CTTI Recruitment Project

Summary of the Multi-Stakeholder Expert Meeting held November 9-10, 2015

DoubleTree by Hilton Hotel Washington D.C. – Silver Spring, MD 20910

CTTI MISSION: To identify and promote practices that will increase the quality and efficiency of clinical trials

Meeting materials, including the agenda, participant list, and presentations, are available on the Clinical Trials Transformation Initiative (CTTI) website at:

https://ctti-clinicaltrials.org/ctti-recruitment-project-expert-meeting/

Publication Date: January 14, 2016

MEETING BACKGROUND

Clinical trial sponsors are facing an increasingly difficult task of meeting recruitment goals. According to the Tufts Center for the Study of Drug Development (CSDD),[1] only 39% of sites achieve their enrollment targets, 37% fail to meet their targets and 11% fail to enroll a single subject into trials in which they agree to participate and study timelines are typically doubled beyond their planned enrollment periods. 32% of sites do not receive any sort of centralized recruitment and retention support, most of which are traditional recruitment tactics such as physician referrals and mass media (newspaper ads and flyers). Fewer than 15% of recruitment strategies focus on new technologies (e.g., electronic medical records, data mining) and web 2.0 (social media and networking, and online advertising).

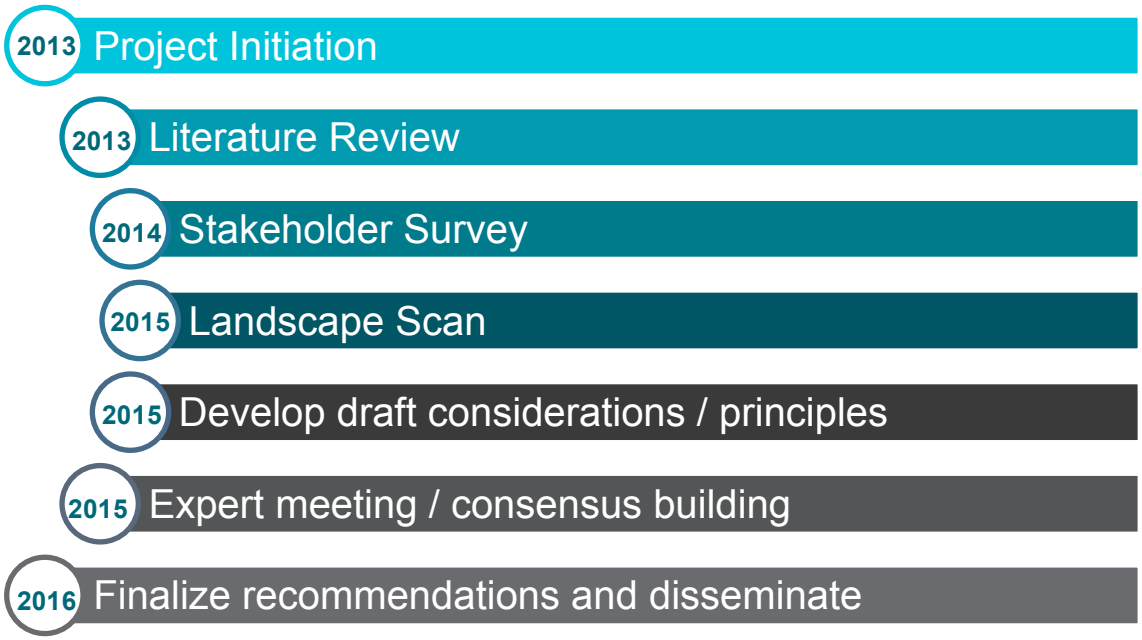
As acknowledged in the CTTI project plan, sub-optimal trial recruitment directly translates into missed opportunities for patients who can benefit from clinical trials, the chance to advance the science and understanding of disease and find new therapies, as well as wasting time, funds, and other resources.

Clinical trials that fail to meet their recruitment goals may be terminated early or be unable to answer their primary research questions as well as exposing potential patients to risk with limited to no meaningful benefit to advancing therapies or scientific understanding. Many explanations have been offered to elucidate the failure to recruit adequate numbers of patients including poor study design, lack of patient engagement, insufficient staff time, inadequate attention to determine and identify available patients who meet eligibility criteria, and inadequate centralized site support. Actionable solutions are needed.

Because of these significant concerns, the Clinical Trials Transformation Initiative's Recruitment Project was initiated to identify barriers (both real and perceived) and optimal approaches to improving recruitment to clinical trials.

The CTTI Recruitment Project Multi-Stakeholder Expert Meeting was convened by the project team to achieve the objectives below. Specifically, change agents in the clinical trial enterprise from multiple disciplines and areas – industry, academia, patients and patient advocates, investigators and federal research funders and regulators – were invited to provide critical feedback and challenge the findings and assumptions of the team intended to help them refine recommendations for improving recruitment to clinical trials. Real and anticipated project progression is illustrated below.

[1] Tufts Center for the Study of Drug Development Impact Report. Vol. 15. No. 1, 2013.



MEETING OBJECTIVES

The objectives of the Recruitment Project Expert Meeting included the following:

- Present findings from the CTTI Recruitment Project's evidence gathering
- Obtain stakeholder perspectives and critical feedback on draft considerations for more effective recruitment planning
- Develop consensus across multiple stakeholder perspectives on the mechanisms for moving recruitment planning upstream and achieving culture change
- Identify implementation barriers to achieving change
- Develop consensus across multiple stakeholder perspectives on the mechanisms for overcoming barriers to achieving change

MEETING EXECUTIVE SUMMARY

The Recruitment Project convened a meeting involving key stakeholders with expertise in this topic on November 9 and 10, 2015. The participants included representatives from academia, nonprofit organizations, government agencies, industry, health systems, patient representatives, site representatives, and professional societies.

The findings and conclusions of CTTI's evidence-gathering methods on the current recruitment landscape were presented and discussed. Recurring themes throughout the meeting focused on the following:

- How to incorporate Quality by Design (QbD) concepts into recruitment planning strategies
- How to identify and engage the appropriate stakeholders
- How to best craft and position messaging to reach the public and the target audiences to improve recruitment efforts
- How to view recruitment through a patient-centric lens
- How to refine the draft points of consideration into actionable recommendations

Patient and public perception of clinical research in general affects recruitment. Previous and past campaigns have been successful in generating awareness and interest in particular conditions or trials, leading to increased enrollment rates; however, the effect of campaigns is usually limited and short-lived. Several speakers emphasized the need to include more consistent efforts overall in informing the public and patients about clinical research (including active clinical trials) and a greater connection among those involved in the clinical trial enterprise (sponsors, local health care providers, investigators, patients/patient advocacy groups, etc.) to more effectively meet recruitment goals.

