
39. Stewart JH, Bertoni AG, Staten JL, Levine EA, Gross CP. Participation in Surgical Oncology Clinical Trials: Gender-, Race/Ethnicity-, and Age-based Disparities. *Ann Surg Oncol*. 2007;14(12):3328-3334. doi:10.1245/s10434-007-9500-y
40. Cook E, Arnold K, Herms J, et al. Impact of supplemental site grants to increase African American accrual for the Selenium and Vitamin E Cancer Prevention. *Clin Trials*. 2010;7(1):90-99. doi:10.1016/j.fertnstert.2010.09.017.Development
41. Fouad MN, Corbie-Smith G, Curb D, et al. Special populations recruitment for the Women's Health Initiative: Successes and limitations. *Control Clin Trials*. 2004;25(4):335-352. doi:10.1016/j.cct.2004.03.005
42. Moinpour CM, Atkinson JO, Thomas SM, et al. Minority recruitment in the prostate cancer prevention trial. *Ann Epidemiol*. 2000;10(8 Suppl):S85-91. <http://www.ncbi.nlm.nih.gov/pubmed/11189097>.
43. Unger JM, Barlow WE, Martin DP, et al. Comparison of Survival Outcomes Among Cancer Patients Treated In and Out of Clinical Trials. *JNCI J Natl Cancer Inst*. 2014;106(3):dju002. doi:10.1093/jnci/dju002
44. Unger JM, Cook E, Tai E, Bleyer A. The Role of Clinical Trial Participation in Cancer Research: Barriers, Evidence, and Strategies. *Am Soc Clin Oncol Educ B*. 2016;36:185-198. doi:10.14694/EDBK_156686
45. United States, Congress, *NIH Revitalization Act of 1993*.
46. National Institutes of Health. Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research. NOT OD 02 001. <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html>. Accessed March 13, 2018.
47. FDA. *Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making: Draft PDUFA V Implementation Plan*.; 2013. Accessed March 13, 2018.
48. O'Leary M, Krailo M, Anderson JR, Reaman GH. Progress in Childhood Cancer: 50 Years of Research. *Semin Oncol*. 2009;35(5):484-493. doi:10.1053/j.seminoncol.2008.07.008. Progress
49. Collins CL, Malvar J, Hamilton AS, Deapen DM, Freyer DR. Case-linked analysis of clinical trial enrollment among adolescents and young adults at a National Cancer Institute-Designated comprehensive cancer center. *Cancer*. 2015;121(24):4398-4406. doi:10.1002/cncr.29669
50. Kohler BA, Sherman RL, Howlader N, et al. Annual Report to the Nation on the Status of Cancer, 1975-2011, Featuring Incidence of Breast Cancer Subtypes by Race/Ethnicity, Poverty, and State. *JNCI J Natl Cancer Inst*. 2015;107(6). doi:10.1093/jnci/djv048
51. Bleyer A, Budd T, Montello M. Adolescents and young adults with cancer: The scope of the problem and criticality of clinical trials. *Cancer*. 2006;107(7 SUPPL.):1645-1655. doi:10.1002/cncr.22102

