VIAL

Barriers and Best Practices for Patient Recruitment in Oncology

White Paper

Barriers and Best Practices for Patient Recruitment in Oncology

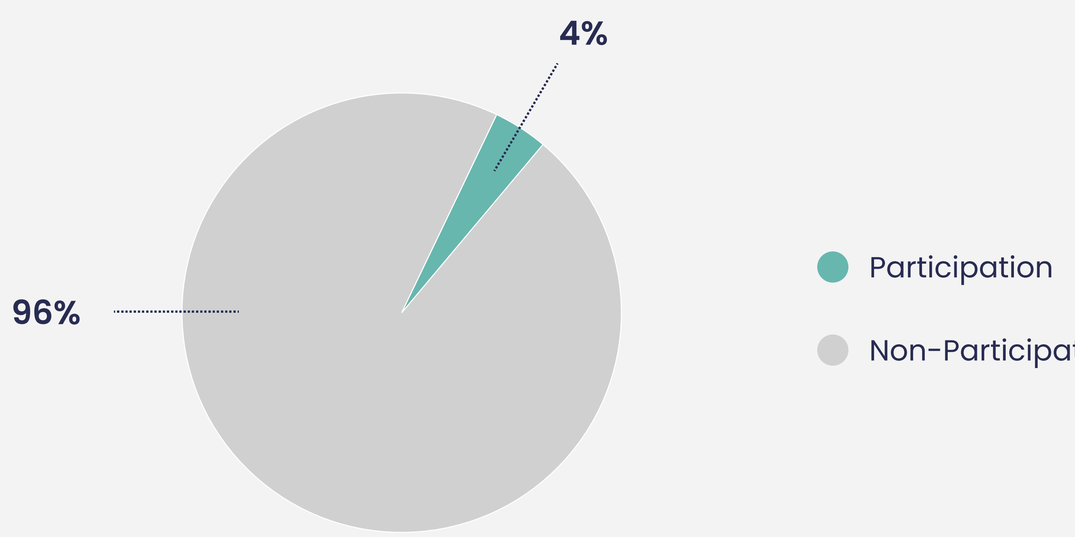
1. Introduction

Clinical trials are the foundation for advancing therapies to improve the lives of patients suffering from a disease or disorder. In order to earn approval for a new treatment, a study must successfully demonstrate its safety and efficacy in qualifying patients. Therefore, collecting such data requires the voluntary participation of many patients. Recruiting a sufficient amount of patients has long since been a monumental task for sponsors of clinical studies. However, implementing several strategies and embodying a patient-centric approach can mitigate the difficulties to recruitment.

2. Patient recruitment in oncology

While patient recruitment can be difficult for many disease indications, oncology patient recruitment has specific nuances that should be considered. According to the American Cancer Society, only about 4% of adult cancer patients take part in oncology clinical trials. Since a cancer diagnosis can oftentimes be a shocking and emotional experience for the patient and their family, adding an additional burden of deciding whether or not to participate in a clinical trial can be taxing. The inclusion criteria to be considered for an oncology clinical trial can also be very specific and granular. Additional laboratory tests, diagnostic imaging, or even surgical biopsies may need to be performed before a patient is considered qualified for participation, which may further hinder the likelihood of participation. Lastly, patients with cancer have a notoriously difficult regimen of hospital visits, treatment schedules, medication routines, and surgical procedures. Some patients may not want to add the additional required activities of a clinical trial to an already burdensome schedule [1].

Figure 1. The number of cancer patients that participate in oncology clinical trials is insufficient to drive adequate data for novel therapies.