Findings from the project's evidence gathering efforts were presented, including the results of a literature review and survey of stakeholders. Evidence consistently pointed to the need for a systematic framework for including strategic recruitment planning as part of the study question design and protocol development process.

Following the presentation of findings and evidence, the team's draft points of consideration were presented. These draft points of consideration identified three main pillars of recruitment planning for discussion: trial design and protocol development, trial feasibility and site selection, and recruitment communication planning. Each pillar has challenges that influence the operation and success of the others. While the pillars are represented linearly in the continuum, activities to address the challenges in each should occur concurrently. Traditionally, these issues are addressed independently of one another, in silos that do not allow the consideration of downstream impacts on recruitment.

Meeting participants were polled on the greatest perceived challenges in each of the pillars and discussed potential solutions during breakout sessions. Many of challenges centered on which stakeholders to include in certain processes and how to actually conduct or implement a point of consideration. Many of the proposed solutions broadly included the following:

- Application of Quality by Design (QbD) principles, which emphasizes thoughtful planning upstream of any activities that may impact recruitment downstream during protocol execution
- Allotting adequate time to identify and engage all the necessary stakeholders at the beginning of study question, trial development and recruitment planning processes
- Providing well-timed and well-positioned messages to the target audiences
- Addressing funding and the investment in necessary resources upfront to avoid downstream or future problems

Suggestions from these discussions will be used to revise the draft points of consideration into actionable recommendations.

Successful recruitment relies on potential participants having access to relevant information on clinical trials in a timely manner. Communication of appropriate messaging and effective delivery were central themes throughout the meeting. Key strategies include identifying the target audience and tailoring the messages to them as imperative to success. Messages can be field-tested by the relevant stakeholder groups before public launch.

To improve recruitment overall, trust and better rapport among research scientists/medical professionals and patients/the public need to be fostered, the correct information needs to reach the target audience, participant concerns need to be addressed directly, thoughtful communication planning needs to be funded, and critical assessments need to be made about trial and site feasibility. Local health care providers and hospital staff can act as agents to deliver messages if they are adequately trained, informed, and invested in the research. Finally, a one-size-fits-all approach to recruitment planning is inadequate; recruitment efforts must be fit for purpose and tailored to individual trials.

The Recruitment Project Team is considering next steps to advance this project, as informed by the expert meeting discussions, and will refine the proposed considerations into actionable recommendations based on the considerable feedback and commentary from the meeting participants.

MEETING SUMMARY

Following welcoming remarks by Jamie Roberts, an initial welcome presentation by Pamela Tenaerts (CTTI) introduced participants to CTTI as an organization, including CTTI's mission, methodology, and history. Experts were reminded of the importance of their contributions and to critically assess solutions proposed in the drafted points of consideration document, which serves as the basis for refinement of the future official CTTI recommendations for trial recruitment.

Presentation Highlights: Session I – An Imperative for Action: Patients are Waiting, presented by Mary Woolley

Session I described the current recruitment landscape and patients' perceptions of clinical trials in general. In her preamble, Mary Woolley acknowledged that, in the past, trial volunteers were not often asked about their needs, desires, or perceptions about participating in trials or what factors would increase their interest in participating in trials. The presentation began with recognizing that clinical trials rely on willing participants, and without them, there are no trials. Following this, she highlighted persistent challenges with conducting clinical trials and with trial recruitment specifically; among others, some key challenges included the following: uncoordinated trial conduct; a disconnection among the interests of researchers, physicians, and patients; a lack of communication from physicians about current research; and the failure to include patients in activities related to clinical trial design and conduct.

Both Congress and the media have publicized the need for more clinical trials, and new legislative initiatives in Congress, such as the 21st Century Cures Act to accelerate clinical trials, are under scrutiny. The mass media has amplified the discussion of new or rare conditions requiring treatment. When Research!America polled American adults, 80% of the respondents indicated that they have heard of clinical trials but only 16% have participated in a trial or have a family member who participated in a trial.

Additional poll results indicate that Americans are generally interested in learning more about clinical trials and willing to share their health information but a lack of awareness, trust, and guaranteed safety prevent them from participating in trials. A major reason for lack of participation may be due to the overall lack of information shared with potential participants: 70% of respondents indicated that a healthcare professional has never broached the topic of clinical trials, but an overwhelming 72% of respondents would be willing or somewhat willing to participate in a trial if their doctor identified a clinical trial for them.

Most American respondents showed high altruism scores, replying that donating organs and blood were virtuous activities. A majority of polled individuals rated their admiration of individuals who donate an organ (69%) or blood (61%) as very high; however, only 37% of respondents had ratings of very high admiration for clinical trial participants. A call to action was made to increase the public's perception of the value of clinical trial participation, and the presenter offered

action recommendations and strategies. Overall, patient engagement was called out as the most important component of success. Clinical trial campaigns can increase public awareness, and a majority of respondents felt that scientists should inform the public about current research.

Presentation and Discussion Highlights: Session II – Key Findings from the CTTI Recruitment Planning Project, presented by Jonca Bull

The second session presented findings from the Recruitment Project Team's evidence-gathering activities (literature review, stakeholder survey, and landscape scan). The literature review identified articles discussing barriers or promoters of trial recruitment; in general, barriers could be categorized into 4 overall areas: design issues, trust/communication issues, logistic/pragmatic issues, and institutional issues. The primary conclusion of the literature review was that authors of studies on recruitment did not provide guidance on resolving these issues, emphasizing the need for future trials to include randomized comparisons of different recruitment strategies.

The stakeholder survey was sent to more than 300 individuals, and 90 responses were returned. Academia, industry, and patient advocacy groups had the highest proportion of respondents, and a majority (71%) of respondents conducts business outside of the US. The most common significant barriers to recruitment included the following:

- Finding patients who meet the eligibility criteria (81%)
- Insufficient staff time for recruitment (67%)
- The length and complexity of consent forms (66%)
- Protocol requirements other than recruitment criteria (60%)

Free text solutions offered by respondents indicated that engaging in effective trial planning, improving the eligibility criteria, and using more effective recruitment methods or technologies could help address the most significant barrier (identifying eligible patients). Better planning, specifically when engaging site staff, was noted as a solution to the second most common barrier; additionally, increasing site commitment to staffing was suggested. To address patient consent issues, free text responses included simplifying consent forms, improving the overall consent process, and shortening consent forms. Respondents suggested simplifying trial design and evaluating the feasibility of the trial protocol to address the barrier of protocol requirements. Moderate and less significant barriers to recruitment included a mistrust of clinical research, negative attitudes of physicians, and safety concerns.

Stakeholders were also polled on their experience with specific methods to improve recruitment. The most effective methods included using medical records and hospital-based registries or other databases to identify patients. Respondents also indicated that patient advocates were viewed as the most effective partners to increase clinical trial recruitment rates. Technology-based

recruitment methods were viewed favorably, and many respondents showed interest in utilizing e-alerts to identify potential trial participants and promoting clinical research through social media.

