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Impediments to Patient Recruitment in Clinical Trials

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Abstract

Recruiting patients into randomized clinical trials (RCTs) remains a serious challenge that may compromise evidence-based medicine's ability to study treatments. In this narrative review, four main domains affecting recruitment were identified: factors related to the RCT, clinician-related factors, patient-related factors, and influences from the community. Some obstacles to recruitment appear relatively easy to resolve: logistical considerations (for example, studies that pay for the patient's parking or other expenses), translated forms for non-native speakers, and preparation to deal with particular patient populations (such as pediatric patients or the disabled). Other obstacles relate to deep-seated individual attitudes about research (altruism versus personal safety) and distrust about the medical community and medical organizations. Suboptimal clinical organization and inadequate teamwork among colleagues can also impede recruitment efforts. In some cases, studies may be designed upfront to better accommodate the needs of the prospective patient population, particularly if special populations are involved, and researchers should take into account how attractive their RCT is to the targeted patient population.

Keywords: Clinical study; Clinical trial; Patient enrollment; Patient recruitment; Randomized controlled trial

Introduction

Randomized controlled trials (RCTs) provide the basis for clinical decision-making in modern evidence-based medicine. Despite their obvious value in determining efficaciousness of various therapies, RCTs are hampered by slow or failing efforts in patient recruitment. In a meta-analysis of RCTs, only 31% could complete enrollment within the planned enrollment period [1]. The majority of RCTs (63%) reported problems specifically in-patient recruitment and 41% had to delay their start because they could not enroll sufficient numbers of patients [1]. In the United Kingdom (UK), the House of Commons Select Committee on Science and Technology 2000 found that less than 5% of adults with solid tumors entered an RCT [2]. The National Cancer Institute estimates that only 4% of eligible patients actually participate in clinical trials and a Center Watch survey found that 90% of clinical trials failed to complete enrollment within their projected timeframe with a mean delay of six weeks [3].

In an analysis of 1,017 RCTs from various countries, the most frequent reason for study discontinuation was poor recruitment and discontinued trials were more likely to remain unpublished than completed RCTs (55.1% *vs.* 33.6%, odds ratio 3.19, 95% confidence interval, 2.29-4.43, $p<0.001$) [4]. Recruitment into RCTs may be challenging due to complex problems surrounding enrollment. In order to better develop strategies to facilitate patient recruitment, this narrative review aims to provide a short overview about the impediments to patient recruitment

Methods

The authors searched the PubMed databases for the following search term: "patient recruitment clinical trials" and limited results to articles published between September 2012 to September 2017 and published in English. This yielded 6,732 articles, most of which were about specific clinical trials and treated the issue of patient recruitment peripherally. The bibliographies of relevant articles were also searched.

Impediments to Recruitment

In a study of 21 multidisciplinary teams recruiting for breast cancer RCTs identified that impediments to recruitment involved three main domains: factors related to the RCT, clinician-related factors, and factors related to the patients [5]. We found community factors also played a role. The impediments are presented here as those related to the patient, the clinicians, the study itself, and the community. There may be some overlap among these four domains (Table 1).

Patient-Related Factors Impeding RCT Participation

It is useful to first consider reasons that patients report for enrolling in an RCT. In a qualitative study using semi-structured interviews of 11 individuals from three clinical research teams, the main motivation for an individual seeking to participate in an RCT was an altruistic objective to advance medical science [6]. In a survey of patients participating in an RCT for either ulcerative or inflammatory bowel disease, altruism played an important role in the decision to participate in a trial and most stated afterward that their overall experience as an RCT patient was positive [7]. This altruism may even supersede the patient's personal interests. In a study of 207 patients with Parkinson disease without dementia who over a five-year period entered an RCT, 63.7% said they did so to advance medical science, 56.0% said they wanted access to better treatment options, and 51.6% said they were acting on the recommendations of their neurologist [8]. A key reason that patients state for participating in an RCT is that they are interested in scientific progress, either because they are affected by the disease or they know someone affected [9].

Of course, self-interest may play a role, and some patients enter a study because they believe the RCT possibly offers to them an advantage, such as better treatment, access to new drugs or other therapies, or even the chance of a cure. This is particularly true for patients who are in situations where treatment options are severely limited [5,10,11].

Table 1: A short summary of the four domains that may contribute to difficulty in recruiting patients into RCTs.