Bibliography

52. Ferrari A, Bleyer A. Participation of adolescents with cancer in clinical trials. *Cancer Treat Rev*. 2007;33(7):603-608. doi:10.1016/j.ctrv.2006.11.005
53. Murthy S, Mandl KD, Bourgeois FT. Industry-sponsored clinical research outside high-income countries: An empirical analysis of registered clinical trials from 2006 to 2013. *Health Res Policy Syst*. 2015;13(1):1-8. doi:10.1186/s12961-015-0019-6
54. Kanapuru B, Singh H, Fashoyin-Aje LA, Myers A, Kim G, Farrell A. FDA analysis of patient enrollment by region in clinical trials for approved oncological indications. *J Clin Oncol*. 2018;35(15_suppl):2539. doi:10.1200/JCO.2017.35.15_suppl.2539
55. Mariotti V, Gonzalez Velez M, Duma N, et al. Early phase clinical trials conducted in North America are more likely to exclude breast cancer patients based on organ function and comorbidities compared to other countries: Analysis of 484 studies. *Eur J Cancer*. 2017;72(Supplement 1):S25. doi:10.1016/S0959-8049(17)30162-4
56. Duma N, Wang Y, Gonzalez Velez M, Kothadia S, Mariotti V, Parrondo R. Comorbidities limiting recruitment of colorectal cancer (CRC) patients in early-phase trials. *J Clin Oncol*. 2017;35(4_suppl):791.
57. Jenkins V, Farewell D, Batt L, et al. The attitudes of 1066 patients with cancer towards participation in randomised clinical trials. *Br J Cancer*. 2010;103(12):1801-1807. doi:10.1038/sj.bjc.6606004
58. Lee SJ, Park LC, Lee J, et al. Unique perception of clinical trials by Korean cancer patients. *BMC Cancer*. 2012;12(594). doi:10.1186/1471-2407-12-594
59. Soares H, Kumar A, Daniels S, et al. Evaluation of new treatments in radiation oncology: are they better than standard treatments? *JAMA*. 2015;293(8):970-978.
60. Djulbegovic B, Kumar A, Soares HP, et al. Treatment Success in Cancer: New Cancer Treatment Successes Identified in Phase 3 Randomized Controlled Trials Conducted by the National Cancer Institute-Sponsored Cooperative Oncology Groups, 1955 to 2006. *Arch Intern Med*. 2008;168(6):632-642. doi:10.1001/archinte.168.6.632
61. Unger JM, Barlow WE, Ramsey SD, LeBlanc M, Blanke CD, Hershman DL. The Scientific Impact of Positive and Negative Phase 3 Cancer Clinical Trials. *JAMA Oncol*. 2016;2(7):875. doi:10.1001/jamaoncol.2015.6487
62. Djulbegovic B. The paradox of equipoise: The principle that drives and limits therapeutic discoveries in clinical research. *Cancer Control*. 2009;16(4):342-347. doi:10.1016/j.biotechadv.2011.08.021.Secreted
63. Peppercorn JM, Weeks JC, Cook EF, Joffe S. Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. *Lancet*. 2004;363(9405):263-270. doi:10.1016/S0140-6736(03)15383-4
64. Edwards SJL, Braunholtz DA, Lilford RJ, Stevens AJ. Ethical issues in the design and conduct of cluster randomised controlled trials. *Br Med J*. 1999;318:1407-1409. doi:10.1136/bmj.318.7195.1407
65. St Germain D, Denicoff AM, Dimond EP, et al. Use of the National Cancer Institute Community Cancer Centers Program Screening and Accrual Log to Address Cancer Clinical Trial Accrual. *J Oncol Pract*. 2014;10(2):e73-e80. doi:10.1200/JOP.2013.001194
66. Wujcik D, Wolff SN. Recruitment of African Americans to National Oncology Clinical Trials through a Clinical Trial Shared Resource. *J Health Care Poor Underserved*. 2010;21(1A):38-50. doi:10.1353/hpu.0.0251
67. Mannel RS, Walker JL, Gould N, et al. Impact of individual physicians on enrollment of patients into clinical trials. *Am J Clin Oncol*. 2003;26(2):171-173. doi:10.1097/01.COC.0000017798.43288.7C
68. Albrecht TL, Eggly SS, Gleason MEJ, et al. Influence of clinical communication on patients' decision making on participation in clinical trials. *J Clin Oncol*. 2008;26(16):2666-2673. doi:10.1200/JCO.2007.14.8114
69. Porter M, Ramaswamy B, Beisler K, et al. A Comprehensive Program for the Enhancement of Accrual to Clinical Trials. *Ann Surg Oncol*. 2016;23(7):2146-2152. doi:10.1245/s10434-016-5091-9
70. Copur MS, Ramaekers R, Gönen M, et al. Impact of the National Cancer Institute Community Cancer Centers Program on Clinical Trial and Related Activities at a Community Cancer Center in Rural Nebraska. *J Oncol Pract*. 2016;12(1):67-68, e44-51. doi:10.1200/JOP.2015.005736
71. Saphner T, Thompson MA, Planton S, et al. Insights From Building a New National Cancer Institute Community Oncology Research Program Site. *WJMJ*. 2016;115(4):191-195. <http://www.ncbi.nlm.nih.gov/pubmed/29099156>. Accessed February 19, 2018.
72. Meropol NJ, Buzaglo JS, Millard J, et al. Barriers to clinical trial participation as perceived by oncologists and patients. *J Natl Compr Canc Netw*. 2007;5(8):655-664. <http://www.ncbi.nlm.nih.gov/pubmed/17927923>. Accessed October 4, 2017.
73. Holcombe RF, Hollinger KJ. Mission-focused, productivity-based model for sustainable support of academic hematology/oncology faculty and divisions. *J Oncol Pract*. 2010;6(2):74-79. doi:10.1200/JOP.091075
74. Martin-Sanchez FJ, Aguiar-Pulido V, Lopez-Campos GH, Peek N, Sacchi L. Secondary Use and Analysis of Big Data Collected for Patient Care. *Yearb Med Inform*. 2017;26(1):28-37. doi:10.15265/IY-2017-008
75. Penberthy L, Brown R, Puma F, Dahman B. Automated matching software for clinical trials eligibility: measuring efficiency and flexibility. *Contemp Clin Trials*. 2010;31(3):207-217. doi:10.1016/j.cct.2010.03.005