The landscape scan of the project team highlighted the need for a systematic framework for thinking about recruitment planning in parallel with trial design and development.

Following these sessions, experts discussed the barriers named, recruitment vs. retention considerations, patient perspectives and roles, financial concerns, and recognition that a one-size-fits-all approach is inadequate. Patient-specific barriers to recruitment were mentioned, many of which related to logistical or financial concerns. In particular, patients need to know what costs they may incur or compensation they may receive during a trial. To this point, participants agreed that sponsors and sites should openly and clearly explain monetary considerations with patients. While funding was often brought up in conversation, financial concerns were recognized as out of the scope of this particular project; however, this is a potential topic for consideration for future research.

Patient advocate participants acknowledged that the subjective experience of the patient will directly influence their desire to participate in the study, which can enhance the "viability" of trial: practical concerns (parking availability) and personal interactions (impolite doctors or staff) can impact the clinical trial experience. Although patients receiving the standard of care may ultimately face the same issues, these inconveniences may not be factored into the patient's treatment decision as they may be assumed to be part of the "costs paid for obtaining care" whereas participation in research is a "voluntary gift" for which the burden should be minimized. This dichotomy highlights the need for greater communication of the importance of clinical trials overall and of the importance of expressing gratitude and recognition to patients. Many patients want to know how they are contributing to scientific research, how they are personally benefiting, and the results of the study in which they participated. Participants then discussed how to improve the patient experience with clinical trials to encourage past participants and patient advocates to generate interest in the broader community.

In addition to the discussion topics and suggestions mentioned above, the following should also be considered to improve recruitment efforts:

- Sponsors should have realistic expectations of enrollment rates
- QbD principles should be applied to recruitment planning and protocol design
- Both objective and subjective input can inform recruitment efforts
- Address potential financial concerns for participants during protocol development

- Increase not only the “feasibility” of protocols but also the “viability” of protocols by incorporating more elements that address the subjective experience and health literacy of participants
- Involve Institutional Review Boards (IRBs) in discussions that influence enrollment rates

Overall, it was agreed that a systematic approach to recruitment planning was needed, beginning with the end in mind, but that one rigid strategy would not be appropriate for all trials.

Presentation and Discussion Highlights: Session III – Presentation of Draft Considerations, presented by Beth Mahon, Beth Harper, and Jim Kremidas

Draft considerations were presented and discussed during Session III. Key assumptions were presented first:

- A one-size-fits-all approach to recruitment is not appropriate
- Context is important
- Recruitment is an iterative process that involves multiple stakeholders
- Better recruitment should naturally lead to improved retention
- There is a critical need to look at all phases of the drug and device development continuum through a patient-centered lens and to incorporate the needs, preferences, and values of patients into the design of trial questions, development of clinical protocols, and dissemination of results

The draft points of consideration were informed by QbD principles and were classified into 3 pillars that uphold the recruitment planning continuum:

1. Trial design and protocol development
2. Trial feasibility and site selection, and
3. Recruitment communication planning

Although these pillars were presented in a linear fashion, presenters explained that all 3 activities should actually occur in parallel.

Draft recommendations included the following:

1. Trial design and protocol development
    - Engage all stakeholders as real partners in the process
    - Ensure the relevance of the scientific question
    - Optimize protocol design and limit complexity
    - Develop realistic eligibility criteria
    - Minimize procedural burden

- Optimize data collection (data parsimony)

2. Trial feasibility and site selection
    - Conduct an evidence-based trial feasibility analysis
    - Establish realistic metrics and milestones
    - Develop an adequate budget and resources
    - Ensure appropriate site selection
    - Engage in suitable site performance monitoring

3. Recruitment communication planning
    - Identify and engage all stakeholders and partners
    - Identify the ideal candidate locations
    - Develop a mission, vision, and messages
    - Develop material and select appropriate channels or delivery
    - Develop a realistic communication budget
    - Monitor and evaluate both process and performance

After a high-level outline of the draft points of consideration for each pillar, the presenters urged meeting participants to critically assess the processes proposed and view the recruitment continuum through a patient-centric lens and consider innovative strategies.

The discussion about trial design and protocol development revolved around QbD principles, identifying and engaging all stakeholders early, and critically assessing the eligibility criteria rather than relying on "cut and paste" techniques previously intended to standardize protocols. Thoughtfulness in protocol design (including real-world eligibility criteria, endpoints/outcomes salient to the population under study and the fewest study procedures/visits necessary to answer the study question and maintain patient safety) and streamlining data collection were emphasized. Regarding the eligibility criteria, FDA representatives indicated the need to maintain safety in a trial; however, they are open to sponsors choosing to relax the eligibility criteria and encourage sponsors to meet with them early to discuss protocol eligibility criteria and design issues. While participants agreed that the clinical trial enterprise is in need of a culture change, thinking beyond trial ***feasibility*** to trial ***viability,*** the main challenge with this goal is addressing HOW to successfully initiate it.

Participants felt it was important for those involved in the clinical trial enterprise to collaborate more often, rather than operate in silos. Identifying and engaging all stakeholders in protocol design can help integrate all perspectives, collaborate

toward compromise, and clarify methodology to all parties. While this process may seem time-consuming, it can help minimize subsequent protocol changes and save time lost due to slow recruitment and multiple protocol amendments downstream. An objective assessment of the protocol by a third party was suggested to ensure that the protocol meets patients' needs and that plans are executable. Another suggestion for improvement was to include mentors for new investigators so that they are informed and invested.

In general, "trade-offs" with cost versus time need to critically evaluated. Consideration of what may become important in the future should inform decisions that influence complexity and the downstream effect on recruitment. Participants also advocated for a toolkit to assist with implementation of future recruitment recommendations for trial design and protocol development; however, experts also advocated that each trial be considered individually. Furthermore, some participants felt that a cost-benefit value model for these processes could be useful.

During the trial feasibility and site selection discussion, major themes included appropriate site selection, site accountability, flexibility, monitoring, and transparency. Sponsors and sites should have realistic expectations for enrollment rates and should prospectively identify potential problem areas and activities prone to "bottlenecking." Some participants called for realistic, data-driven feasibility at both the protocol and site level. It was acknowledged that some site enrollment rates are based on anecdotal accounts and not hard evidence.

