Clinical Trials Transformation Initiative (CTTI)
Recruitment Recommendations Webinar: Q&A Follow-Up

This document is intended to provide responses to questions that speakers did not have time to answer during the Q&A session of CTTI's webinar, Recommendations for Recruitment: Moving Recruitment Planning Upstream to Reduce Barriers, hosted on May 19, 2016.*

1. How can patient advocates be helpful in the recruitment process?

The ideal situation is when an advocate is involved from the very beginning of concept development (see Tool #1: Decision Tree for Optimizing Protocol Design). This will ensure that the scientific question being asked is important to patients, the inclusion and exclusion criteria are necessary for participant safety and directly relevant to the scientific question being asked, the visits and procedures required of participants will not make it too difficult or expensive for them to comply with trial requirements, the data being gathered are necessary to answer the scientific question and do not just provide information that would be "interesting to know," and, hopefully, that the trial has the potential to make a real difference for patients. Some funders now require the participation of advocates; others are interested in having advocates participate but do not know how to engage with them. Individual advocates or advocacy groups can contact sponsors involved in developing and conducting clinical trials and ask about becoming involved. Such organizations may include a research facility, a funding organization, another advocacy group, or an institutional review board at a local hospital. Research sponsors should consider having at least one patient advocate serve on steering committees, advisory boards, protocol and consent working groups, and/or data monitoring committees.

2. Are there specific suggestions on how make trials more meaningful and rewarding to the study participant (as a key motivation to recruitment and retention)?

Identifying and engaging with stakeholders will help researchers and their partners identify the motivations that are meaningful and rewarding to various participants (from potential study volunteers to investigators, clinicians and site staff). In other words, the only way to find out is to engage, build partnerships, ask questions and absorb insights. For information on how to identify and engage the right stakeholders, please see Tool #2: Stakeholder Identification and Analysis Tool and the examples provided.

3. Are there specific suggestions for meeting recruitment targets in trials for orphan disease indications? How can we enroll more patients in these trials?

Identifying and engaging with the ***right*** stakeholders will be necessary, including site staff, current and prospective investigators, clinicians, the sponsor, and/or potential

**Some questions have been edited for length and clarity.*

participants or patient advocacy organizations. In the case of a study that is ongoing and in need of rescue, how that should be done needs to be carefully considered as many patient advocacy organizations are becoming much more savvy about managing their relationships and do not always like to be approached when a study is in need of rescue. Rather, they prefer to be approached at the study design phase so that they can be meaningfully contribute to determining which endpoints are relevant to their constituents and their needs, whether the schedule of events and risk/benefit ratio are tolerable, the inclusion/exclusion criteria are appropriate, the communication materials are relevant, etc. This is not to say that researchers should not pursue assistance from a local or national patient advocacy organization when in need of support for recruitment and/or retention; rather, the recommendation is to approach those organizations with the intention of building long-term relationships that engage them as true partners in the research effort. CTTI's Recommendations for Best Practices with Patient Groups in Clinical Trials will be a useful resource for when starting the process of engaging with patient advocacy organizations.
As stated above, other stakeholders to engage with may include other investigators or clinicians, staff from other sites, and the sponsor if appropriate. Tool #2: Stakeholder Identification and Analysis Tool of the Recruitment Recommendations is an additional resource.

4. With so many different patient populations, from pregnant women to newborns to adults, is it reasonable to expect that a one-size approach fits all?

It is true that a one-size-fits-all approach likely will not work. The CTTI Recruitment Project Recommendations recommend a fit-for-purpose approach such that careful thought is given to recruitment during the development process of every trial protocol, when appropriate; that process should be dependent upon identifying and engaging with the right stakeholders, which will very likely be different for nearly every protocol. Recall that potential stakeholders don't just include patient participants but clinicians, prospective investigators and site staff, vendors, regulators, etc., any or all of whom may have relevant input that can help shape a recruitable trial.

With different patient populations, there will likely be different protocol considerations that also need to be further evaluated to reduce obstacles to participation. For example, frequent blood draws in a study involving neonates or infants will likely present a significant obstacle to enrollment and study completion, whereas such procedures may not pose a significant barrier in studies with healthy adults. In addition, adequate appreciation of how the investigational product performed in early-phase studies across different study populations may help inform new recruitment planning needs and practices for future studies.

5. When addressing diversity, are there communication tools that have proven most effective for participant recruitment outside of the use of community groups?

The CTTI Recruitment Project did not research the issue of diversity specifically but recommends that the necessary formative research be done as a clinical trial question and protocol are being developed. This involves identifying and engaging with the right stakeholders (including expanding the pool of potential investigators as needed) so that they may assist in the development of the most appropriate communication tools and messages, as well as the right channels for delivery, ***based on the needs and culture of the community***. Engaging those communities in developing research questions, protocols, communication material and channels for delivery will ensure success.