76. Embi PJ, Jain A, Clark J, Bizjack S, Hornung R, Harris CM. Effect of a Clinical Trial Alert System on Physician Participation in Trial Recruitment. *Arch Intern Med.* 2005;165(19):2272. doi:10.1001/archinte.165.19.2272
77. Oncology Nursing Society. *2016 Oncology Clinical Trials Nurse Competencies Project Team Members.* https://www.ons.org/sites/default/files/OCTN_Compencies_FINAL.PDF. Accessed March 14, 2018.
78. Speicher LA, Fromell G, Avery S, et al. The Critical Need for Academic Health Centers to Assess the Training, Support, and Career Development Requirements of Clinical Research Coordinators: Recommendations from the Clinical and Translational Science Award Research Coordinator Taskforce*. *Clin Transl Sci.* 2012;5(6):470-475. doi:10.1111/j.1752-8062.2012.00423.x
79. Downhour M. HR Challenge: *Hiring Clinical Research Nurses;* 2016. <http://www.medixteam.com/clients/hr-challenge-hiring-clinical-research-nurses/>.
80. Showalter BL, Cline D, Yungclas J, Frentz K, Stafford SR, Maresh KJ. Clinical Research Nursing: Development of a Residency Program. *Clin J Oncol Nurs.* 2017;21(5):633-636. doi:10.1188/17.CJON.633-636
81. Raikar S. *The Impact of Study Coordinators Effectiveness on Trial Site Efficiency: Evidence from a Pilot Study;* 2016.
82. National Cancer Institute. NCI-Designated Cancer Centers. <https://www.cancer.gov/research/nci-role/cancer-centers>. Accessed March 13, 2018.
83. NCI Community Oncology Research Program. About NCORP. <https://ncorp.cancer.gov/about/>. Accessed March 13, 2018.
84. National Cancer Institute. *National Clinical Trials Network Program Guidelines;* 2012. https://ctep.cancer.gov/initiativesprograms/docs/nctn_program_guidelines.pdf.
85. Institute of Medicine. *A National Cancer Clinical Trials System for the 21st Century.* Washington, D.C.: National Academies Press; 2010. doi:10.17226/12879
86. IQVIA. Site Relationships and Networks. <https://www.iqvia.com/solutions/research-and-development/site-relationships-and-networks>. Accessed March 13, 2018.
87. ICON. Site Recruitment and Site Management. <http://www.iconplc.com/services/late-phase/icon-lifecycle-sciences-g/site-recruitment-and-site/>. Accessed March 13, 2018.
88. Corneli A, Pierre C, Hinkley T, et al. One and done: Reasons principal investigators conduct only one FDA-regulated drug trial. *Contemp Clin Trials Commun.* 2017;6:31-38. doi:10.1016/J.CONCTC.2017.02.009
89. English RA, Lebovitz Y, Griffin RB. *Transforming Clinical Research in the United States, Challenges and Opportunities: Workshop Summary;* 2010. doi:10.17226/12900
90. Siminoff LA, Zhang A, Colabianchi N, Sturm CMS, Shen Q. Factors That Predict the Referral of Breast Cancer Medical Oncologists. *J Clin Oncol.* 2000;18(6):1203-1211.
91. Somkin CP, Altschuler A, Ackerson L, et al. Organizational Barriers to Physician Participation in Cancer Clinical Trials. *Am J Manag Care.* 2005;11(7):413-421. <http://www.ajmc.com/journals/issue/2005/2005-07-vol11-n7/jul05-2081p413-421>.
92. Benson AB, Pregler JP, Bean JA. Oncologist's reluctance to accrue patients onto clinical trials: an Illinois Cancer Center study. *J Clin* 1991;9(11):2067-2075. <http://jco.ascopubs.org/cgi/content/abstract/9/11/2067>.
93. Belkora J, Miller M, Crawford B, et al. Evaluation of question-listing at the Cancer Support Community. *Transl Behav Med.* 2013;3(2):162-171. doi:10.1007/s13142-012-0186-8
94. Comis RL, Miller JD, Colaizzi DD, Kimmel LG. Physician-related factors involved in patient decisions to enroll onto cancer clinical trials. *J Oncol Pract.* 2009;5(2):50-56. doi:10.1200/JOP.0922001
95. *Memorial Sloan Kettering Cancer Center National Clinical Trials Survey Findings Overview;* 2016.
96. Kinney AY, Richards C, Vernon SW, Vogel VG. The effect of physician recommendation on enrollment in the Breast Cancer Chemoprevention Trial. *Prev Med (Baltim).* 1998;27(5 Pt 1):713-719. doi:10.1006/pmed.1998.0349
97. Ulrich CM, James JL, Walker EM, et al. RTOG physician and research associate attitudes, beliefs and practices regarding clinical trials: Implications for improving patient recruitment. *Contemp Clin Trials.* 2010;31(3):221-228. doi:10.1016/j.cct.2010.03.002
98. Parreco LK, DeJoice RW, Massett HA, Padberg RM, Thakkar SS. Power of an Effective Clinical Conversation: Improving Accrual Onto Clinical Trials. *J Oncol Pract.* 2012;8(5):282-286. doi:10.1200/JOP.2011.000478
99. Simon M, Du W, Flaherty L, et al. Factors Associated With Breast Cancer Clinical Trials Participation and Enrollment at a Large Academic Medical Center. *J Clin Oncol.* 2004;22(11):2046-2052. doi:doi.org/10.1200/JCO.2004.03.005
100. Dilts DM, Sandler AB. Invisible barriers to clinical trials: the impact of structural, infrastructural, and procedural barriers to opening oncology clinical trials. *J Clin Oncol.* 2006;24(28):4545-4552. doi:10.1200/JCO.2005.05.0104
101. Multiple Myeloma Research Foundation. About the MMRC. <https://www.themmr.org/research-partners/clinic/about-the-mmrc/>. Accessed March 13, 2018.
102. Mirowski P, Van Horn R. The contract research organization and the commercialization of scientific research. *Soc Stud Sci.* 2005;35(4):503-548. doi:10.1177/0306312705052103