A recommendation to evaluate the validity of current metrics was made. To encourage better site performance overall, it was suggested that poorly performing sites be critically evaluated to determine if they are the right fit after considering the trial phase (early vs. late), the patient population and where they are located, and work flow, among other considerations, including the site's strengths in conducting safety studies (e.g., phase I-II pharmacodynamic/pharmacokinetic studies) vs. safety and efficacy studies (phase III and beyond). Sites that do not meet the trial's requirements or needs should not be added; site selection should be on a trial-by-trial basis. Performance monitoring of sites should be outlined in the protocol as well as consequences for not meeting trial goals. It was also acknowledged that site performance largely hinges on the investigator and site coordinator; therefore, the focus of "site performance" may be shifted to the people performing the tasks rather than generalizing it to the "site."

Overall, the traditional milestones of site performance need to be re-evaluated. Sites that perform well may serve as models to identify the key performance measures and indicators of success. Leveraging the currently available technology can assist with site performance evaluation and boost efficiency. For example, a packaged platform for monitoring performance and process evaluation may be considered; however, this concept is still under development. A thoughtful, innovative, and adequately funded approach to site selection can help identify potential healthcare providers in areas that serve the patients

needed for a particular trial, thereby enhancing recruitment of the target population.

Other suggestions that emerged from the "trial feasibility and site selection" discussion included the following:

- Communication between sponsors and sites was also emphasized, specifically regarding the "patient pathway," to facilitate site understanding of the patient population, which can improve recruitment efforts
- The budget should be considered early on in trial and recruitment planning
- The value proposition for both the investigator/site staff and the patient should be considered when conducting feasibility assessments and evaluating recruitment strategies

During discussion of recruitment communication planning, it was recognized that each protocol and trial is unique, so a single strategy or set of tactics will not be appropriate for all trials or sites. However, the recommendation of developing a mission, vision, and message was acknowledged as being a very important first step in informing recruitment communication planning in any trial. Communication planning not only applies to patients but also to community physicians and hospital staff. It is important for local healthcare providers to be informed about current clinical trials and to be honest about what is known and unknown. Those individuals who interact with patients (e.g., local healthcare providers, hospital staff) should be well educated on currently active or upcoming clinical trials and ready to answer potential participants' questions about these trials.

Messaging constructed to boost patient/potential participant interest should be field-tested with patient groups or advocates to ensure relevance. A greater understanding of the "patient path" can help with timing the messages throughout trial execution. Campaigns reach a wide audience, but a targeted approach is more successful for enrollment of specific patient populations. Transparent communication, personalized messages, appreciation for participation, and clear visuals/graphics can all be utilized to enhance patient interest and comfort. Additionally, more resources should be allocated to recruitment efforts early on in the trial development process.

Leveraging the available technology to assist with recruitment communication was also suggested.

A resulting motto from this session was to "bring the trials to the patients."

Presentation and Discussion Highlights: Session IV – What Can We Do Tomorrow? What Can't Be Done Until We Colonize Mars and Why? An Interactive Presentation, presented by Beth Harper and Jim Kremidas

Session IV asked the question "which recommendations may be most difficult to implement" to inform the breakout sessions to be conducted on Day 2. After an

overview of the root cause analyses already provided by CTTI, participants were polled for the greatest perceived challenge with recommendations in each of the 3 pillars. The top 3 responses for each are presented below.

Trial design and protocol development:

- Engage all stakeholders as real partners in the process (63%)
- Optimize protocol design and limit complexity (25%)
- Minimize procedural burden / optimize data collection (4% each)

Trial feasibility and site selection:

- Develop and adequate budget and resources (29%)
- Conduct an evidence-based trial feasibility analysis (24%)
- Establish realistic metrics and milestones (24%)

Recruitment communication planning:

- Develop a mission, vision, and messages (36%)
- Develop a realistic communication budget (20%)
- Monitor and evaluate both process and performance (16%)

Presentation and Discussion Highlights: Session IV - A New Framework for Innovation: Trial Recruitment as a Mechanism of Action, presented by Joseph Kim

The final presentation on Day 1 described a new framework for thinking about recruitment. Traditional methods and calculations used for enrollment planning are not sufficient because dependent variables, such as the screening rate, are often not taken into account. Today's recruitment mainly draws from the pool of known patients, usually neglecting to advertise to (and engage) unknown patients. Additionally, once an enrolled patient leaves a trial (due to withdrawing consent, screen failures, drop outs, etc.), they are not often engaged at a later time to assess satisfaction or rationale for leaving a trial.

A proposed model for increased patient recruitment incorporates several tactics including patient advocates, past participants, earned and paid media, e-consent, and post-trial engagement, which should be applied within an overall recruitment communication strategy. Earned and paid media is not currently well utilized; however, gains in public awareness are invaluable (e.g., the ice-bucket challenge). Post-study engagement allows for patient feedback and possible re-engagement for new trials. Former trial subjects can act as clinical research advocates. By fostering a community around clinical research, information on clinical trials is more likely to travel via word-of-mouth.

The discussion following the presentation generally supported the views presented. Patient advocates mentioned that intermediary data collected during

the study can be valuable to trial participants and should be communicated to them to maintain enthusiasm even if results are not final. Also presented was the idea that trial participants may desire to have something to show for their participation. This may be in the form of results, but it may also be something more innovative or nontraditional, such as a piece of art or involvement in social media topics. The art of storytelling in relation to clinical research can be a powerful mechanism to engage and retain participants.

Presentation and Discussion Highlights: Session V – Why It's Time for a National Public Education Campaign, presented by Ken Getz

The second day began with a presentation on the need for clinical trial information to reach a wider audience to increase trial recruitment. Similar to earlier presentations, when the public was polled, respondents indicated high willingness to participate in clinical trials; however, this does not necessarily translate into participation. Many respondents also indicated some degree of general knowledge about and confidence in clinical trials, but a vast majority cannot name a research scientist. In contrast to earlier results, the respondents to this poll did not rate the recognition and appreciation of clinical trial participants highly. Generally, public interest in clinical trials seems to increase when it is relevant to personal matters.

To deliver the message of the importance of clinical trials to the public, in general, campaigns have been successful in publicizing information. Short-lived outreach campaigns can attract patients to a particular trial or can help with the launch of a new drug, but many of these campaigns can be uncoordinated or have other limitations. Often, local health care providers are not informed of these efforts yet their participation in message delivery is a critical element to recruiting the right patients to relevant trials. Successful national campaigns have resulted in increased public interest, which was reflected in search terms and queries on clinicaltrials.gov. The impact of a regional launch of the Medical Heroes campaign was a 140% improvement in local trial enrollment rates.

Key elements to a successful campaign were discussed:

- Establishes a personal connection or communicates personal relevance
- Involves the patient community
- Are cohesive and consistent
- Provides clear contact information
- Incorporates multimedia formats
- Includes input from multiple stakeholders
- Has culturally sensitive and educational messages
- Are recognizable

- Have longevity and continuity
- Are coordinated successfully across the clinical trial enterprise

Sensitivity to the language used in the messaging and promotion of clinical trials can determine a success or failure. Targeting the appropriate audience is critical, and ensuring the audience receives the information relies on the correct placement/positioning of the message.