Domain related to	Key Issues	Explanation	Comments
The RCT itself	Age	Older patients may categorical refuse RCT participation	
	Convenience	Logistical considerations, expense	Patients may balk at studies where they must pay for parking, child-care, and other expenses
	Fears	Taking new drugs, being exposed to experimental treatments	
	Informed Consent	May bottleneck registration process	Patients may not always read and/or understand Informed Consent
Clinician	Clinical versus Research Duties	Healthcare professionals may feel torn between two conflicting roles	
	Dedicated Study Coordinator	A dedicated coordinator offers continuity and bridges gap between research and clinical practice	May be helpful in achieving enrollment goals
	Organizational Design	Teamwork and communication among healthcare professionals must be supported	Tools are available
	Resources	Limited human resources can slow enrollment	Documentation and paperwork can be overwhelming to small teams
Patient	Special Populations	Cognitively impaired, disabled, pediatric, and many other patient populations present special challenges	Informed Consent can be difficult
	Demanding or Long-Term Studies	Complicated or long-term studies are less attractive to patients	Home visits may be helpful for some long-term studies
	Highly Restrictive Inclusion Criteria	Rare conditions; finding a homogeneous group in a heterogeneous population	
	Media	Negative image of clinical studies, big pharma, modern medicine can deter patients	
	Placebo-controlled Studies	Patients may want to be assured they are getting active treatments	Active-comparator trials may be helpful
Community	Bias	Clinicians may preferentially approach or enroll certain patients	Bias may be unintentional
	Community Involvement	Lack of outreach into specific patient populations may hinder enrollment	Partnerships in the patient population communities can be helpful
	Cultural and Ethnic Considerations	Lack of trust in medical establishment or specific procedures among certain groups may hurt enrollment	Cultural sensitivity may help enrollment
	Language Barriers	Lack of translated materials and multilingual staff can rule out certain otherwise eligible patients	Certain groups may be under-represented in RCTs because of language barriers
	Mobility	Urban populations may be more mobile and less rooted in the community	Community identification can help support RCT enrollment
	Physician Identification	Patients who do not know or do not particularly trust a physician may hesitate to enroll in a study	
	Research Fatigue	Some research centers may try to attract the same patient populations over and over again	
	Trust in Medical Establishment	Patients who do not trust in the hospital or modern medicine are unlikely to join an RCT	Such prejudices may be personal, familial, or cultural
	Urban Sprawl	Congestion, commuter times, parking fees may deter some patients	Studies that require regular visits to clinics in high-traffic areas may suffer

Age

Advanced age may be a factor ŧ for refusing to participate in an RCT. A study of 408 patients recruited for participation in an RCT of arthritis education evaluated patients by their level of refusal. A Stage 1 Refuser declined participation during the initial screening interaction. A Stage 2 Refuser initially expressed interested but neither completed the baseline survey questionnaire nor provided informed consent. Enrollees were the group that expressed interest, completed the questionnaire, provided informed consent, and entered the study. In this survey, 47.3% of patients were Stage 1 Refusers, 19.9% Stage 2 Refusers, and 32.8% Enrollees. Significantly more patients ≥ 65 years of age were Stage I (58% *vs.* 37%, p=0.0003). Educational attainment, working status, insurance, and sex were not found to influence outcome [12].

Convenience

Logistical concerns can cause a person to decline participation in a clinical trial even if he or she is otherwise qualified and willing [6]. About a third of patients (34.1%) who were eligible to participate in an RCT for Parkinson disease declined because the trial was inconvenient to them) [8].

Fears

Some individuals refuse to participate in an RCT because they harbor one or more fears: taking a new drug, having side effects, being exposed to experimental treatments, having their privacy compromised (for example, by storing genetic information), and new diagnoses that might emerge with extended evaluations [6]. Some patients are fearful of allocation after randomization, thinking they might not get the treatment they wanted or that they might be subjected to unnecessary or harmful treatment [5]. Some patients do not want to be a "*guinea pig*" [10]. Some patients do not want to risk getting a placebo [13]. Some patients have very specific ideas and preferences about the treatment they want to receive and are afraid they lose control over their care by entering a study.

