



## 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

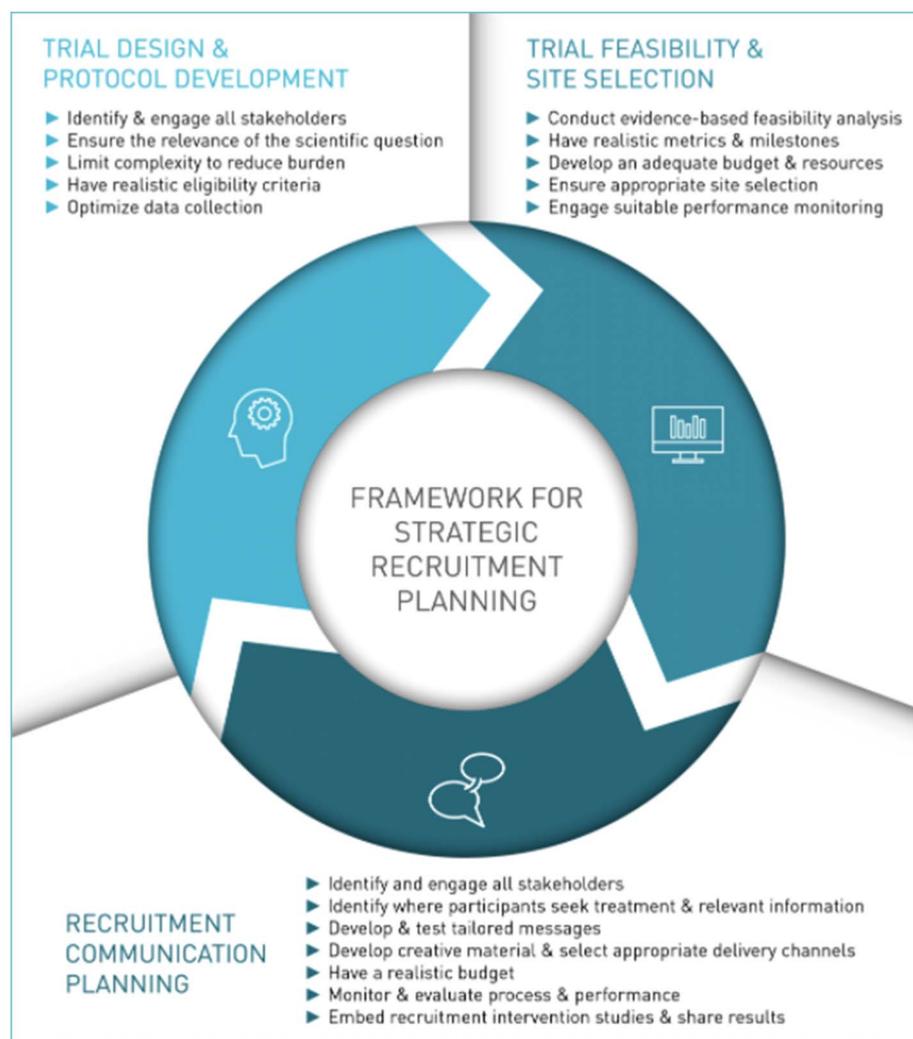


Fig. 1. CTTI Framework for Strategic Recruitment Planning.

people and factors that are difficult to change after the trial is launched. While many of these are frequently considered in planning, obtaining more in-depth or broader perspectives may be required to help inform decisions. Given the ultimate reliance on sites to achieve recruitment targets, these elements focus on incorporating better partnerships to ensure trial viability and the use of data, tools, and evidence to better identify participant cohorts and sites (such as electronic health record queries, ICD-9 and ICD-10 deidentified records, and geo-targeting disease data).

*Recruitment Communication Planning.* The clinical trial enterprise often takes communication as an assumed function in the trial development phase. Yet, it may be unclear how to fully engage an audience for a deeper understanding of their attitudes and perspectives. To successfully complete enrollment for a trial, it is essential that study teams are aware of stakeholder needs in order to maximize their engagement and support. With a data-driven approach, it is possible to elicit these insights. By developing more engaging messages deployed through the right channels, study teams will gain the attention of the target audiences.

#### 4. Discussion

CTTI's strategic recruitment planning recommendations define common recruitment challenges that can and should be targeted in the early stages of trial planning and development. Further, the recommendation's three organizing themes—protocol design, site selection, and communication—have the potential to create synergies in

overall recruitment planning. For example, patients can inform the importance of the study question, while study sites can provide insights on the numbers of individuals who are potentially eligible to answer the question. In turn, both groups can work together to create the optimal strategy for reaching out to patient and provider communities and to maximize the effectiveness of the messages. Examples of these strategies demonstrate the feasibility and potential of the approach.