A final thought in the presentation was the call for earlier education on clinical research. If the importance of clinical trials can be taught to children or adolescents in their formative years, this can seed a more appreciative and informed culture around clinical research for the future.

Discussion revolved around many of the key points broached in the presentation: appropriate language with messaging, teaching children about clinical research, and the correct positioning of the messages to reach the target audience. Discussion around messaging touched on the general success with branding efforts, illustrating the power of word choices and social marketing principles. In particular, the use of the "hero" label for clinical trial participants is not always appropriate. Some potential participants are uncomfortable with the term and it can cause alarm for others (i.e., the implication that the situation may be dangerous or risky). Many of the meeting discussions focused on trial participants that had a condition or disease; it was recognized that participants may also be healthy volunteers. Therefore, the messaging should also take into account their perspectives and interests.

To assist with increased public engagement, meeting particpants felt that the following suggestions may help:

- Increased community and media presence for medical/research scientists (e.g., TV or radio interviews, social media presence)
- Foster a stronger connection to local health care providers so that they can be agents to deliver information related to local clinical trials
- Bring clinical research education to schools
- Encourage past trial participants to broadcast their positive experiences with participation
- Provide direction to the public on if/how they can help research efforts easily and immediately

Breakout Sessions: Interactive Problem Solving

The sessions that followed were interactive breakout sessions to brainstorm solutions to the top 3 challenges for each pillar of the draft points of consideration for recruitment planning (see Session IV).

Trial Design and Development Breakout Session

Because the challenges of “minimize procedural burden” and “optimize data collection” received only 4% of votes each, the breakout group mainly discussed the top 2 challenges. For the top challenge, some time was spent defining who “all” stakeholders were and what “real partners” means. “Engaging all stakeholders” includes an inherent assumption that there are perspectives relevant to the trial design process that are not being incorporated. Once the stakeholder groups are identified, “champions” in each group may be sought to guide protocol design and development. These champions can provide a financial benefit as well because their enthusiasm may naturally lead to more productive trial conduct. A suggestion was made that appropriate identification and engagement of stakeholders become a routine within the trial design process. Mentorship was also mentioned as potentially beneficial for new investigators, and the team recognized more inclusive mentoring models may be useful (e.g., a patient advocate mentor may be as informative as a seasoned investigator mentor). Environmental design (i.e., the atmosphere in which the trial is conducted) is as important as scientific design to influence recruitment. When needed, it may be beneficial for scientists to address the community before developing a concept. This is aligned with potential benefits from conducting a needs assessment to identify unmet needs.

Useful tools that may warrant consideration include “stakeholder analysis tools.”

Trial Feasibility and Site Selection

The breakout session team recognized that sponsors and sites may have a different view of what feasibility means; therefore, it is important to align these views when possible. Additionally, site feasibility varies by site. Following a discussion about what feasibility means for an individual site, the team thought that sponsor-site communication could be improved. Sponsors can define for themselves what constitutes a “deal breaker” with a site to inform an open discussion about site capabilities.

Identifying which evidence on site performance is most meaningful is critical: past performance does not always predict present or future performance. It was questioned whether or not data were available to assess the feasibility of the protocol, and if they are available, they should be provided to sites. Members of the group had experience with reliable data that are accurately predictive. These members highlighted the benefits of shared databases and recognized the importance of understanding all the resources needed for success.

Recruitment Communication Planning Breakout Session

To begin, experts questioned whether the goal of “develop a mission, vision, and messaging” was applicable to every individual trial or could be applied to a broad campaign. The goal is relevant to both situations; however, the considerations may be different. Campaigns can convey an element of brand messaging.

It was also acknowledged that the need for recruitment communication planning may not be obvious due to the tendency to make basic assumptions that may be unfounded (e.g., that there is satisfactory communication between the investigator/coordinator and site staff). Therefore, it is important to challenge assumptions and critically consider all points in the process. Additionally, when the patient pathway may not be apparent or understood, research and discussion is encouraged to appropriately craft messaging to the target patient audience. Message development should occur after the other priority stakeholders (based on their influence on recruitment) are identified. Following this, to understand the motivations of stakeholders to participate, it is important to talk to or actively engage with them to develop hypotheses and create messages that can be tested with the appropriate stakeholder pool.

Tools that were mentioned for consideration include templates that can be easily tailored to an individual trial and a decision-tree.

Session VI Highlights – Interactive Problem Solving Report Outs

Following the individual breakout sessions, groups reported back to the main room to share their insights on the issues in each pillar.

Trial Design and Development Breakout Session Highlights

The top challenge for this pillar was "engaging all stakeholders as real partners in the process," which was discussed at length. Team members felt that this issue could not be resolved until "stakeholders" and "real partners" were clearly defined. The team concluded that the term "stakeholder" encompassed any individual that can affect decisions made in the clinical trial enterprise, was affected by the decisions made in the clinical trial enterprise, or believes that they are affected by decisions made in the clinical trial enterprise. After defining this term, the team described that "real partners" are active participants in clinical research decisions and processes. There was a consensus that thought processes around trial design need to change and that there is a need to cultivate a ***research community***. Team members raised the idea that "champions" of this need should be involved in key decisions on design and that skeptical or tepid stakeholders also be encouraged to voice dissenting opinions or constructive criticism. The call for actionable, practical tools was made in this area. The QbD toolkit was mentioned as a successful example of a CTTI-developed tool, and it was suggested that a similar tool/toolkit be developed to ensure the following:

- "All stakeholders" could be identified and engaged by adhering to a standard definition of "stakeholder"
- "Real" partnerships can be built through suggested processes that are clearly outlined to facilitate active participation

It was suggested that a needs assessment tool and case studies also be presented as concrete examples of how to successfully accomplish the above objectives.

The second- and third-highest rated challenge in this pillar were very closely related: 1. Optimize protocol design and limit complexity and 2. Minimize procedural burden. It was recognized that addressing the first issues would naturally solve the second issue as well. The team proposed that the second point be changed from "minimize procedural burden" to "optimize procedural burden." QbD principles can also assist with optimizing and streamlining protocols by emphasizing the need for a thoughtful approach and to preemptively address critical choices very early in the protocol design and planning processes. A type of "steering committee" may help with integrating all stakeholder perspectives into protocol design choices.

To provide guidance to sponsors, a set of analysis tools was suggested, which may include a cost/benefit analysis tool, a SWOT analysis, and/or timeline planning tools. Other suggestions from the breakout team included determining the value proposition for each stakeholder/group, focusing on essential endpoints, encouraging thoughtful justification of add-ons (to avoid "mission creep"), and considering how each decision will influence the trial timeline.