Informed Consent

In a focus group study of clinical research associates tasked with recruiting patients into various Phase III oncology studies, most identified that their key role in the recruitment process was the ability to present and explain informed consent to the patient, in terms of both content and presentation style. These clinical research associates reported that they thought their degree of success in recruiting patients was directly related to these skills [11]. Informed consent is an established ethical and legal requirement for participation in an RCT, yet there is no validated instrument to ascertain whether or not patients truly understand the consent agreement prior to study enrollment [14]. An evaluation tool has been proposed for Participatory and Informed Consent and is described in the literature [14].

However, an in-depth discussion of benefits and risks of the trial and a thorough examination of the informed consent paperwork can slow down the interview process and bottleneck patient enrollment [6]. When ethics committees or other entities required patients to fill out long and very detailed forms, investigators sometimes reported that patients found this off-putting [6]. A particular concern with informed consent paperwork is that patients do not necessarily read it. In a study of researchers who submitted to semi-structured interviewers, one participant estimated that about 98% of patients enrolling in RCTs do not read the informed consent form and instead relied on the investigator or coordinator to mention the key points [6]. The use of illustrations and better "readability" have been mentioned as factors that might improve the informed consent form in terms of making it more patient friendly [6].

Participation in Other Studies

Although participation in one study has been proposed as being a potential factor that might make a patient more likely to participate in another study, the opposite may be true in that participation in one research study may be an obstacle to participating in another [12]. In some cases, participating in one study within a specified time period

too great (71%) [22]. These clinicians thought that if these obstacles could be overcome, enrollment might increase in studies by up to 20%.

Study-Related Factors Impeding Patient Participation

Studies may offer such highly specific inclusion and exclusion criteria that it severely limits the potential pool of eligible patients, impeding recruitment efforts. In a systematic review of 172 RCTs discontinued for poor enrollment, one of the most frequently mentioned reasons for study failure was the overestimation of prevalence of eligible potential participants [23]. Other studies may suffer poor enrollment if the enrollment period is short [24]. Certain types of patient populations have inherent enrollment difficulties, such as studies of pediatric patients, cognitively impaired patients or patients in emergent settings. Moreover, study design can impede enrollment when it imposes too many inconveniences for the patient. Examples of reducing patient inconveniences presented in the literature include: allowing patients to have blood tests or lab work done in their community (or by their primary care physician), evening and weekend appointments, and reimbursement for transportation expenses to and from the study center [6]. Recruitment strategies should be considered as the study is being conceived and planned, including making the studies as patient-friendly as possible [6].

Cognitively Impaired Patients and Special Populations

Studies involving patients who may be cognitively impaired, elderly, disabled, or lack motor skills can also meet with extreme recruitment challenges. Indeed, some studies (such as studies of Alzheimer disease) may seek to enroll patients who are unable to provide their own informed consent. In a cross-sectional study of 90 Parkinson disease patients (30 each grouped as normal, borderline, and impaired), only 17% and 3% of the impaired patients were deemed capable of understanding informed consent for drug and surgery trials, respectively. In the borderline group, 67% and 57% were considered capable of providing informed consent for drug and surgery trials, respectively [25].

Demanding or Long-Term Studies

Recruitment becomes more difficult when the patient is required to make a significant commitment to the study in terms of time and/or intensity of participation. Studies of short duration, with a simple and straightforward protocol, and asking only for a few visits find it easier to win recruits than longer, more complex studies, which require ongoing visits over a long period of time.[6] In a study of 108 partners of patients with very mild to severe Alzheimer disease, study design issues were often cited as reasons to decline study participation. Home visits to the patients increased the likeliness of participating in a trial by 27% [26]. Offering home visits combined with low risk associated with the study and a higher chance that the patient would receive active treatment predicted willingness to participate in the study of 60% [26].

Highly Restrictive Inclusion Criteria

Recruitment difficulties may be inherent in efforts to select a highly homogeneous sample from a heterogeneous disease population, for example, finding a specific subset of diabetes or arthritis patients [16]. Extensive exclusion criteria may also rule out otherwise willing patients. Study designers and clinicians may overestimate the centers' access to certain highly specific patient populations required for RCTs.

Media

The media sometimes do not portray medical research in a positive light, at times sometimes focusing on stories about research failures, fraud, corporate greed, "big pharma," and mistakes. This leads to the conclusion that RCT participants are "guinea pigs" rather than noble individuals necessary to advance medical science [3]. It is not clear if and to what extent negative portrayals of clinical research may influence patient participation.