6. Please give an example of an "evidence-based trial feasibility analysis."

A ***study-level*** evidence-based feasibility assessment should be conducted at the time of study design and protocol development to ensure the target study population exists and can be accessed. A ***detailed, site-specific***, evidence-based analysis should be performed with each potential site being considered for the trial.

At the sponsor level, this involves gathering data to document the availability of the patient population in general (disease incidence and prevalence data), along with the use of health care claims data and sampling of electronic health record (EHR) queries for select sites across representative geographic regions and site types (e.g., academic medical centers, community clinics, private practices, dedicated research sites). By evaluating the potential number of patients available against a set of inclusion and exclusion criteria that can be coded and queried, researchers can gain a sense of what the conversion ratio will be from number of potential participants available to number that will qualify for pre-screening for the trial. From this number, researchers should apply historical loss ratios, or information from qualitative site and patient interviews, across the recruitment funnel to estimate how many patients will decline the study opportunity (consent declines), be disqualified during screening (screen failures), and drop out post-randomization. This will yield an overall conversion ratio of patients ***identified to randomized*** to provide a clearer picture of the total number of patients who will have to be identified or reached in order to achieve the randomization goals.

At the site-level, a similar process is applied wherein each site should conduct a database search or EHR query of the inclusion and exclusion criteria that can be coded and easily searched. From the results of this query, a representative sample of charts (e.g., 10% or 20-30 charts) should be reviewed in depth to assess the losses of potential participants for the remaining criteria that cannot easily be searched through a query. The overall conversion ratio for that site should then be estimated (along with the other estimated loss ratios based on qualitative discussions or historical metrics for similar trials). If the site does not have at least a

minimum number of potential participants, then the site and sponsor should seriously question whether they are an appropriate site to include in the trial, unless the site can demonstrate they have a well thought out recruitment action plan to identify and enroll participants from external sources. This process also ensures compliance with ICH GCP 4.2.1, which states that:

"The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period."

7. In order to perform an adequate feasibility analysis, investigators need data-driven recommendations for recruiting a particular group of patients but quite often the investigator does not have this. Are there suggestions for how this data should be collected?

Please see Tool #3: Monitoring Recruitment Process and Performance. The CTTI Recruitment Project recommends that trial-specific recruitment interventions (or tactics) be embedded into clinical trials in order to develop an evidence base for the science of recruitment to clinical trials. Best practices will very likely be population and trial specific as more formative research is conducted and more patient-centric studies are developed. The clinical research enterprise must begin measuring the impact of recruitment interventions across different populations and trial types so that others may benefit from the knowledge of which methods are effective and which are not. For example, development of recruitment plans, tactics, or interventions for a drug trial for pediatric asthma will likely be much different from those developed for a trial of a new cholesterol medication in adults over age 45. However, what is learned from a fit-for-purpose recruitment plan for that pediatric asthma trial may be useful to other similar pediatric trials and help to build an evidence base of effective recruitment interventions. Such work will support the efforts of other trialists and add to the science of recruitment to clinical trials.

8. Many of these improved recruitment methods require extra funding for more staff and marketing. Where should this extra funding come from?

Research sponsors must determine the trade-off between time and costs: extra money spent on the front-end of a study to ensure the study is well planned and the communication strategy is well-researched, appropriately targeted, and successfully deployed may be worth it to achieve efficient and effective communication and outreach efforts that help promote timely recruitment. Recruitment support should be adequately budgeted for and strategies developed to ensure that sites have funding available to support the time and staff needed to enroll. Given that the majority of trials fail to enroll in the planned time-frame, spending time, effort, and resources on the front-end to engage in early partnerships and formative research in order to develop a recruitable protocol should ensure that the trial completes according to plan, saving money on the back-end. Well-built and maintained partnerships will also facilitate subsequent studies.

9. **The recommendations stress that trials must be "marketed." However, research protocols often put limitations on methods for reaching out to potential participants, which can prevent the development of materials that are engaging enough to raise awareness about a particular study. Did any of these issues come up as a factor limiting recruitment?**

   It is true that there are limitations to the way that a study may be "marketed." Factors such as coercion, misinformation, etc., must be avoided when communicating about a trial. However, the appropriate use of social marketing principles to help develop the right communication messages can be appropriate, and messages can be developed that include appropriate "calls to action" that are not coercive or misleading. That said, all direct-to-patient communication materials should be reviewed and approved by the appropriate IRB prior to implementation.

10. **Please provide examples of "meaningful metrics" to track when evaluating the process and performance of recruitment communications plans (e.g., reach, number consented).**

    The most meaningful process and performance metrics will likely be study specific.