Trial Feasibility and Site Selection Breakout Session Highlights

The breakout session group named key factors that influence trial feasibility and site selection: time, money, resources, training, and relationships with investigators. It was noted that protocol feasibility can be a function of the budget and that more resources at the beginning of protocol planning and design could facilitate the creation of more feasible protocols. For greater success with trial feasibility, the group made the following suggestions:

- Sponsors should provide sites with more information (protocol details, eligibility criteria, and a draft budget)
- Sponsors should ask sites for a robust, honest evaluation of the site's internal processes and performance
- Sponsors should conduct their own assessment of site performance, select the top performing sites, and be willing to pay them appropriately to encourage consistent performance

For the top-rated challenge (conduct an evidence-based trial feasibility analysis), the group agreed that defining feasibility and how to assess it was an important first step. Site feasibility depends, in part, on the interest and availability of competent investigators, the motivation of the site staff, appropriate allocation of resources, and access to patients. Similar to the first breakout group, the site selection team recognized that involving all stakeholders and addressing their concerns at the beginning of protocol planning would increase trial feasibility. Centralized information sources may assist with evaluating site feasibility.

To address the second issue (establishing realistic metrics and milestones, specifically for predicting enrollment), the group re-iterated that sites need adequate information as early as possible. Appropriate staff training and close communication with the investigator can help formulate the appropriate metrics. It was suggested that a shared site-performance database be created. Actionable solutions and potential tools mentioned included site networks with shared infrastructure, standard operating procedures for the recruitment process, and process maps for startup activities. To address how to develop an adequate budget and resources, this breakout team felt that sites needed to know about financial information and competing interactions as soon as possible. The following suggestions for actionable items were made:

- Identify processes that sites have and pay them appropriately to complete their processes
- Negotiate the budget transparently with a budget template
- Include a highly detailed budget, including a better description of overhead costs

Recruitment Communication Planning Breakout Session Highlights

A critical element to developing a mission, vision, and message (the top-rated challenge in this pillar) is knowledge of the target audience and the best methods to direct messages to them. The first step is that the scope of the communication plan needs to be realized and can be guided by disease indication, study priorities, and type of study, among other considerations. In regard to messaging, stakeholders should be identified and prioritized.

Because many patients are often the target audience, a patient pathway map worksheet can be useful for tracking the patient narrative and identifying key communicators in their journey (e.g., health care providers, hospital staff, other patients). This information should be incorporated into the messaging and message positioning. Other evidence-gathering activities (e.g., literature reviews, interviews with physicians, research on patient groups through online resources/social media) can also inform messaging or marketing decisions. After the messages have been developed, they should be tested/vetted by the appropriate stakeholder group(s) before public launch. Actionable suggestions put forth by the team included the following:

- Asking sites HOW they plan to enroll patients, not just the anticipated numbers
- Creating templates for communication planning that can be tailored to individual studies with the caveat that these templates not be used without careful evaluation of the relevance to the individual study
- Creating an online decision-tree
- Convening focus groups when needed

- Utilizing Gantt charts and other project management tools for development and implementation communication plans

To facilitate the development of a realistic communication budget (the second top-rated challenge), the group felt that determining communication goals was the first step. Following this, the stakeholders and items to be included in the budget need to identified and clearly listed rather than be included as a lump sum. Additionally, the type of outreach/media necessary to deliver the message must be determined, and funds should be allocated or considered to address these plans. Leveraging available resources and using dissemination avenues that are already available can help to broadcast the message. The team suggested tools that incorporate the concept of a straw man for media budget development and templates for deliverables and goals.

To monitor and evaluate both processes and performance in recruitment communication planning (third challenge), several factors must first be determined/defined: metrics that define success for each individual channel, what is necessary to measure, how to define success at each stage of the process, key performance indicators for each tactic, and leading indicators throughout the entire process. Suggested products to monitor and evaluate the process included screening logs, templates to assist with evaluation, website and/or call center contact from patients, referral tracking, and surveys for “customer”/patient satisfaction at multiple points in the trial. Other key messages that emerged from this breakout session included the need to customize messaging to each stakeholder group, the need to emphasize the value of communication planning to study sites, and the need for sponsors to be held accountable for recruitment performance and be more proactive in the recruitment process.

Discussions during the breakout group presentations centered on how to define and incorporate the necessary stakeholders, including those individuals that might not usually be identified as a stakeholder (e.g., IT personnel). Meeting participants agreed that recruitment planning should be viewed as a “co-creation process” among the involved stakeholders and that information and lessons learned should be freely shared to improve recruitment rates overall. Other topics of discussion included the reality/possibility of site competition, utilization of site enthusiasm and momentum, and reliable information gathering.

Presentation and Discussion Highlights: Session VII – Getting the Word Out, facilitated by Matthew Harker and Jamie Roberts

The last session of the meeting discussed the dissemination plan for Recruitment Recommendations and next steps for the project overall. During the dissemination presentation and discussion, it was noted that the greatest challenge to implementing change in the clinical trial enterprise was the nature and culture of the enterprise itself being slow to change. Financial support upstream may help tailor dissemination efforts to ensure better success. The usual routes of CTTI dissemination will be utilized: recommendations, manuscripts, tools, webinars, website, and workshops. The discussion addressed 3 main questions:

- Who does CTTI need to reach?
- What are the best products to influence change?
- Where do they (i.e., the appropriate audience) seek information?

Experts discussed these questions and how dissemination materials may be best positioned by exploring conference options for presenting or networking, journal options for publications, strategic use of infographics in website material, and opportunities with social media (e.g., outreach, networking, and forum discussions). It was recognized that many people connect emotionally with patient stories, so these can be strategically positioned within the messaging to draw and hold interest. Big initiatives can act as models for dissemination: it may be possible to develop recruitment education centers or do educational outreach to hospitals that want to be involved in clinical research. Finally, timing can be leveraged to increase the impact of information (e.g., after trials have failed). Overall, dissemination efforts can benefit from a coordinated multilayered approach.

Prior to adjournment, the proposed future direction of the Recruitment Project was presented. Key messages from the meeting presentations and discussions were highlighted. Next steps outlined included reviewing feedback, refining the recommendations based on the expert discussions, building tools, obtaining approval, and disseminating the information. The meeting ended with emphasizing the importance of patients to the recruitment process.

FUNDING STATEMENT

Funding for this meeting was made possible, in part, by the Food and Drug Administration through grant R18FD005292, as well as CTTI membership fees. Views expressed in this publication do not necessarily reflect the official policies of the Department of Health and Human Services, nor does any mention of trade names, commercial practices, or organizations imply endorsement by the U.S. government.

ABOUT CTTI

The Clinical Trials Transformation Initiative (CTTI) is a public-private partnership to identify and promote practices that will increase the quality and efficiency of clinical trials. The CTTI vision is a high quality clinical trial system that is patient-centered and efficient, enabling reliable and timely access to evidence-based prevention and treatment options.