Active engagement of diverse stakeholders interested in protocol design is aligned with “participatory design,” in which patients contribute to how the study is developed and conducted. Some models describe a community engagement framework that addresses the values and operational needs of communities [25]. The Patient-Centered Outcomes Research Institute (PCORI) promotes such patient engagement in the United States [26, 27], and in the United Kingdom, efforts like INVOLVE have presented novel participatory approaches [28]. Others report using technology for collaborative clinical trial protocol-writing that incorporates participatory design concepts [29, 30]. The Veterans Health Administration has been increasingly engaging its sites that provide care for their Veteran participants in the design and feasibility assessments for its cooperative studies [31]. Other collaborative efforts, such as the PCORnet Clinical Data Research Networks and Trial Innovation Network, emphasize engagement in recruitment and retention as well as evidence-based site selection and feasibility using available electronic health record data networks for eligible cohort discovery and collaborator identification [32].

One international effort, supported by the United States Agency for International Development (USAID) and others, developed a handbook

**Table 1**  
Recommendations for efficient and effective clinical trial recruitment planning.

Recommendation	Practical steps
<i>Trial Design and Protocol Development</i>	
Identify and engage all stakeholders as equal partners in the process	<ul style="list-style-type: none"> <li>● Include as diverse a group of interested parties including patients, caregivers, patient groups, investigators, sponsors, funders, site staff, key opinion leaders, and providers.</li> <li>● Incorporate their input and include appropriate partner representation on committees (e.g., advisory, steering, protocol writing).</li> </ul>
Ensure the relevance of the scientific question to stakeholders	<ul style="list-style-type: none"> <li>● Determine the relevance of the scientific question and impact at trial conclusion (e.g., filling unmet need, relevance of outcomes to patients, generalizability).</li> </ul>
Limit protocol complexity to reduce the burden of participation	<ul style="list-style-type: none"> <li>● Reduce procedures to those directly related to the scientific question.</li> <li>● Consider invasiveness and risks.</li> <li>● Limit activities that create additional work for sites and patients.</li> </ul>
Develop realistic eligibility criteria	<ul style="list-style-type: none"> <li>● Identify and eliminate items that are not necessary for ensuring safety of participants.</li> <li>● Eliminate items that are not directly relevant to answering the primary research question.</li> </ul>
Optimize data collection to only what's necessary to maintain patient safety and answer the scientific question	<ul style="list-style-type: none"> <li>● Collect only the data necessary to maintain participant safety and/or address the primary and secondary objectives.</li> </ul>
<i>Trial Feasibility and Site Selection</i>	
Conduct an evidence-based trial feasibility analysis	<ul style="list-style-type: none"> <li>● Do an environmental scan or SWOT (strengths, weaknesses, opportunities, threats) analysis. Targets may include competition, policy, seasonal fluctuations, awareness, disease stage and rarity, satisfaction with current therapies, and economic concerns.</li> </ul>
Establish realistic metrics and milestones	<ul style="list-style-type: none"> <li>● Incorporate site activation, screening, and enrollment factors.</li> <li>● Map out anticipated events to identify potential pitfalls and bottlenecks in setting expectations.</li> <li>● Use historic and benchmarked data to estimate realistic timelines.</li> </ul>
Develop an adequate budget and resources	<ul style="list-style-type: none"> <li>● Develop an initial recruitment budget that accounts for appropriate factors and appropriate patient outreach.</li> <li>● Emphasize site activation timelines and realistic enrollment periods in resource determination.</li> </ul>
Ensure appropriate site selection	<ul style="list-style-type: none"> <li>● Develop an ideal site profile that includes investigator experience, site capabilities, site infrastructure, institutional resources, and target population access.</li> </ul>
Engage in suitable site performance monitoring	<ul style="list-style-type: none"> <li>● Develop a plan to regularly meet with sites.</li> <li>● Schedule timely teleconferences/meetings to discuss recruitment successes and challenges.</li> <li>● Create a short survey for persons offered enrollment but who decline to participate.</li> <li>● Ask sites what they need to support efficient and effective recruitment.</li> </ul>
<i>Recruitment Communication Planning</i>	
Identify all stakeholders and partners	<ul style="list-style-type: none"> <li>● Identify and include stakeholders who are critical to study communication.</li> </ul>
Identify participant locations based on where participants may seek treatment and relevant information	<ul style="list-style-type: none"> <li>● Identify potential participant pathways into the study so that barriers and bottlenecks may be addressed while the protocol is in development.</li> </ul>
Develop and test tailored messages	<ul style="list-style-type: none"> <li>● Develop messages on key points related to the study (e.g., reason for study, importance, value) for study participants, research staff and providers.</li> </ul>
Develop creative material and select appropriate channels for delivery	<ul style="list-style-type: none"> <li>● Develop creative material and identify channels for reaching audiences.</li> <li>● Conduct formative research such as focus groups, social listening exercises, and semi-structured interviews.</li> </ul>
Develop a realistic communication budget	<ul style="list-style-type: none"> <li>● Plan the budget early to ensure that recruitment costs are anticipated and covered.</li> <li>● Ensure a well-researched communication strategy is deployed in order to achieve efficient and effective communication and outreach efforts.</li> </ul>
Monitor and evaluate both the recruitment process and performance with meaningful metrics	<ul style="list-style-type: none"> <li>● Develop a method for successful recruitment performance monitoring and evaluation: <ol style="list-style-type: none"> <li>1. Securing stakeholder buy-in.</li> <li>2. Define measurable recruitment goals.</li> <li>3. Identify meaningful metrics for each goal.</li> <li>4. Define success for each metric.</li> <li>5. Identify the required data for each metric.</li> <li>6. Collect process and performance data.</li> <li>7. Analyze the data.</li> </ol> </li> <li>● Consider embedding recruitment intervention studies into clinical trials and share the results (good and bad)</li> </ul>