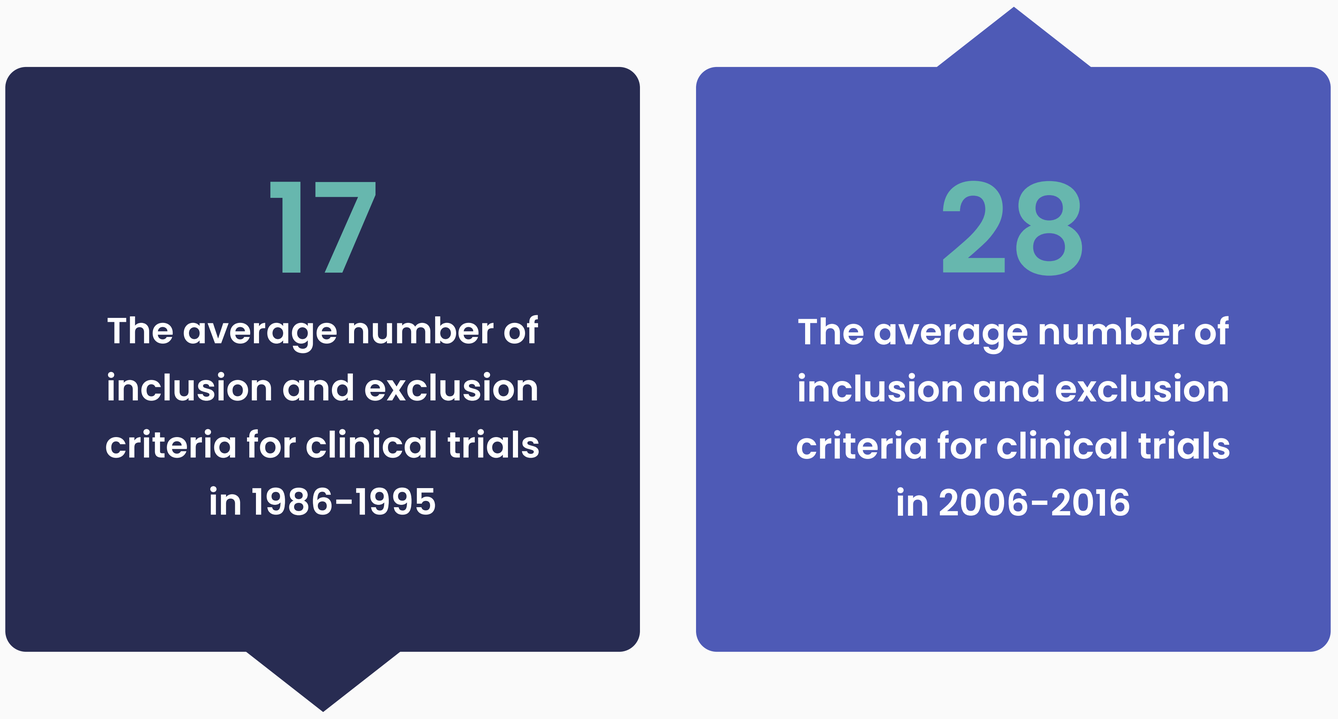


If a patient's treatment(s) has been unsuccessful, there may be a level of urgency that initiates their quest to participate in a clinical trial. All patients approached to participate in a clinical trial must be educated on the background of the study, potential side effects, and necessary study activities and procedures. Patients must fully understand that the treatment does not guarantee a response and, in some cases, the patient may receive a placebo instead of the investigative product. Similarly, patients must be informed about potential side effects of the study drug and the different requirements for each trial such as additional clinic visits, laboratory tests, surgical procedures, and follow-up activities. Only after a patient has received all of this information can they be considered ready to make a true informed consent [2].

3. The impact of study types on patient recruitment

Factors related to study design that can greatly affect patient recruitment is whether a study is interventional or observational. Interventional studies aim to understand the direct impact of a treatment on a disease whereas observational studies assess causation of the relationship between treatment exposure and certain outcomes [3]. Interventional studies, which are the more common type of oncology study that advances therapies and will be the focus of this article moving forward, have their own set of advantages and disadvantages when it comes to patient recruitment. Oftentimes, later phase interventional clinical trials attract patients based on the innovative therapy of focus. By participating in a clinical trial, patients can have a tremendous response with the novel therapy. However, it's important for patients to understand the randomization schema used in each trial.

> **Figure 2. There has been an exponential increase in the complexity and number of inclusion and exclusion criteria for clinical trials over the last several decades.**



While patient recruitment overall presents several challenges, these difficulties can be stratified based on different types of clinical trials. Phase I trials can be the first time a drug is used in humans and therefore can be challenging for a patient to commit too. Recruitment in phase I clinical trials also represent a unique challenge because of the endpoints that are typically defined in these earlier studies [4].

Oftentimes, phase I trials are more focused on the safety aspect of a drug, whereas the efficacy is a secondary endpoint [5]. Cancer patients do not necessarily have the luxury of deprioritizing efficacy. Therefore, it may be difficult to recruit patients for Phase I oncology trials because the efficacy has not yet been determined. Despite these challenges, there is work underway to identify the ideal patients that could balance the risks and benefits of entering into a Phase I trial through a prognostic score to ensure that patient selection is appropriate [6].