For more information, contact the Recruitment Project Manager, Jamie Roberts, at Jamie.roberts@duke.edu or visit http://www.ctti-clinicaltrials.org.

Appendix A. Meeting Agenda

Monday, November 9, 2015

7:30-8:00 **Breakfast (*Provided*)**

8:00-8:25 **Welcoming Remarks**
Jamie Roberts, Clinical Trials Transformation Initiative, CTTI
Pamela Tenaerts, CTTI

Session I
The Landscape
Objectives:
- Learn about the landscape of clinical trial recruitment
- Learn about the patients' perceptions of clinical research

8:25-9:00 **An Imperative for Action: Patients Are Waiting**
Mary Woolley, Research!America

Session II
Background, Findings, and Current Status of Project
Objectives:
- Learn about the background of the project and our evidence gathering process
- Review key findings from the project

9:00-9:45 **Key Findings from the CTTI Recruitment Planning Project**
Jonca Bull, Food and Drug Administration

9:45-10:15 **Panel Discussion with Recruitment Project Team Leaders and Audience**

Facilitator: Jamie Roberts
Panelists: Patricia Furlong, Parent Project Muscular Dystrophy (PPMD); Beth Mahon, Janssen; Jonca Bull, FDA

10:15-10:30 **Break**

Session III
Presentation of Draft Considerations and Discussion
Objectives:
- Review draft points of consideration for improving recruitment planning
- Obtain critical feedback on points of consideration through interactive discussion

10:30-10:45 **Trial Design and Protocol Development**

Beth Mahon, Janssen

10:45-11:45 **Open Discussion with Panel and Audience**
Facilitator: Grant Huang, Department of Veterans Affairs
Panelists: Beth Mahon, Janssen; Jonca Bull, FDA; Patricia Furlong, PPMD; Anuja Rastogi, FDA; Barbara LeStage, Patient Representative

11:45-12:15 **Lunch** *(Provided)*

Session III *(Continued)*

12:15-12:30 **Trial Feasibility Analyses and Site Selection**
Beth Harper, Clinical Performance Partners

12:30 - 1:30 **Open Discussion with Panel and Audience**
Facilitator: Kelly McKee, Merck
Panelists: Ashish Oza, St. Jude Medical; Beth Harper, Clinical Performance Partners; Claire Meunier, The Michael J Fox Foundation (MJFF)

1:30 - 1:45 **Recruitment Communication Planning**
Jim Kremidas, Association of Clinical Research Professionals (ACRP)

1:45 - 2:45 **Open Discussion with Panel and Audience**
Facilitator: Claire Meunier, MJFF
Panelists: Holly Massett, National Institutes of Health (NCI); Leslie Kelly, Duke University; David Ciavarella, CR Bard; Jim Kremidas, ACRP

2:45 - 3:00 **Break**

Session IV
Anticipated Implementation Challenges, Root Cause Analyses & Prioritization
Objectives:
- Rank which considerations will be the most difficult to implement
- Review the Implementation Root Cause Analysis Process and Prioritization
- Expectations for the Discussion Session

3:00 - 3:30 **What Can We Do Tomorrow? What Can't Be Done Until We Colonize Mars and Why? An Interactive Presentation**
Beth Harper & Jim Kremidas

3:30-4:30 **Open Discussion with Audience**
Facilitators: Beth Harper & Jim Kremidas

4:30-5:00 **A New Framework for Innovation: Trial Recruitment as a Mechanism of Action**
Joseph Kim, Eli Lilly and Company

5:00 **Day One Highlights and Wrap-Up**
Kelly McKee, Merck

5:15-7:30 **Dinner Reception** *(Connection I, second level)*

Tuesday, November 10, 2015

7:30-8:00 **Breakfast** (*Provided in Connection I, Second Level*)

8:00-8:15 **Welcome, Overview of Day One, Game Plan for Day Two**
Jamie Roberts, CTTI
Objectives:
- Identify implementation challenges, brainstorm solutions
- Begin to build consensus on solutions to implementation challenges

Session V:
Why It's Time for a National Public Education Campaign
Objective:
- Discuss the need for, and critical success factors associated with, establishing an effective national engagement campaign

8:15 - 8:45 **Establishing Engagement through Coordinated National Outreach**
Ken Getz, Tufts University School of Medicine

8:45-10:45 **Breakout Sessions: Interactive Problem Solving**
- **Trial Design and Development**
  Facilitators: Grant Huang, VA & Jonca Bull, FDA
- **Site Selection and Feasibility**
  Facilitators: Beth Harper, Clinical Performance Partners & Claire Meunier, MJFF
- **Recruitment Communication Planning**
  Facilitators: Jim Kremidas, ACRP & Kelly McKee, Merck

10:45-11:00 **Break**

Session VI

Interactive Problem Solving Report Outs

11:00-11:40 **RCA: Trial Design and Development Group Report Out & Open Discussion: Recommendations & Needed Tools**
Grant Huang, VA

11:40-12:20 **RCA: Group Site Selection and Feasibility Report Out & Open Discussion: Recommendations & Needed Tools**
Beth Harper, Clinical Performance Partners

12:20 - 1:00 **RCA: Group Recruitment Communication Planning Report Out & Open Discussion: Recommendations & Needed Tools**
Jim Kremidas, ACRP

Working Lunch (*Provided*)

Session VII
Getting the Word Out

1:30 - 2:00 **A Dissemination Plan Discussion**
Facilitator: Matthew Harker, CTTI
Objectives:
- Identify who needs to learn of the recommendations
- Identify the best channels and champions for dissemination