Placebo-Controlled Studies

While placebo-controlled studies are highly respected in the medical community, patients often express a desire to

may be an exclusion criterion. This is particularly the case when studies run concurrently and patients may feel overwhelmed by the demands of reporting for more than one trial. Researchers are encouraged to be mindful of conflicting demands on the patient pool when recruiting patients who may already be committed to another study [12].

Clinician-Related Factors Impeding Patient Participation

Physicians, nurses, and other healthcare professionals all play a role in recruiting patients into clinical trials. Patient recruitment involves identification of potential study participants, explaining the study to them, and then obtaining an informed consent. These can be formidable challenges in the already hectic healthcare setting where clinicians may feel overburdened attending to the most urgent clinical tasks.

Clinical *vs.* Research Duties

The interface between clinical activities and research may be a source of conflict for some clinicians tasked with RCT recruitment. In a study of 32 physicians and 40 nurses or other healthcare professionals actively recruiting patients into a variety of trials, these conflicts were exposed when, for example, physicians might have been torn between their desire to enroll an appropriate patient into a study (to advance research) but wanting to safeguard that patient (as the caregiver)[15].When a physician has a clear preference for the patient's treatment, that may also serve as an impediment even if the patient is an appropriate study candidate and is agreeable to study participation. The conflict between clinical care and research is even more pronounced among nurses, who typically tried to define their role as caring nurse first, subordinating their research activities [15].

Dedicated Study Coordinator

Not all RCTs have the benefit of a dedicated study coordinator or study manager. Study coordinators can play an essential role not just in terms of day-to-day operations and administrative tasks such as data collection and transmission, but also in terms of patient recruitment. A study coordinator who understands the disease state, study objectives, and inclusion/exclusion criteria can be invaluable to the study if he or she is effective at sharing this information to patients in an unbiased way. The continuous presence of a study coordinator can be reassuring to patients who choose to participate in the study. Coordinators can also be the bridge to help form teams among researchers, reach out to the local community organizations, and engage healthcare professionals [16].

A study coordinator involved in study recruitment can also help to establish appropriate distance from the physician, particularly if the patient has reservations about the study but is unwilling to challenge the recommendations of a physician held in high regard [16]. In a study of 114 RCTs, the majority of trials that were able to successfully meet their recruitment goals had a dedicated study coordinator [17].

Organizational Design

A series of semi-structured interviews conducted in the UK among principal investigators, other physicians, and research assistants (n=11) found that adequate staffing and organizational design were important to successfully identify potential study candidates and to optimize recruitment efforts once the proper patients were identified [18]. In a study of seven healthcare professionals in the United States who were active in recruiting patients into RCTs, the main impediments were organizational [19]. In particular, the crucial role of teamwork and communication between the clinical and research professionals emerged in a series of semi-structured interviews (n=21) at three centers conducting studies in surgical oncology [20]. Techniques have been developed to help facilitate teamwork and clear recruitment obstacles at this level, such as the Quanti-Qualitative Appointment Timing [21].

Resources

In a survey conducted among physicians, nurses, and administrators involved with clinical studies in Germany, clinical trial participation was limited by human resources (74%) limited technical resources (52%), and that the burden of documentation imposed by clinical trials was

be in the group administered an active agent rather than placebo [8]. This suggests that active-comparator trials may be more appealing to patients. In many cases, regulatory or other requirements necessitate a placebo-controlled RCT.

Community-Related Factors Impeding Patient Participation

Cultural sensitivity to the needs of specific ethnic groups and populations may be required to encourage recruitment into clinical trials. Many studies would benefit from an ethnically diverse patient population, so efforts should be made to recruit patients from under-represented groups. Many factors may impede such desired diversity.

Bias

Bias can taint the results of a study and safeguards against bias (although imperfect) are important to assure the quality and applicability of study results. Selection bias, for example, may be controlled by blinding the study [27]. However, bias may still intrude if recruiters enroll disproportionately low numbers of certain groups. For example, patients from certain ethnic, racial, and socioeconomic groups may have limited access to specialized healthcare and thus may not be even considered for recruitment in an RCT. Those under-represented in clinical trials tend to be minority patients, geriatric patients, rural residents, and individuals of low socioeconomic status. In a review of the literature (n=65 studies) found that these groups faced numerous barriers to recruitment into oncology RCTs. Furthermore, even if recruited, these patients might face other obstacles that would prevent study participation, such as lack of insurance, no reliable transportation, and inability to bear the incidental expenses (such as childcare) [28]. In countries with national healthcare, the insurance issue does not come into play, but transportation and incidental expenses might.