Bibliography

103. Klabunde CN, Keating NL, Potosky AL, et al. A Population-Based Assessment of Specialty Physician Involvement in Cancer Clinical Trials. *JNCI J Natl Cancer Inst.* 2011;103(5):384-397. doi:10.1093/jnci/djq549
104. Chen L, Grant J, Cheung WY, Kennecke HF. Screening intervention to identify eligible patients and improve accrual to phase II-IV oncology clinical trials. *J Oncol Pract.* 2013;9(4):e174-81. doi:10.1200/JOP.2012.000763
105. Weiner BJ, Jacobs SR, Minasian LM, Good MJ. Organizational designs for achieving high treatment trial enrollment: a fuzzy-set analysis of the community clinical oncology program. *J Oncol Pract.* 2012;8(5):287-291. doi:10.1200/JOP.2011.000507
106. Ellis PM, Butow PN, Tattersall MH, Dunn SM, Houssami N. Randomized clinical trials in oncology: understanding and attitudes predict willingness to participate. *J Clin Oncol.* 2001;19(15):3554-3561. doi:10.1200/JCO.2001.19.15.3554
107. Prescott R, Counsell C, Gillespie W, et al. *Barriers to Participation in Randomized Controlled Trials: A Systematic Review.* Vol 3.; 1999. doi:Health Technology Assessment
108. Truong TH, Weeks JC, Cook EF, Joffe S. Altruism among participants in cancer clinical trials. *Clin Trials.* 2011;8(5):616-623. doi:10.1177/1740774511414444
109. Go RS, Frisby KA, Lee JA, et al. Clinical trial accrual among new cancer patients at a community-based cancer center. *Cancer.* 2006;106(2):426-433. doi:10.1002/cncr.21597
110. Guarino MJ, Masters GA, Schneider CJ, et al. Barriers exist to patient participation in clinical trials. *J Clin Oncol.* 2005;23(16_suppl):6015-6015. doi:10.1200/jco.2005.23.16_suppl.6015
111. Klabunde CN, Springer BC, Butler B, White MS, Atkins J. Factors influencing enrollment in clinical trials for cancer treatment. *South Med J.* 1999;92(12):1189-1193. <http://www.ncbi.nlm.nih.gov/pubmed/10624912>. Accessed October 4, 2017.
112. St. Germain D, Didmond E, Olesen K, et al. *The NCCCP Patient Navigation Project.*; 2014.
113. Joseph G, Dohan D. Diversity of participants in clinical trials in an academic medical center. *Cancer.* 2009;115(3):608-615. doi:10.1002/cncr.24028
114. Ford JG, Howerton MW, Lai GY, et al. Barriers to recruiting underrepresented populations to cancer clinical trials: A systematic review. *Cancer.* 2008;112(2):228-242. doi:10.1002/cncr.23157
115. Wendler D, Kington R, Madans J, et al. Are Racial and Ethnic Minorities Less Willing to Participate in Health Research? Gill P, ed. *PLoS Med.* 2005;3(2):e19. doi:10.1371/journal.pmed.0030019
116. Hoos WA, James PM, Rahib L, Talley AW, Fleshman JM, Matrisian LM. Pancreatic Cancer Clinical Trials and Accrual in the United States. *J Clin Oncol.* 2013;31(27):3432-3438. doi:10.1200/JCO.2013.49.4823
117. Moffitt K, Brogan F, Brown C, et al. Statewide cancer clinical trial navigation service. *J Oncol Pract.* 2010;6(3):127-132. doi:10.1200/JOP.200006
118. Umutyán A, Chiechi C, Beckett LA, et al. Overcoming barriers to cancer clinical trial accrual. *Cancer.* 2008;112(1):212-219. doi:10.1002/cncr.23170
119. Michaels M, Weiss ES, Guidry JA, et al. "The Promise of Community-Based Advocacy and Education Efforts for Increasing Cancer Clinical Trials Accrual." *J Cancer Educ.* 2012;27(1):67-74. doi:10.1007/s13187-011-0271-6
120. Du W, Mood D, Gadgeel S, Simon MS. An Educational Video to Increase Clinical Trials Enrollment among Lung Cancer Patients. *J Thorac Oncol.* 2008;3(1):23-29. doi:10.1097/JTO.0B013E31815E8BB2
121. Du W, Mood D, Gadgeel S, Simon MS. An educational video to increase clinical trials enrollment among breast cancer patients. *Breast Cancer Res Treat.* 2009;117(2):339-347. doi:10.1007/s10549-009-0311-7
122. Stiles C, Johnson L, Whyte D, Nergaard TH, Gardner J, Wu J. Does Increased Patient Awareness Improve Accrual Into Cancer-Related Clinical Trials? *Cancer Nursing.* 2011;34(5):E13-E19. doi:10.1097/NCC.0b013e31820254db
123. *Report on General Perceptions and Knowledge on Clinical Research - Analysis for Cancer Patients.*
124. Gansler T, Jin M, Bauer J, et al. Outcomes of a Cancer Clinical Trial Matching Service. *J Cancer Educ.* 2012;27(1):11-20. doi:10.1007/s13187-011-0296-x
125. Cartmell KB, Bonilha HS, Matson T, et al. Patient participation in cancer clinical trials: A pilot test of lay navigation. *Contemp Clin Trials Commun.* 2016;3:86-93. doi:10.1016/j.conctc.2016.04.005
126. American Cancer Society. Road to Recovery. <https://www.cancer.org/treatment/support-programs-and-services/road-to-recovery.html>. Accessed March 13, 2018.
127. Biedrzycki BA. Research Information Knowledge, Perceived Adequacy, and Understanding in Cancer Clinical Trial Participant. *Oncol Nurs forum.* 2011AD;38(4):E291-E296. <https://doi.org/10.1188/11.ONF.E291-E296>.
128. FDA. Informed Consent for Clinical Trials. https://www.fda.gov/ForPatients/ClinicalTrials/InformedConsent/default.htm#What_is_Informed_Consent_. Accessed March 13, 2018.
129. Paasche-Orlow MK, Taylor HA, Brancati FL. Readability Standards for Informed-Consent Forms as Compared with Actual Readability. *N Engl J Med.* 2003;348(8):721-726. doi:10.1056/NEJMsa021212
130. Davis TC, Williams M V., Marin E, Parker RM, Glass J. Health Literacy and Cancer Communication. *CA Cancer J Clin.* 2002;52(3):134-149. doi:10.3322/canjclin.52.3.134

