



Clinical trials recruitment planning: A proposed framework from the Clinical Trials Transformation Initiative

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ABSTRACT

Patient recruitment is widely recognized as a key determinant of success for clinical trials. Yet a substantial number of trials fail to reach recruitment goals—a situation that has important scientific, financial, ethical, and policy implications. Further, there are important effects on stakeholders who directly contribute to the trial including investigators, sponsors, and study participants. Despite efforts over multiple decades to identify and address barriers, recruitment challenges persist.

To advance a more comprehensive approach to trial recruitment, the Clinical Trials Transformation Initiative (CTTI) convened a project team to examine the challenges and to issue actionable, evidence-based recommendations for improving recruitment planning that extend beyond common study-specific strategies. We describe our multi-stakeholder effort to develop a framework that delineates three areas essential to strategic recruitment planning efforts: (1) trial design and protocol development, (2) trial feasibility and site selection, and (3) communication. Our recommendations propose an upstream approach to recruitment planning that has the potential to produce greater impact and reduce downstream barriers. Additionally, we offer tools to help facilitate adoption of the recommendations. We hope that our framework and recommendations will serve as a guide for initial efforts in clinical trial recruitment planning irrespective of disease or intervention focus, provide a common basis for discussions in this area and generate targets for further analysis and continual improvement.

1. Introduction

There is universal recognition that patient recruitment is a key determinant of success for clinical trials. A 2015 analysis of registered trials revealed that 19% were closed or terminated early because they could not accrue enough participants [1]. Trials can also experience significant delays related to recruitment. As much as 86% of clinical trials do not reach recruitment targets within their specified time periods [2–4]. Data suggest that study timelines have potentially doubled beyond planned enrollment periods due to low recruitment rates [5]. Failures in meeting recruitment goals have important scientific, financial, ethical, and policy implications [6–8]. Intangible

consequences, from disappointment in lost opportunities to ethical concerns arising from not completing the work, have demoralizing effects on investigators, participants, and sponsors. Perhaps most important, the inability to meet recruitment and overall study goals affects patients by hindering efforts to more effectively diagnose, treat, or prevent disease. Despite efforts over multiple decades to systematically describe barriers to identifying and enrolling study participants [4, 9], recruitment challenges persist.

In a review of factors that potentially contribute to recruitment success, researchers have examined trial design, study staff issues, recruitment strategies, and the need to revise recruitment targets and timelines [10–12]. Others have looked at enhancing recruitment and

Abbreviations: CTTI, Clinical Trials Transformation Initiative; ICD, International Classification of Diseases; QbD, Quality by Design; PCORI, Patient-Centered Outcomes Research Institute; ROI, return on investment; SWOT, strengths, weaknesses, opportunities, threats; USAID, United States Agency for International Development

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retention by giving greater consideration to participant contact and convenience, financial support for patient recruiters, incentives and compensation for participation, and other human factors [13]. Processes, policies, and resources at clinical trial sites are also among the factors influencing recruitment even when there is sufficient availability of patients [14, 15]. A critical time in a clinical trial's life cycle—the upstream planning and design phase—may be the best target for positively influencing downstream recruitment efforts. However, given the layers of complexity involved in designing and executing a “recruitable” trial [16, 17], effective planning will require input not only from those who have traditionally led this effort—clinician—investigators, biostatisticians, and study team members—but also from a range of stakeholders including patients and patient advocacy groups, sponsors, funders, site staff, and healthcare providers.

The scope of factors that affect recruitment to clinical trials suggests a fundamental need for more inclusive and proactive approaches that extend beyond common study-specific strategies. To advance a more comprehensive approach to trial recruitment, the Clinical Trials Transformation Initiative (CTTI) convened a project team to examine the challenges and to issue actionable, evidence-based recommendations for improving recruitment planning. These activities were conducted as part of CTTI's mission to develop and drive adoption of practices that will increase the quality and efficiency of clinical trials [18]. We describe our multi-stakeholder effort to develop recommendations and tools for more effective clinical trial planning in order to reduce barriers to recruitment. At its core, this work is intended to promote thoughtful discussion and implementation of practices related to trial recruitment at the outset of the planning phase—even as early as development of the key research question.