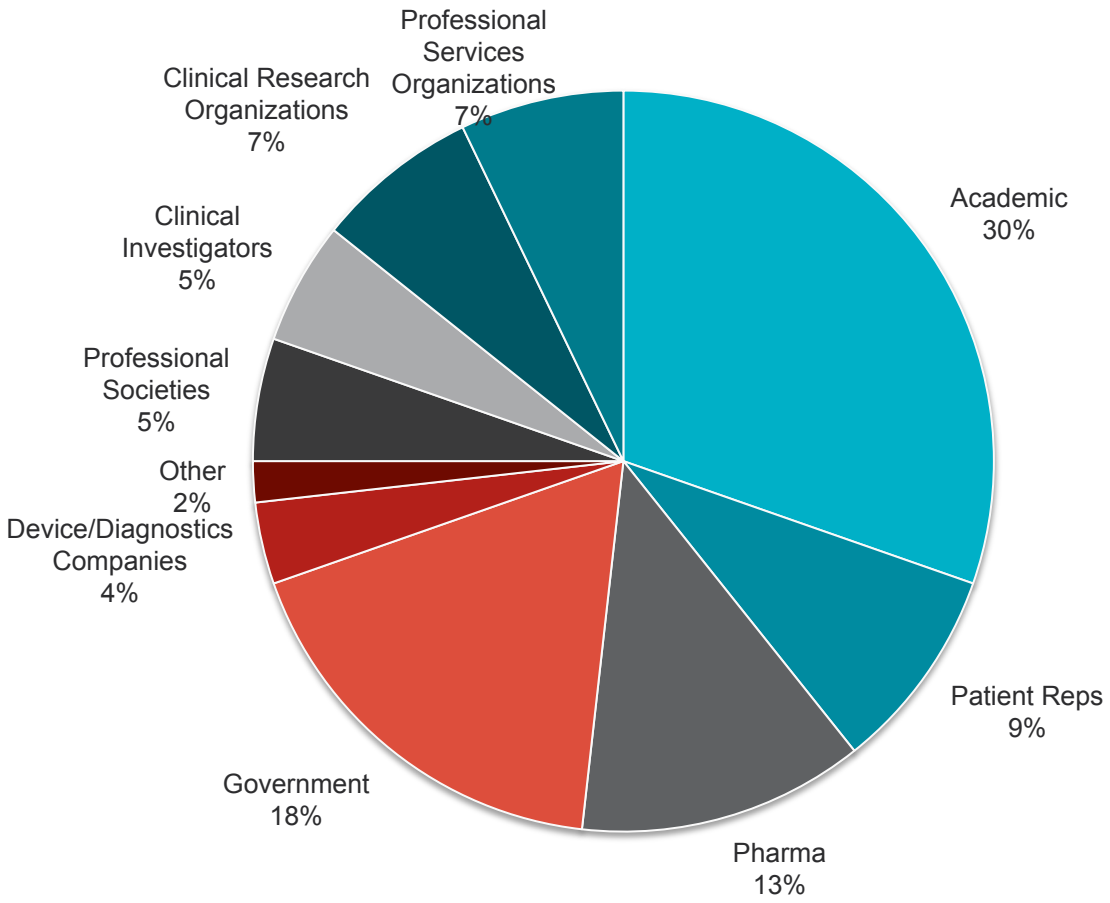
2:00-2:30 **Taking Recruitment Planning to the Next Level: Where Do We Go From Here? Panel and Audience Discussion**
Facilitator: Jamie Roberts, CTTI
Panelists: Grant Huang, VA; Beth Harper, Clinical Performance Partners; Jim Kremidas, ACRP

2:30pm **Adjourn**

Appendix B. Meeting Participants

Our Multi-Stakeholder Expert Meeting participants include representatives from a broad cross-section of the clinical trial enterprise including regulators, government sponsors of clinical research, academia, industry, patient advocates, clinical investigators, and other interested parties. Participants are expected to be actively engaged in dialogue both days.

STAKEHOLDERS REPRESENTED



MEETING PARTICIPANTS

Participant	Affiliation
Patricia Adams	Duke University
Terry Ainsworth	Duke Office of Clinical Research
Nassim Azzi	EyeforPharma
Charlotte Bhasin	Case Western Reserve University CTSA
Rose Blackburne	PPD, Inc.
Jonca Bull	Food and Drug Administration, OC, OMH
Elizabeth Carfioli	Alnylam Pharmaceuticals
David Ciavarella	CR Bard, Inc.
Debra Condon	Minneapolis VA Health Care System
Michelle Culp	National Institutes of Health, NCATS
Dixie Ecklund	University of Iowa
Cindy Geoghegan	Patient and Partners
Ken Getz	Tufts University School of Medicine
Karin Gulbrandsen	Janssen
Anjali Gupta	SBP Medical Discovery Research Institute
Matthew Harker	Clinical Trials Transformation Initiative
Beth Harper	Clinical Performance Partners, Inc.
Grant Huang	Department of Veterans Affairs
Lara Jehi	Cleveland Clinic
Cheryl Jernigan	Susan G Komen
Jeff Kasher	Patients Can't Wait
Leslie Kelly	Duke University
Tawni Kenworthy-Heinige	VA Health Care Systems
Kelly Kilibarda	Whitsell Innovations
Joseph Kim	Eli Lilly & Co.
Jim Kremidas	Association of Clinical Research Professionals
Edward Kuczynski	Tufts Medical Center
Aisha Langford	New York University
Barbara LeStage	Patient Representative
Bob Lindblad	SCT
Amy MacKenzie	Thomas Jefferson University
Beth Mahon	Janssen
Holly Massett	National Institutes of Health, NCI
Anna McBride	CATO Research. LTD
Alison McDonald	University of Aberdeen, UK
Kelly McKee	Merck
Ann Meeker-O'Connell	Johnson & Johnson
Claire Meunier	The Michael J Fox Foundation
Steve Morin	Food and Drug Administration, OC
John Needham	Patient Recruitment Strategy (*on behalf of ACRES*)

Participant	Affiliation
Ashish Oza	St. Jude Medical
Jane Perlmutter	Gemini Group
Christine Pierre	Society for Clinical Research Sites (SCRS)
Mary Purucker	National Institutes of Health, NCATS
Anuja Rastogi	Food and Drug Administration, CBER
Douglas Reichgott	Tufts Medical Center
Jamie Roberts	Clinical Trials Transformation Initiative
David Sall	Patient Enrollment Advisors, LLC
Erika Siegrist	MedStar Health Research Institute
Mark Sloan	Boston University Medical Center
Brian Smith	Duke University
Denise Snyder	Duke Office of Clinical Research
Pamela Tenaerts	Clinical Trials Transformation Initiative
Craig Tendler	Janssen
Bernadette Tosti	Quintiles
Suresh Vedantham	Washington University St. Louis
Tonya Ward-Kiser	PMG Research, Inc
Louise Wolf	Montefiore Medical Center
Mary Woolley	Research!America
Immo Zadezensky	Food and Drug Administration, CDER
Jeffrey Zucker	Worldwide Clinical Trials

CTTI RECRUITMENT PROJECT TEAM MEMBERS

Jonca Bull* (Food and Drug Administration, CDER)
David Ciavarella (CR Bard)
Pat Furlong* (Parent Project Muscular Dystrophy [PPMD])
Beth Harper (Clinical Performance Partners)
Grant Huang (Department of Veterans Affairs)
Adwoa Hughes-Morley (Systematic Techniques for Assisting Recruitment to Trials [START])
Leslie Kelly (Duke University)
James Kremidas (Association of Clinical Research Professionals [ACRP])
Barbara LeStage (Patient Representative)
Elizabeth Mahon* (Janssen)
Holly Massett (National Institutes of Health, NCI)
Claire Meunier (The Michael J Fox Foundation [MJFF])
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