Community Involvement

Recruitment may be facilitated when a community has a specific health need and clinicians can earn their trust for research efforts. This occurred in South Dakota for a study of the ataxia telangiectasia mutated gene associated with cancer, which disproportionately afflicts American Indians. Building partnerships within the community has helped facilitate recruitment efforts, in particularly as community members saw the research as important for their group [29]. Conversely, when clinicians have no particular inroads to a local community, patient recruitment can be particularly difficult.

Cultural and Ethnic Considerations

Ethnicity is an important factor in patient recruitment and may affect the degree of trust individuals have in the medical establishment [30]. For example, in focus groups related to smoking cessation interventions, African-Americans and Native American participants reported feelings of mistrust and/or negative experiences with physicians which would discourage them from RCT participation [31]. In other cases, some ethnic groups viewed the role of medicine differently than RCT organizers. For instance, Hmong and Vietnamese participants trusted physicians, but did not see them as a resource for quitting smoking, because they had low knowledge levels about the role of pharmacological therapy in smoking cessation [32] On the other hand, Native Americans may actually hold negative views about pharmacotherapeutic interventions to quit smoking [31]. Thus, cultural and ethnic sensitivity may be needed to improve patient recruitment.

Language Barriers

In a series of semi-structured interviewers of 11 clinical researchers in the UK tasked with recruiting patients into studies, it was revealed by several participants that patients without a good grasp of English are unable to participate in many studies because few studies provide funding for interpreters and translators [6]. In fact, willing study candidates may be turned away solely because of the language barrier [6]. In a British review supplemented by interviews of 15 South Asian RCT participants, 25 health professionals, and 60 South Asians who did not take part in an RCT, the language barrier was reported as a common reason for low participation of South Asians in clinical trials [33]. These latter patients were sometimes not even

told about RCTs; this is a form of passive exclusion that may occur in part because clinicians are too busy to devote the extra time and resources to recruiting patients of different cultures who do not speak English well.[33] In a British study of 1,682 patients (36% South Asians, 26% white, 11% black and other ethnicities, 27% no ethnicity cited), 56% said that they had no awareness of local research efforts [34]. Patients themselves may be aware of their exclusion from RCTs. In semi-structured interviews of South Asians who participated in various RCTs in England (n=15), participation reasons included altruism to advance medical science but also an awareness of the under-representation of South Asians in such studies and a desire to rectify this [35].

Mobility

In addition to ethnic populations, there are also regions characterized by highly mobile populations. These urban populations may not wish to commit to a long-term study or who might move away before the study is completed. Further, mobile populations typically feel less rooted and loyal to the community and thus may not participate in an RCT because they do not feel particular trust in their physician or connection to a local research center.

Physician Identification

In some communities, it may be difficult for a physician-recruiter outside of that population to enroll patients into an RCT. In some cases, a lack of physician-recruiters may translate into a lack of patients from that same community. For example, Latino physicians (defined as people of Cuban, Mexican, Puerto Rican, South American, Central American, or other Spanish origin or culture regardless of race) are significantly less likely to be involved in RCTs than white physicians and in a survey of 695 physicians grouped by ethnicity, Latino physicians placed less scientific value on RCTs than white physicians [36]. Latino physicians are also more likely to practice in community hospitals than university hospitals, where more studies are likely to be carried out [36]. For that reason, it may be difficult for non-Latino physicians to recruit Latinos into their studies.

Research Fatigue

Communities with university hospitals or other large research organizations can create a community "fatigue" in terms of RCTs in that studies likely go on all of the time and patients may be repeatedly approached for participation.

Trust in Medical Establishment

Trust in medical research was found to be lower among African-American physicians and physicians of all groups who had a high proportion of minority patients. Trust in medical research by the physician (regardless of race or ethnicity) seemed to mirror the trust level of his or her patients [37]. Thus, trust must be built up with these physicians and their patients to gain greater access to these patients.