Later phase trials, on the other hand, could have efficacy data to drive patient recruitment. As investigative products reach later phase studies, the focus becomes more on efficacy as well as long-term safety, side effects, and drug-drug interactions. In order to obtain statistical power to accurately and irrefutably determine conclusions, significantly more patients are needed to participate in later phase studies. In addition to an increase in patient numbers, the eligibility criteria becomes more granular and complex with each subsequent phase. It was shown that in previous decades, the average number of individual eligibility criteria that must be met for a patient to participate in a trial was 17 and has since risen to 28 [7]. While eligibility criteria is necessary to maintain patient safety and ensure robust data, the complexity of the criteria may unnecessarily limit enrollment. For this reason, the FDA and many groups within the oncology community such as ASCO (American Society of Clinical Oncology) and ECOG (Eastern Cooperative Oncology Group), are working to make eligibility criteria for oncology clinical trials less complex and more inclusive while also maintaining patient safety and the integrity of the data [8]. One way in which these groups are accomplishing this goal is by creating more adaptive clinical trials [9] in which trials can be altered as data or other information comes to light.

In order to understand if a new therapy is superior to an existing therapy (or standard of care (SoC)), the study design has to be set up in a way that randomly assigns each participant to either the new treatment or the SoC. In addition to the randomization schema, there is also a level of blinding that is typically done in interventional studies in which the therapy a patient is assigned to is not disclosed. The blinding of the patient, the research staff, or the sponsor ensures that there is no bias in expectation that could potentially skew the data [10]. When it comes to patient recruitment, blinding and randomization can be a deterrent to participating in a clinical trial.

A patient must fully consent to the fact that there is an equal chance that they will receive the placebo or new therapy while also understanding that they will not know which intervention they are receiving until several months after the conclusion of the study. For some patients, this level of unknown is not worth the benefit of potentially receiving a novel therapy. In contrast, some patients believe the risk of accepting these unknowns is outweighed by their prognosis. Patients should take consolation in the fact that all patients enrolled in clinical trials tend to have better outcomes than those who do not participate in a study, regardless of if they receive the investigative treatment or standard of care. This is due to the fact that patients enrolled in clinical trials have easier communication access to healthcare professionals, their adverse events are managed more readily and the increased number of clinic visits and testing can prevent complications before they happen [11]. Despite the advantages and disadvantages, the decision to ultimately participate in an interventional study is complex and deeply personal between a patient, their family, and their care team.

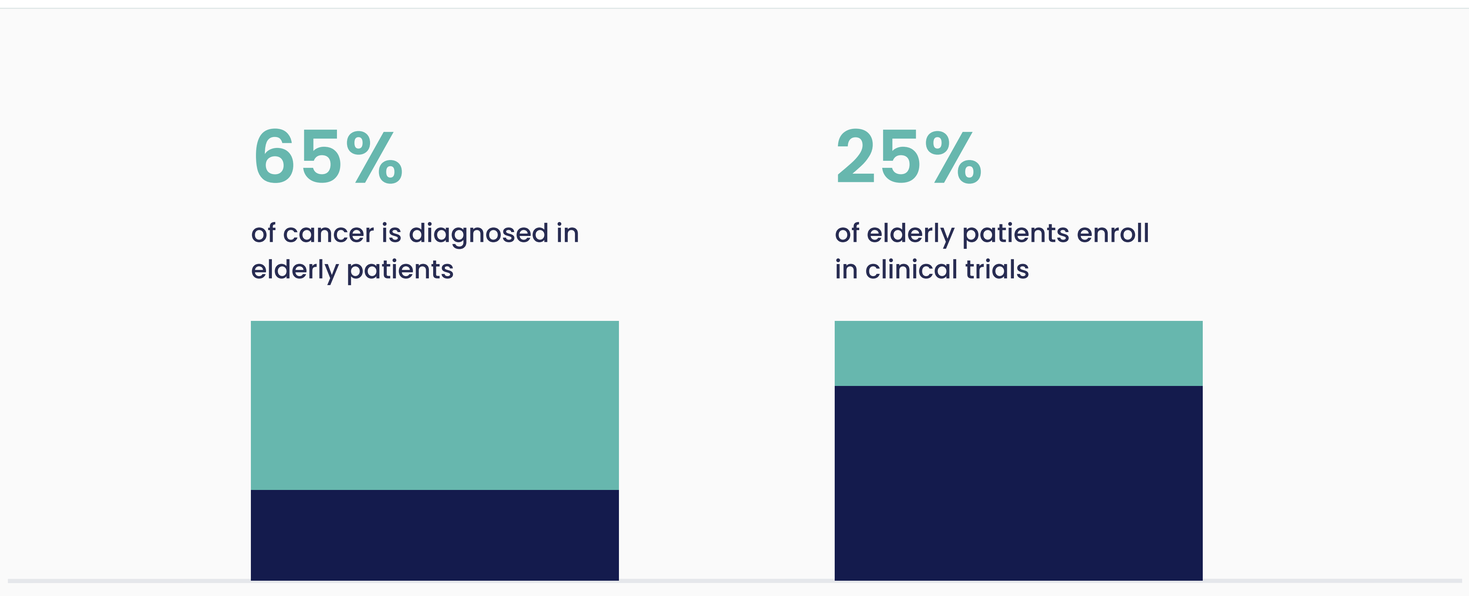
One predictor of low accrual and enrollment in clinical trials is when there are multiple trials enrolling the same patient population at a specific institution, often called competing trials [12]. Before initiating a site, sponsors and CROs should understand all studies undergoing enrollment at a certain institution to avoid competing trials.