    Process evaluation requires tracking metrics that indicate whether the project is achieving its process goals (i.e., did the project accomplish what it planned to do?). Examples of process goals include deploying 3 paid ads in local newspapers or operationalizing a centralized recruitment call center. ***Performance*** evaluation requires collecting and analyzing metrics that measure the impact of deployed interventions (e.g., did enrollment increase by 10% with the planned intervention? did our ad garner 1,000 impressions?). When it comes to recruitment campaigns, the most meaningful metric is probably cost per participant enrolled or randomized. Particularly with Internet and social media–based campaigns, it is much easier to track number of website views, click-through rates, number of referrals to the site, etc., but these metrics are meaningless if the campaign reach did not translate into actual participants enrolled in the trial.

    Success from recruitment campaigns can further be defined as how did the campaign work per expectations? For example, in a rare disease trial, if 2 participants were enrolled at a cost of $250,000 each that may be considered a success. However, if only 2 were enrolled and the plan was to enroll 20 participants, then clearly the campaign was not successful. For a more common condition, analysis may be able to show that the cost per participant enrolled was $4.25, but if only 5 out of a planned 50 participants were enrolled, the campaign may not have been successful. In essence, success is a function of expectations (total contribution, contribution over time, cost per contribution, etc.), so being clear on defining success and expectations is critical to evaluating recruitment performance.

11. **Please provide examples of technology recruitment tools encountered during the landscape survey conducted by the project team.**

    Recruitment technology tools are vast and ever increasing. They range from informatics and database tools that help to identify potential sites and participants, to social media tools to build awareness campaigns and recruit participants, to patient and site engagement apps to stay in communication with sites and participants. They also include tools and templates that sponsors consider proprietary (hence, we were not able to collect them). The technologies cover the spectrum of the recruitment planning process, from tools that help during the planning and feasibility stages, to tools that help optimize the site selection and start-up process, to tools that help study implementation. Because many of the technology providers come and go and the landscape is ever changing, there is no a consolidated list of stable service providers. At this stage, vendor selection and due diligence are necessary to determine which support tools/technologies are appropriate for which type of trial to ensure the proper "fit for purpose."

12. **Clinical trial recruitment companies were not mentioned among the various stakeholders that should be engaged. Please provide any thoughts on engaging them to help with the recruitment planning process.**

    Clinical research organizations (CROs) and other trial vendors (e.g., recruitment firms, digital technologists) can provide insight into feasibility, available market data, site experience, and participant availability. Early engagement with these vendors may help eliminate downstream recruitment barriers. See Tool #2: Stakeholder Identification and Analysis Tool and the examples for additional insight into how to identify and engage with the most appropriate stakeholders to help create a recruitable trial.

13. **Can you discuss current informed consent practices and effect on recruitment?**

    Evidence gathered indicated that the length and complexity of consent forms present a significant challenge for recruitment; hence, the project recommends that stakeholders be involved in the development of the consent form and process for any trial. Please see the CTTI Informed Consent Recommendations for additional information about improving the informed consent process and document.

14. **There will always be trials that are important to pharmaceutical companies from a strategic standpoint but are not inherently appealing to other stakeholders. Any advice in those cases?**

Sites must make careful decisions regarding the studies in which they elect to participate, especially when they want to be successful enrollers. Talking with other stakeholders during the decision-making process will help sites identify appropriate studies. Factors to consider include whether an adequate number of participants can be successfully identified and recruited, the importance of the research question, the existence of competing studies, etc. It might also be advantageous for a potential site to run a sample of the population in the target geographic area (using whatever data are available, e.g. population served, demographic data, EHR) to see if it will be able to recruit enough participants that will meet the inclusion/exclusion criteria in a specified timeframe. If not, the site should be willing to make the often difficult decision to choose ***not*** to participate in a study. This will also allow the site to be compliant with ICH GCP 4.2.1, which states that:

"The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period."

When developing trials, sponsors should consider the needs and concerns of other stakeholders, including potential study participants, clinicians, investigators and site staff, which will result in trials that are more likely to appeal to them because they have been engaged in the process.

15. **Please provide a link to the survey findings manuscript that was referenced during the presentation.**

http://www.appliedclinicaltrialsonline.com/barriers-clinical-trial-recruitment-and-possible-solutions-stakeholder-survey?pageID=1

16. **Where will the webinar slides be made available?**

The slides will be made available on the CTTI website: https://www.ctti-clinicaltrials.org/briefing-room/webinars/ctti-presents-recommendations-recruitment-moving-recruitment-planning

You can also email the project manager, Jamie Roberts, at Jamie.Roberts@duke.edu.