131. Beardsley E, Jefford M, Mileskin L. Longer consent forms for clinical trials compromise patient understanding: so why are they lengthening? *J Clin Oncol*. 2007;25(9):2005-2006. doi:10.1200/JCO.2006.10.3341
132. The National Academies Press. *Informed Consent and Health Literacy (Workshop Summary)*; 2015. doi:https://doi.org/10.17226/19019
133. Hoffner B, Bauer-Wu S, Hitchcock-Bryan S, Powell M, Wolanski A, Joffe S. "Entering a clinical trial: Is it right for you?" *Cancer*. 2012;118(7):1877-1883. doi:10.1002/cncr.26438
134. U.S Department of Health and Human Services. Common Rule. 45 CFR §46. <https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html>. Accessed March 13, 2018.
135. Hopkins J, Mumber MP. Patient navigation through the cancer care continuum: an overview. *J Oncol Pract*. 2009;5(4):150-152. doi:10.1200/JOP.0943501
136. Guadagnolo BA, Boylan A, Sargent M, et al. Patient navigation for American Indians undergoing cancer treatment. *Cancer*. 2011;117(12):2754-2761. doi:10.1002/cncr.25823
137. Fouad MN, Acemgil A, Bae S, et al. Patient Navigation As a Model to Increase Participation of African Americans in Cancer Clinical Trials. *J Oncol Pract*. 2016;12(6):556-563. doi:10.1200/JOP.2015.008946
138. Ghebre RG, Jones LA, Wenzel JA, Martin MY, Durant RW, Ford JG. State-of-the-science of patient navigation as a strategy for enhancing minority clinical trial accrual. *Cancer*. 2014;120(57):1122-1130. doi:10.1002/cncr.28570
139. Lara PN, Higdon R, Lim N, et al. Prospective Evaluation of Cancer Clinical Trial Accrual Patterns: Identifying Potential Barriers to Enrollment. *J Clin Oncol*. 2001;19(6):1728-1733. doi:10.1200/JCO.2001.19.6.1728
140. Avis NE, Smith KW, Link CL, Hortobagyi GN, Rivera E. Factors associated with participation in breast cancer treatment clinical trials. *J Clin Oncol*. 2006;24(12):1860-1867. doi:10.1200/JCO.2005.03.8976
141. Carlson RH. Using Telemedicine to Increase Trial Accrual. *Oncol Times*. 2014;36(6):32-33. <http://search.ebscohost.com/login.aspx?direct=true&db=cin20&AN=107899795&site=ehost-live>.
142. FDA. Digital Health. <https://www.fda.gov/MedicalDevices/DigitalHealth/default.htm>. Accessed March 13, 2018.
143. Strom L, Mulryne J, Tsang L. *Clinical Trial Consent: There Is An App For That*; 2017. <https://www.digitalhealthdownload.com/2017/03/clinical-trial-consent-app/>.
144. Woodcock J, LaVange LM. Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. Drazen JM, Harrington DP, McMurray JJV, Ware JH, Woodcock J, eds. *N Engl J Med*. 2017;377(1):62-70. doi:10.1056/NEJMra1510062
145. Comstock J. 21 clinical trials that are using Fitbit activity trackers right now. *Mobi Health News*. <http://www.mobihealthnews.com/content/21-clinical-trials-are-using-fitbit-activity-trackers-right-now>. Published March 16, 2016.
146. Galsky MD, Shahin M, Jia R, Shaffer DR, Gimpel-Tetra K, Tsao C-K. Telemedicine-Enabled Clinical Trial of Metformin in Patients With Prostate Cancer. *JCO Clin Cancer Informatics*. 2017. doi:10.1200/CCI.17.00044
147. Bennett CL, Stinson TJ, Vogel V, et al. Evaluating the financial impact of clinical trials in oncology: results from a pilot study from the Association of American Cancer Institutes/ Northwestern University clinical trials costs and charges project. *J Clin Oncol*. 2000;18(15):2805-2810. doi:10.1200/JCO.2000.18.15.2805
148. Fireman BH, Fehrenbacher L, Gruskin EP, Ray GT. Cost of Care for Patients in Cancer Clinical Trials. *JNCI J Natl Cancer Inst*. 2000;92(2):136-142. doi:10.1093/jnci/92.2.136
149. Wagner JL. Incremental Costs of Enrolling Cancer Patients in Clinical Trials: a Population-Based Study. *J Natl Cancer Inst*. 1999;91(10):847-853. doi:10.1093/jnci/91.10.847
150. Goldman DP, Berry SH, McCabe MS, et al. Incremental Treatment Costs in National Cancer Institute–Sponsored Clinical Trials. *JAMA*. 2003;289(22):2970. doi:10.1001/jama.289.22.2970
151. Streeter SB, Schwartzberg L, Husain N, Johnsrud M. Patient and plan characteristics affecting abandonment of oral oncolytic prescriptions. *J Oncol Pract*. 2011;7(3 Suppl):46s-51s. doi:10.1200/JOP.2011.000316
152. Lara PN, Paterniti DA, Chiechi C, et al. Evaluation of factors affecting awareness of and willingness to participate in cancer clinical trials. *J Clin Oncol*. 2005;23(36):9282-9289. doi:10.1200/JCO.2005.02.6245
153. Ellis SD, Carpenter WR, Minasian LM, Weiner BJ. Effect of state-mandated insurance coverage on accrual to community cancer clinical trials. *Contemp Clin Trials*. 2012;33(5):933-941. doi:10.1016/j.cct.2012.06.001
154. Klamerus JF, Bruinooge SS, Ye X, et al. The Impact of Insurance on Access to Cancer Clinical Trials at a Comprehensive Cancer Center. *Clin Cancer Res*. 2010;16(24):5997-6003. doi:10.1158/1078-0432.CCR-10-1451
155. National Cancer Institute. Insurance Coverage and Clinical Trials. <https://www.cancer.gov/about-cancer/treatment/clinical-trials/paying/insurance>. Accessed March 13, 2018.
156. Kehl KL, Fullmer CP, Fu S, et al. Insurance Clearance for Early-Phase Oncology Clinical Trials Following the Affordable Care Act. *Clin Cancer Res*. 2017;23(15):4155-4162. doi:10.1158/1078-0432.CCR-16-3027