Additionally, sites can delay enrollment for one study until enrollment is reached, or closes, for a competing study. These strategies can prevent the ethical decision of enrolling a patient for one study compared to another.

4. Diversity in oncology clinical trials

Minorities within healthcare have long since been underrepresented in clinical trials even after the NIH sponsored the Revitalization Act in 1993 that is meant to include women and minorities in clinical research more broadly [13]. There are many reasons that minorities are not included in oncology clinical trials and there are several strategies to increase diversity through patient recruitment. Given the oppressive history of clinical research on the African American and Hispanic/Latino community, the lack of trust can be a major contributor to a patient's decision not to participate in a trial [14]. In order to gain and give trust to persons of different ethnic or cultural backgrounds, a relationship between the patient and the provider must be stable. Similarly, the patient's concerns and hesitancy must be validated and addressed by the entire clinical research team. In addition, obstacles such as language barriers and cultural preferences should be considered for those of ethnic minorities. Consistency of care must be upheld from recruitment and consent to treatment follow-up in order to build and maintain trust throughout the duration of the trial.

Figure 3. Most cancer diagnoses occur in elderly patients but only a small percentage of elderly patients enroll in clinical trials.



Elderly patients are typically excluded or underrepresented in clinical trials, despite making up a majority of cancer diagnoses

Another deterrent for patient recruitment lies in the socioeconomic status of a particular population. A patient's social standing, whether that be education, income, or occupation, can greatly impact their ability or willingness to volunteer for a clinical trial [15]. Patients considered low socioeconomic status can have difficulty arranging time off work, plan for child care, or maintain reliable transportation to participate in necessary study activities. These constraints are further exacerbated for cancer patients when they are put in conjunction with their traditional infusions and disease management appointments. Therefore, modifications should be made to accommodate patients with barriers associated with low socioeconomic status. Examples of adaptations that can be made to alleviate these barriers include extended clinic hours, compensation for travel or facilitation of insurance coverage to manage adverse events whether or not they are study-related.