2. Methods

The CTTI Recruitment Project Team involved a multi-stakeholder group of experts in clinical trial recruitment challenges representing trial sponsors, patient advocacy groups, federal agencies, academic institutions, and clinical research professional organizations. The goals of the project were to describe the barriers and solutions for identifying, engaging, and enrolling patients in trials, and to identify methods and strategies to move recruitment planning upstream in the study development process, thereby facilitating more efficient recruitment. In accordance with CTTI project methodology [19], the team employed four main strategies—literature review, survey, planning framework, and expert meeting—with the ultimate goal of achieving actionable recommendations for clinical trial recruitment planning.

2.1. Literature review and survey

We first evaluated the literature to identify barriers and potential solutions to successful, effective recruitment and retention. PubMed®, Embase® and the National Cancer Institute's AccrualNet™ were used to search for peer-reviewed systematic reviews, limiting to those published in English between 2003 and 2013. Data were abstracted on 46 articles meeting predefined eligibility criteria (Supplement 1).

Among the findings of the “review of reviews” was that data are limited for how successful trialists have been in overcoming recruitment barriers, or how barriers have affected the outcome of trials. Some facilitators of recruitment are promising, including use of an open rather than blinded trial design, use of opt-out procedures, telephone reminders to non-responders, and financial incentives for participants—but the evidence for these and other strategies remains limited. Thus, to further examine key challenges of recruitment, the team created a web-based survey to elicit from stakeholders their (1) experience with various recruitment methods, (2) methods to overcome perceived barriers, (3) knowledge of effective partnerships to increase recruitment, and (4) outlook on the future of clinical trial recruitment. The survey was distributed to clinical trial stakeholders that included

patient advocates, site staff, investigators, and sponsors using a “snowballing” sampling method in July and August 2014. Data from 90 completed surveys were included in the analysis. Detailed methods and results of the survey are described elsewhere [20].

2.2. Framework development and expert meeting

Team discussions after the survey centered on developing a strategy to change recruitment paradigms more broadly. Survey findings suggested that, rather than focusing on specific recruitment activities and tools, stakeholders would benefit from a strategic framework to guide a comprehensive recruitment plan for their clinical trial. A major theme from the survey was dissatisfaction with an ongoing pattern of addressing recruitment problems as they arise instead of preventing them. Our framework thus sought to identify elements common to clinical trials that could be subject to earlier planning as well as to failure-examination and root-cause analyses. We also wanted to draw parallels to other CTTI activities, particularly those related to Quality by Design (QbD), aimed at improving trials at earlier stages [21, 22]. The framework delineates three areas essential to recruitment planning efforts: (1) trial design and protocol development, (2) trial feasibility and site selection, and (3) communication. The team recognized that these areas were applicable irrespective of sponsor or disease focus and potentially allowed for broader application of any resulting recommendations and tools.

The team next convened a multi-stakeholder expert meeting in November 2015 to obtain wider input on the recruitment planning framework and potential recommendations. This meeting was conducted among 60 stakeholders representing professional service organizations, clinical research organizations, clinical investigators, professional societies, drug and device industries, federal government, patient advocacy groups, and academia [23]. Findings and key themes from the survey and focus group discussions were presented. Attendees were encouraged to discuss and challenge project team assumptions and to identify remaining gaps and implementation challenges. In breakout sessions, attendees refined the elements of the framework and fleshed out specific recommendations aligned with each of the three themes. The team used discussion from the meeting to further refine recommendations through an iterative process of consensus-building that focused on core values of inclusiveness, shared control, and flexibility.

3. Results

Following the expert meeting, the team synthesized all multi-stakeholder input into a set of actionable recommendations for efficient and effective clinical trial recruitment planning. These were published on the CTTI website in May 2016, along with four tools to facilitate collaborations [24]. Fig. 1 illustrates the CTTI framework for the three target areas.

3.1. Actionable recommendations

Table 1 briefly describes the final recommendations with practical steps for each planning element (full details are available at the CTTI website [24]). Next, we offer some key considerations for sponsors, investigators, and other stakeholders that are not necessarily specific to a recommendation.

Trial Design and Protocol Development. These recruitment planning elements center on sources of input, design elements, and activities that drive recruitment. These elements have an impact on recruitment but cannot easily be revised after a study launches.

Trial Feasibility and Site Selection. These planning elements encourage the proactive consideration of trial feasibility and site selection issues earlier in the timeline because of their dependency on

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