Bibliography

157. Mackay CB, Antonelli KR, Bruinooge SS, Saint Onge JM, Ellis SD. Insurance denials for cancer clinical trial participation after the Affordable Care Act mandate. *Cancer*. 2017;123(15):2893-2900. doi:10.1002/cncr.30689
158. Wu J. Insurance Standards Bulletin Series — INFORMATION — Extension of Transitional Policy through Calendar Year 2018: Extended Transition to Affordable Care Act-Compliant Policies. 2017. <https://www.cms.gov/CCIIO/Resources/Regulations-and-Guidance/Downloads/Extension-Transitional-Policy-CY2018.pdf>.
159. Executive Order. No. 13813, 2017.
160. ASCO. Insurance Coverage of Clinical Trials. <https://www.asco.org/research-progress/clinical-trials/insurance-coverage-clinical-trials#Medicaid>. Accessed March 13, 2018.
161. Nipp RD, Powell E, Chabner B, Moy B. Recognizing the Financial Burden of Cancer Patients in Clinical Trials. *Oncologist*. 2015;20(6):572-575. doi:10.1634/theoncologist.2015-0068
162. Nipp RD, Lee H, Powell E, et al. Financial Burden of Cancer Clinical Trial Participation and the Impact of a Cancer Care Equity Program. *Oncologist*. 2016;21(4):467-474. doi:10.1634/theoncologist.2015-0481
163. Walter JK, Burke JF, Davis MM. Research Participation by Low-Income and Racial/Ethnic Minority Groups: How Payment May Change the Balance. *Clin Transl Sci*. 2013;6(5):363-371. doi:10.1111/cts.12084
164. LUNGeVity. *Barriers to Clinical Trial Participation as Perceived by Lung Cancer Patients and Caregivers*; 2017. <https://lungevity.org/sites/default/files/file-uploads/Barriers-to-Clinical-Trial-Participation-Study.pdf>. Accessed March 13, 2018.
165. Grady C, Ph D, Cummings SR, et al. Informed Consent. *N Engl J Med*. 2017;376(9):856-867.
166. Halpern SD, Raz A, Kohn R, Rey M, Asch DA, Reese P. Regulated Payments for Living Kidney Donation: An Empirical Assessment of the Ethical Concerns. *Ann Intern Med*. 2010;152(6):358. doi:10.7326/0003-4819-152-6-201003160-00005
167. United States, Congress, *Social Security Act*.
168. Largent EA, Grady C, Miller FG, Wertheimer A. Money, coercion, and undue inducement: attitudes about payments to research participants. *IRB*. 2012;34(1):1-8. <http://www.ncbi.nlm.nih.gov/pubmed/22338401>. Accessed October 4, 2017.
169. FDA. Letter to the Honorable Pete Sessions, House of Representatives. 2017.
170. FDA. Payment and Reimbursement to Research Subjects - Information Sheet. <https://www.fda.gov/regulatoryinformation/guidances/ucm126429.htm>. Accessed March 18, 2018.
171. American Cancer Society. Hope Lodge. <https://www.cancer.org/treatment/support-programs-and-services/patient-lodging/hope-lodge.html>. Accessed March 18, 2018.
172. Lazarex Cancer Foundation. <https://www.lazarex.org/>. Accessed March 18, 2018.
173. Friends of the Clinical Center. Mission. <http://www.foccccharities.org/Mission.html>. Accessed March 18, 2018.
174. Cheng S, Dietrich M, Finnigan S, et al. A sense of urgency: Evaluating the link between clinical trial development time and the accrual performance of CTEP-sponsored studies. *J Clin Oncol*. 2009;27(18S):CRA6509-CRA6509. doi:10.1200/jco.2009.27.18s.cra6509
175. Korn EL, Freidlin B, Mooney M, Abrams JS. Accrual Experience of National Cancer Institute Cooperative Group Phase III Trials Activated From 2000 to 2007. *J Clin Oncol*. 2010;28(35):5197-5201. doi:10.1200/JCO.2010.31.5382
176. Bennette CS, Ramsey SD, McDermott CL, Carlson JJ, Basu A, Veenstra DL. Predicting Low Accrual in the National Cancer Institute's Cooperative Group Clinical Trials. *J Natl Cancer Inst*. 2016;108(2):djv324. doi:10.1093/jnci/djv324
177. Stensland KD, McBride RB, Latif A, et al. Adult Cancer Clinical Trials That Fail to Complete: An Epidemic? *JNCI J Natl Cancer Inst*. 2014;106(9). doi:10.1093/jnci/dju229
178. London JW, Balestrucci L, Chatterjee D, Zhan T. Design-phase prediction of potential cancer clinical trial accrual success using a research data mart. *J Am Med Informatics Assoc*. 2013;20(e2):e260-e266. doi:10.1136/amiainl-2013-001846
179. Tang J, Shalabi A, Hubbard-Lucey VM. Comprehensive analysis of the clinical immuno-oncology landscape. *Ann Oncol*. December 2017. doi:10.1093/annonc/mdx755
180. National Cancer Institute. *CTEP-Sponsored Cooperative Group Phase III Trials: Early Stopping Guidelines for Slow Accruing Trials*. https://ctep.cancer.gov/protocolDevelopment/docs/slow_accrual.pdf. Accessed March 18, 2018.
181. National Cancer Institute. Letter of Intent (LOI). https://ctep.cancer.gov/protocoldevelopment/letter_of_intent.htm. Accessed March 18, 2018.
182. Printz C. New national clinical trials network faces challenges: Budget cuts and enrollment caps have group leaders concerned. *Cancer*. 2014;120(15):2223-2224. doi:10.1002/cncr.28886
183. Tran G, Harker M, Chiswell K, et al. Comparison of cancer incidence to available oncology clinical trial slots. In: *ASCO Annual Meeting*; 2018.
184. Beaver JA, Ison G, Pazdur R. Reevaluating Eligibility Criteria - Balancing Patient Protection and Participation in Oncology Trials. *N Engl J Med*. 2017;376(16):1504-1505. doi:10.1056/NEJMp1615879