for clinical trial communications, an example containing tools that complement the CTI recommendations [33]. A recent study on the effectiveness of communications among inner city and rural populations for cancer trials found that television advertising was influential [34]. These activities are encouraging, and our recruitment recommendations support the need to extend recruitment communications across more domains.

While recommendations can help with strategic approaches to recruitment, the project team repeatedly heard that the availability of tools is vital for adoption and implementation of the recommendations. Recruitment involves multiple stakeholders, and while resourcing and support often come from sponsors [35], the act of recruitment still depends on study personnel. Practical tools and methods that incorporate greater engagement, particularly of potential participants, can help study teams carry out these strategies. The CTI Recruitment Project Team has developed tools that support this effort [36]. These

tools address decision making for engaging stakeholders, methods for identifying stakeholders, a plan-do-check-act approach to monitoring recruitment performance, and considerations for patient-reported outcomes. Other tools for improving quality such as fishbone diagrams for root-cause analysis or Pareto charts also may be valuable [37]. These tools could augment strategies currently used once studies launch including having contingency plans (e.g., backup sites) and others identified in our stakeholder survey [20].

#### 4.1. Limitations

Despite best efforts to provide a more comprehensive approach to recruitment planning, recommendations of this nature have limitations. The CTI Project Team recognizes that there is no single solution to the complexity of clinical trial recruitment. Individual clinical trials represent a unique set of protocols, rationales for conducting the research,

and diverse stakeholders. Our recommendations are intended to provide a starting point to encourage sponsors, investigators, sites, and patients to more actively seek solutions to the chronic challenges in recruitment. A second limitation is that the project team did not address the issue of participant retention, another area in vital need of improvement with an equal number of diverse considerations that can influence success. However, the team believes that using the recruitment planning framework could help improve retention.

Furthermore, while there may be “face validity” for these recommendations, broader adoption will require a shift in operational approaches at the sponsor level along with the recognition of a positive return on investment (ROI). The inability to systematically evaluate and report on the recommendations as ROI could be a barrier for progress in this area.

Finally, for recommendations to be effective, they need to be disseminated to stakeholders and ideally adopted and implemented. Contributors to activities that generated these recommendations have been encouraged to be “champions” to help promote ideas. Additionally, while CTTI meetings and newsletters have presented these points and promoted additional discussions, more efforts to touch a broader number of individuals and groups committed to clinical trials success are needed. The ability to transform recruitment paradigms will require a continual improvement framework beyond publishing recommendations and discussions. We hope that those utilizing this framework will not only involve a greater number of those needed for recruitment success (i.e., investigators, participants, sponsors and others) but also use it as a basis for generating feedback and evolving approaches to future recruitment planning activities.

## 5. Conclusions

Various groups have offered solutions to improving recruitment. Yet, few efforts to date have developed a series of directed steps that incorporate broad stakeholder input for the purpose of developing more comprehensive, strategic recruitment recommendations. In response to continued calls to improve how clinical trial recruitment is conducted, CTTI has proposed an upstream approach to recruitment planning that has the potential to produce greater impact and reduce downstream barriers. 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.

## Conflicts of interest

The authors report no conflicts of interest.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cct.2018.01.003>.

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