Urban Sprawl

Communities with urban congestion may also set up difficulties for patients who do not wish to spend long times traveling back and forth to the center or who may not want to deal with city traffic on a regular basis [6].

Discussion

One of the biggest and most costly impediments to RCTs remains patient recruitment. Since inadequate patient enrollment and participation can jettison an otherwise costly and important study, it seems worthwhile to consider the many things that can thwart effective patient enrollment. To that end, a narrative review of the literature found study-related, patient-related, clinician-related, and community-related factors that might stall or block patient enrollment.

Since patient enrollment is both crucial and a known pitfall, it seems incumbent upon study designers to consider patient enrollment in the conceptual phase of study design. Patient-friendly study features-such as reimbursement for childcare on appointment days, home visits or lab tests that can be done locally rather than at the center—should all be considered. Studies should be designed in ways that do not overtax busy patients, in that it appears

from the literature that inconvenience can cause an otherwise willing patient to reject study participation.

Electronic medical records may be a boon to clinical trials, in that, when properly implemented, they can help study centers sort through patient data to identify potential study candidates. The Patient Identification Platform (Patient iP, Rochester, New York, USA) is such an electronic tool to create visual analytics of thousands of patient records. Other applications may further reduce the time needed to manually sort through potential records. However, validation of diagnoses is often a necessary and important part of quality assurance in clinical studies.

Diversity in clinical trials is a laudable goal but one that cannot be achieved without making express efforts to include specific minority populations. In general, African-Americans, Latinos, and women are under-represented in RCTs [38-39]. The problem may be worse than suspected because not all RCTs report racial and ethnic demographics [39]. In a review of dermatologic RCTs in the U.S. that did report race and ethnicity (n=13,681),74.4% of study participants were white [40]. While a lack of diversity among clinical trial participants is not an impediment to recruitment per se, it suggests that there are untapped patient populations who may benefit from RCT participation and medicine certainly will benefit from studies that enroll more women and minorities. There are numerous potential ways to address this lack of diversity in clinical trials, including culturally sensitive outreaches to the target communities, building trust with patients, having patients recognize the value of RCTs and their participation in them, and a willingness to overcome obstacles to reaching that community, such as offering translated materials and interpreters or creating studies that facilitated participation of these minority groups (such as those that might reimburse for transportation to and from the study center).

Our paper exposed an area of difficulty in clinical research that needs to be highlighted and which may play a larger-than-suspected role in limiting patient recruitment to studies, in that many study investigators have dual identities in these studies. On the one hand, investigators are trained clinicians and have a professional responsibility to the care and well-being of their individual patients. On the other hand, these same investigators are trying to recruit patients into a study to advance scientific knowledge. In some cases-particularly when the clinician had formed an opinion as to the risks and benefits of a particular RCT-the clinician may feel conflict between these two roles.

This speaks to the role of a dedicated study coordinator, a person who works over the entire course of the clinical trial, from patient identification to recruitment to enrollment and throughout the study. In some ways, the study coordinator serves as the "anchor" for patients participating in the trial. Studies with such coordinators often seem to overcome impediments to recruitment in that there is a single person who is able to identify potential study participants and explain the study effectively to them in an unbiased manner. Recruitment materials should be patient friendly but still fully disclose risks and benefits of the study. To the extent possible, illustrations and diagrams should be incorporated in these materials to facilitate learning. Investigators should consider whether more diverse patient populations can be recruited with outreach efforts to local community leaders or translated study materials.

In our review of the impediments to RCT patient recruitment and enrollment, it seems that most of the issues are things that can be overcome with resource allocation, revised materials, awareness of the obstacles, and other specific efforts. The knowledge that patient participation is often based on altruism and a desire to advance medical science is also helpful, in that patient materials may explore these themes along with the risks and benefits of clinical trials. Although it goes beyond the scope of this article to discuss the issues inherent in informed consent, clear and patient-friendly informed consent is needed so that patients understand the study objectives and any potential risks to themselves as well as possible benefits.

Conclusion

RCTs are a mainstay of modern evidence-based medicine but identification, recruitment, and enrollment of patients remains one of the main obstacles to successful

study completion. Numerous factors adversely affect patient participation in RCTs and these factors can be grouped into four domains: those associated with the study, the clinicians, the patients themselves, and their communities. A thorough knowledge and consideration of these factors in the design phase of an RCT may facilitate patient participation.

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