185. Kim ES, Bruinooge SS, Roberts S, et al. Broadening eligibility criteria to make clinical trials more representative: American society of clinical oncology and friends of cancer research joint research statement. *J Clin Oncol.* 2017;35(33):3737-3744. doi:10.1200/JCO.2017.73.7916
186. Lin NU, Prowell T, Tan AR, et al. Modernizing Clinical Trial Eligibility Criteria: Recommendations of the American Society of Clinical Oncology-Friends of Cancer Research Brain Metastases Working Group. *J Clin Oncol.* October 2017;JCO2017740761. doi:10.1200/JCO.2017.74.0761
187. Jin S, Pazdur R, Sridhara R. Re-evaluating eligibility criteria for oncology clinical trials: Analysis of investigational new drug applications in 2015. *J Clin Oncol.* 2017;35(33):3745-3752. doi:10.1200/JCO.2017.73.4186
188. Gore L, Ivy SP, Balis FM, et al. Modernizing Clinical Trial Eligibility: Recommendations of the American Society of Clinical Oncology-Friends of Cancer Research Minimum Age Working Group. *J Clin Oncol.* October 2017;JCO2017744144. doi:10.1200/JCO.2017.74.4144
189. Lichtman SM, Harvey RD, Damiette Smit MA, et al. Modernizing clinical trial eligibility criteria: Recommendations of the American society of clinical oncology-friends of cancer research organ dysfunction, prior or concurrent malignancy, and comorbidities working group. *J Clin Oncol.* 2017;35(33):3753-3759. doi:10.1200/JCO.2017.74.4102
190. Uldrick TS, Ison G, Rudek MA, et al. Modernizing clinical trial eligibility criteria: Recommendations of the American society of clinical oncology-friends of cancer research HIV working group. *J Clin Oncol.* 2017;35(33):3774-3780. doi:10.1200/JCO.2017.73.7338
191. Steuer C, Papadimitrakopoulou V, Herbst R, et al. Innovative Clinical Trials: The LUNG-MAP Study. *Clin Pharmacol Ther.* 2015;97(5):488-491. doi:10.1002/cpt.88
192. McNeil C. NCI-MATCH Launch Highlights New Trial Design in Precision-Medicine Era: *J Natl Cancer Inst.* 2015;107(7):djv193. doi:10.1093/jnci/djv193
193. CMS. *Proposed Decision Memo for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450N)*; 2017. <https://www.cms.gov/medicare-coverage-database/details/nca-proposed-decision-memo.aspx?NCAId=290&bc=AAAAAAAAAAQAAA%3D%3D>. Accessed March 18, 2018.
194. Garcia SF, Rosenbloom SK, Beaumont JL, et al. Priority Symptoms in Advanced Breast Cancer: Development and Initial Validation of the National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy-Breast Cancer Symptom Index (NFBSI-16). *Value Heal.* 2012;15(1):183-190. doi:10.1016/j.jval.2011.08.1739
195. Wiering B, de Boer D, Delnoij D. Patient involvement in the development of patient-reported outcome measures: a scoping review. *Heal Expect.* 2017;20(1):11-23. doi:10.1111/hex.12442
196. Basch E, Spertus J, Adams Dudley R, et al. Methods for Developing Patient-Reported Outcome-Based Performance Measures (PRO-PMs). *Value Heal.* 2015;18(4):493-504. doi:10.1016/j.jval.2015.02.018
197. Marsden J, Bradburn J, Consumers' Advisory Group for Clinical Trials, Lynda Jackson Macmillan Centre. Patient and clinician collaboration in the design of a national randomized breast cancer trial. *Heal Expect.* 2004;7(1):6-17. doi:10.1111/j.1369-7625.2004.00232.x
198. Lee DJ, Avulova S, Conwill R, Barocas DA. Patient engagement in the design and execution of urologic oncology research. *Urol Oncol.* 2017;35(9):552-558. doi:10.1016/j.urolonc.2017.07.002
199. Andejaski Y, Bisceglia IT, Dickersin K, et al. Quantitative impact of including consumers in the scientific review of breast cancer research proposals. *J Womens Heal Gen Based Med.* 2002;11(4):379-388. doi:10.1089/152460902317586010
200. Brett J, Staniszevska S, Mockford C, et al. Mapping the impact of patient and public involvement on health and social care research: a systematic review. *Heal Expect.* 2014;17(5):637-650. doi:10.1111/j.1369-7625.2012.00795.x
201. Staley K, Minogue V. User involvement leads to more ethically sound research. *Clin Ethics.* 2006;1(2):95-100. doi:doi.org/10.1258/147775006777254489
202. Levitan B, Getz K, Eisenstein EL, et al. Assessing the Financial Value of Patient Engagement. *Ther Innov Regul Sci.* 2017. doi:doi.org/10.1177/2168479017716715
203. The Patient Centered Outcomes Research Institute. <https://www.pcori.org/>. Accessed March 18, 2018.
204. Frank L, Basch E, Selby J V. The PCORI Perspective on Patient-Centered Outcomes Research. *JAMA.* 2014;312(15):1513. doi:10.1001/jama.2014.11100
205. United States, Congress, *21st Century Cures Act.*; 2016.
206. Horn L, Keedy VL, Campbell N, et al. Identifying Barriers Associated With Enrollment of Patients With Lung Cancer into Clinical Trials. *Clin Lung Cancer.* 2013; 14(1):14-18. doi:10.1016/j.clc.2012.03.008
207. Zaleta AK, Miller MF, Johnson J, McManus S, Buzaglo JS. Perceptions of Cancer Clinical Trials Among Racial and Ethnic Minority Cancer Survivors. in: American Psychological Association Annual Convention. 2017.

Glossary

Unless indicated, definitions are derived from <https://www.cancer.gov/publications/dictionaries>

Accreditation – A process of review that allows healthcare organizations to demonstrate their ability to meet regulatory requirements and standards established by a recognized accreditation organization.¹

Accrual – The process of placing patients in a clinical trial.²

Biomarker – A biological molecule found in blood, other bodily fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition. Also called molecular marker and signature molecule.

Blinded trial – A type of trial in which the patients (single-blinded) or the patients and their doctors (double-blinded) do not know which drug or treatment is being given. The opposite of a blinded trial is an open label trial.

Clinical trial – A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. Also called a clinical study.

Cohort – A group of individuals who share a common trait, such as birth year. In medicine, a cohort is a group that is part of a clinical trial or study and is observed over a period of time.

Comorbidity – The condition of having two or more diseases at the same time.

Control group/arm – In a clinical trial, the group that does not receive the new treatment being studied. This group is compared to the group that receives the new treatment, to see if the new treatment works.

Eligibility criteria – In clinical trials, requirements that must be met for a person to be included in a trial. These requirements help make sure that participants in a trial are like each other in terms of specific factors such as age, type and stage of cancer, general health, and previous treatment. When all participants meet the same eligibility criteria, it is more likely that results of the study are caused by the intervention being tested and not by other factors or by chance.

Equipoise – The assumption that there is not one “better” intervention present (for either the control or experimental group) during the design of a randomized controlled trial. It provides the principled basis for medical research involving patients randomly assigned to different treatment arms of a clinical trial, and is considered a necessary feature for clinical service practitioners to ethically enroll patients into clinical trials.³

Exclusion criteria – The factors specified in a trial protocol that disqualify someone from participating in a clinical trial.⁴ (see also eligibility criteria)

Experimental group/arm – The group in a clinical research study that receives the drug, vaccine, or other intervention being tested.

Genomic/genetic signature – Most specific fingerprint that can unambiguously identify most people on earth.⁵ It is the complete blueprint for the construction of proteins. Much like people, cancer tumors also have unique genomic signatures.⁶

Histology – The study of tissues and cells under a microscope.

Inclusion criteria – The factors specified in a trial protocol that allow someone to participate in a clinical trial.⁷ (see also eligibility criteria)

Informed consent – A process in which patients are given important information, including possible risks and benefits, about a medical procedure or treatment, genetic testing, or a clinical trial. This is to help them decide if they want to be treated, tested, or take part in the trial. Patients are also given any new information that might affect their decision to continue. Also called consent process.