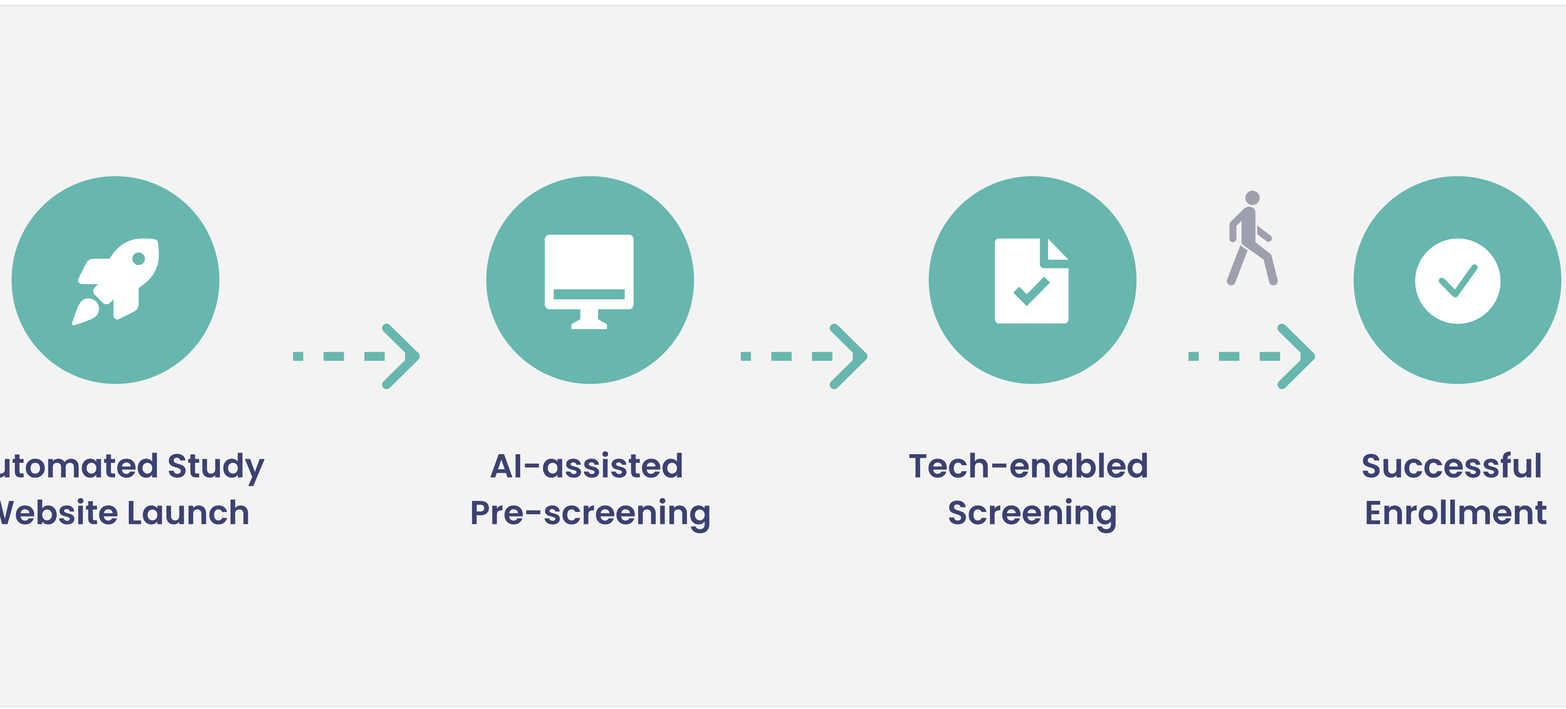
There is also the matter of including older individuals and both genders equally in clinical research. In terms of inclusion of elderly patients, there is data to support that although 61% of new cancer cases occur among the elderly, they only make up 25% of patients in clinical trials [16]. It was determined that one cause of under-representation of the elderly is due to comorbidities that make them ineligible for participation. Sometimes, the exclusion criteria of a study protocol puts limits on the age of a patient that are allowed to be included or there is a reluctance by the patient's physician to recommend them for an experimental treatment [17]. While there are good intentions to omit older patients based on safety, physician education and the broadening of comorbidity inclusion criteria could enhance elderly patient recruitment in oncology studies.

Men and women have also not been equally represented in oncology clinical trials. While some cancer types are gender-based, such as breast cancer or prostate cancer, there is still not an equal number of men and women participating in non-gender-based cancer trials. In colorectal cancer and lung cancer, older men were more likely to enroll in a clinical trial than older women [18]. One reason why younger women may not feel comfortable participating in clinical trials relates to their child-bearing potential. Oftentimes, when an enrolled woman is of child-bearing potential, there are significant precautions that must be taken to ensure that she is not pregnant while undergoing experimental treatment. This is a safety precaution since it is typically not clear how most new therapies affect a fetus but it can oftentimes deter women from participating in clinical trials. Despite these barriers, there is recent evidence that indicates women are becoming increasingly represented [19].

5. Advancements in oncology patient recruitment

In order to ensure a study is set up for success, the sponsor or CRO must prioritize initiating sites in a way that guarantees the target patient population can be accessed. Sites should be profiled by their previous enrollment record, the dedication of the investigator, and the qualification of their research staff [20]. Due to the increased challenges surrounding patient recruitment, there has been significant investigation into advancing techniques to identify and engage eligible patients. Typically, patients are identified when a clinical researcher matches a patient's information to the inclusion criteria of a particular study. However, this can be quite time consuming and contribute to the bottleneck of data readouts, which highlights the need for better methods.