Master protocols – One overarching trial protocol designed to answer multiple questions. Master protocols may involve one or more interventions in multiple diseases or a single disease with multiple interventions.⁸

Navigator – An individual who could educate and empower patients, serving as their advocate in navigating the health care system.⁹

Observational study – A type of study in which individuals are observed or certain outcomes are measured. No attempt is made to affect the outcome (for example, no treatment is given).

Patient-reported outcome (PRO) – Any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else.¹⁰

Phase I trial – The first step in testing a new treatment in humans. A phase I trial tests the safety, side effects, best dose, and timing of a new treatment. It may also test the best way to give a new treatment (for example, by mouth, infusion into a vein, or injection) and how the treatment affects the body. Phase I clinical trials usually include only a small number of patients who have not been helped by other treatments.

Phase II trial – A trial that tests whether a new treatment works for a certain type of cancer or other disease (for example, whether it shrinks a tumor or improves blood test results). Phase II trials may also provide more information about the safety of the new treatment and how the treatment affects the body.

Phase III trial – A trial that tests the safety and how well a new treatment works compared with a standard treatment. In most cases, treatments move into phase III trials only after they meet the goals of phase I and II trials. Phase III trials may include hundreds of people.

Phase IV trial/Real World trial/late phase trial – A type of clinical trial that studies the side effects caused over time by a new treatment after it has been approved and is on the market. These trials look for side effects that were not seen in earlier trials and may also study how well a new treatment works over a long period of time. Phase IV trials may include thousands of people.

Placebo – An inactive substance or other intervention that looks the same as, and is given the same way as, an active drug or treatment being tested. The effects of the active drug or other intervention are compared to the effects of the placebo.

Prescreening – Basic patient matching to cancer clinical trial eligibility criteria based at the very least on age, sex, cancer location, and stage.¹¹

Principal investigator (PI) – The person(s) in charge of a clinical trial or a scientific research grant. The PI prepares and carries out the clinical trial protocol (plan for the study) or research paid for by the grant. The PI also analyzes the data and reports the results of the trial or grant research.

Proteomic signature – The complete set of proteins produced. Different cancers and tumors vary in the types and amounts of proteins they produce, which allows them to be profiled and categorized into subtypes based on these variations.¹²

Randomization – The process by which human subjects are assigned by chance to separate groups that compare different treatments or other interventions. Randomization gives each participant an equal chance of being assigned to any of the groups.

Registrational clinical trial – A trial that is planned to move forward for review by the FDA, either as a new agent or to expand labeling for new indications.¹³

Trial protocol – A detailed plan of a scientific experiment. It states what the trial will do, how it will be done, and why it is being done. It explains how many people will be in the trial, who is eligible to take part in it, what drugs or other interventions will be given, what tests will be done and how often, and what information will be collected.

Glossary

Acronyms

AMC – Academic medical center

CBPR – Community-based participatory research

CoC – Commission on Cancer

CRA – Clinical Research Associates

CRC – Clinical Research Coordinator

CRO – Contract research organization

CTA – Clinical Trial Agreements

ETCTN – Experimental Therapeutics Clinical Trials Network

FDA – U.S. Food and Drug Administration

IND – Investigational New Drug

IRB – Institutional Review Board

NCI – National Cancer Institute

NCTN – National Clinical Trials Network

NIH – National Institutes of Health

PCORI – Patient-Centered Outcomes Research Institute

PI – Principal investigator

PRO – Patient-reported outcome

SMO – Site Management Organization

1. Accreditation Commission for Health Care. "About Accreditation." <https://www.achc.org/about-accreditation.html>.
2. ASCO Cancer.Net. "One in Five Clinical Trials for Adults with Cancer Never Finish – New Study Examines the Reasons." <https://www.cancer.net/one-five-clinical-trials-adults-cancer-never-finish-%E2%80%93-new-study-examines-reasons>.
3. Cook, Chad, and Sheets, Charles. "Clinical Equipoise and Personal Equipoise: Two Necessary Ingredients for Reducing Bias in Manual Therapy Trials." *J Man Manip Ther* 19, no. 1 (2011): 55-57. doi: 10.1179/106698111X12899036752014.
4. National Institutes of Health. "Learn About Clinical Trials." Last modified January 2017. <https://clinicaltrials.gov/ct2/about-studies/learn>.
5. Fricke, Florian, Cebula, Thomas, and Ravel, Jacques. "Genomics." In *Microbial Forensics*, edited by Bruce Budowle, Steven Schutzer, Roger Breeze, Paul Keim and Stephen Morse. San Diego: Academic Press, 2011.
6. Hicks, John. (2003). Genome, Proteome, and Metabolome: Where Are We Going?. *Ultrastructural pathology*, 27 (2003): 289-94. doi: 10.1080/716100783.
7. National Institutes of Health. "Learn About Clinical Trials." Last modified January 2017. <https://clinicaltrials.gov/ct2/about-studies/learn>.
8. Woodcock, Janet and LaVange, Lisa M. "Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both." *N Engl J Med* 377, (2017): 62-70. doi: 10.1056/NEJMra1510062.
9. Hopkins, Janet and Mumber, Matthew. "Patient Navigation Through the Cancer Care Continuum: An Overview." *Journal of Oncology Practice* 5, no. 4 (2009): 150-152. doi: 10.1200/JOP.0943501.
10. National Quality Forum. "Patient-Reported Outcomes." https://www.qualityforum.org/Projects/n-r/Patient-Reported_Outcomes/Patient-Reported_Outcomes.aspx.
11. Wujcik, Debra, Blakeney, Natasha, and Michaels, Margo. "Making a Difference in Clinical Trials Accrual: The Integration of Prescreening All Patients for Eligibility." *Applied Clinical Trials*, November 8, 2013. <http://www.appliedclinicaltrialsonline.com/making-difference-clinical-trials-accrual-integration-prescreening-all-patients-eligibility>
12. The Human Protein Atlas. "The Cancer Proteome." <https://www.proteinatlas.org/humanproteome/cancer>.
13. 42 C.F.R. Part 11 § 801.



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