Figure 4. Vial CRO has a unique approach to modernize the recruitment process to make clinical trials more efficient and cost-effective.



The Vial CRO is committed to implementing a patient recruiting strategy powered by technology. This platform uses multi-channel marketing techniques and powerful technology to identify and pre-screen the most eligible patients. Vial has tested over 30 marketing channels across clinical trials to determine the best methods. They have found that social media advertisements, direct mail flyers, radio commercials, and even phone call inquiries are some of the best ways to announce the need for patients to participate in a trial. From these various channels, patients can complete a screening questionnaire and healthcare experts from a US-based call center can determine if they qualify for an enrolling study. Each patient would speak with a US-based team member with extensive research experience and the call software utilized allows for streamlined workflows and efficient scheduling on behalf of clinical sites.

In addition, Vial uses EMR filtering software to find patients that qualify for a study already established at a particular institution. By inputting study criteria, the software can filter through the EMR and find patients with specific laboratory values, diagnoses, and previous treatments. Vial's novel processes has onboarded 90% of sites in less than 30 days which can lead to faster patient engagement and eases the burden on the clinical research team.

Another new method to circumvent traditional recruitment constraints is by utilizing artificial intelligence (AI) to identify these patients without tying up valuable researcher's time. One study showed that the use of AI in patient recruitment resulted in a 24%-50% increase in patient identification compared to traditional methods [21]. The study also showed that overall trial activities were performed more efficiently based on the increased time availability of study staff. Utilizing AI can decrease time from study start to completion of enrollment which saves significant study funds and valuable time of the staff.

Web-based applications have also been used to enhance patient recruitment. More than ever, patients are encouraged to take autonomy over their care. Since oncology studies have very specific and intricate criteria, patients oftentimes search for appropriate clinical trials through a search engine [22]. Therefore, it is wise for sites, hospital affiliates, and sponsors to regularly update which trials are currently enrolling and contact information so patients can determine if they are eligible. Similarly, there are recruitment companies that connect sponsors, CROs, and research sites with patients interested in participating in clinical trials. While patients identified by these outside vendors still need to be screened for eligibility, this can be a great way to engage potential subjects for recruiting studies.

Lastly, modifications to traditional methods can be just as effective at drawing patients to join a clinical trial. Traditional methods include appealing stipends, investigator identification, and pre-screening through the EMR. Increasing stipends to account for travel, lodging, and participation as well as building a trusting relationship with the oncologist that recommends a patient for the trial can go a long way in driving recruitment.

6. Patient retention and beyond

The challenges of clinical trial patient management do not end with recruitment. Once a patient is enrolled, it is also vital that a patient stays the course and participates in all activities throughout the follow-up period. Later phase trials have longer follow-up periods, which can make it difficult to retain patients throughout the entire study.

Strategies to improve participation during the follow-up period include stressing the importance of continued involvement to the patient early on. Scheduling the next activity at the current visit is helpful to ensure patients have a plan before they ever leave the clinic.

While telephone calls to patients can be hit-or-miss, one study observed that calling later in the afternoon or after work hours was helpful in reaching patients [23]. Similarly, patients that are non-responsive to telephone calls or mailers can oftentimes be more engaged by receiving information directly from their provider. The aforementioned study also showed that patients were 35% more responsive after receiving study updates about the interim data generated by their contribution. These data suggest that patients take great pride in their involvement to advance cancer therapies for the next generation.

Figure 5. By providing interim study results to patients participating in a clinical trial, there was a 35% increase in responsiveness throughout the follow-up period.

+35%

increase in responsiveness throughout the follow-up period.

7. Conclusion

Patient enrollment is the cornerstone of a successful clinical trial, but that's not to say it comes without its challenges. A cancer diagnosis is often a life-altering event for a patient, which makes volunteering for an oncology clinical trial all the more personal. Although there are many reasons why patients are not indicated for a study, are overlooked, or choose not to participate, it is the responsibility of the sponsor, CRO, and site staff to be proactive in their efforts to enroll eligible patients. By utilizing the many advancements in recruitment techniques and retention methods, oncology clinical trials can retain the patients necessary to ensure new cancer treatment can improve the life of everyone affected by this terrible disease.

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