CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

Recommendations for Strengthening the Investigator Site Community

October 2017

CTTI MISSION: To develop and drive adoption of practices that will increase the quality and efficiency of clinical trials

Clinical Trials Transformation Initiative. CTTI recommendations for strengthening the investigator site community. Published October 2017. https://ctti-clinicaltrials.org/our-work/investigators-and-sites/investigator-community/

INTRODUCTION

CTTI's Strengthening the Investigator Site Community Project was prompted by the need to understand the reasons for high rates of turnover among investigators who lead clinical trials at research sites. Because investigator knowledge and experience directly affect the quality and ultimate success of clinical trials, the answers to these questions have important implications for the research enterprise, as well as the patients and other stakeholders who depend on it. Evidence suggests that many investigators are leaving clinical research due to difficulty balancing workload, time requirements to conduct trials, data and safety reporting burdens, and financial issues. However, the professional and personal rewards of conducting research are also evident, and the ability to overcome challenges associated with clinical research is clearly articulated.

Substantial time and resources are needed to initiate and train new site investigators in clinical trial processes. However, analyses of Form FDA 1572s ("Statement of Investigator") suggest that rates of turnover among U.S.-based pharmaceutical trial site investigators are high and increasing. High attrition rates for U.S.-based investigators—and the resultant need to initiate new investigators to sustain an adequate pool of investigators—increase the costs of performing clinical trials and threaten the quality and efficiency of trial conduct.

CTTI offers these recommendations for all clinical research stakeholders to strengthen the site investigator community and the clinical research ecosystem. The recommendations focus on approaches for strengthening four key categories of site-based research activity:

1. Developing site-based research infrastructure and staff;
2. Optimizing trial execution and conduct;
3. Improving site budget and contract negotiations; and
4. Discovering additional trials to conduct.

CTTI RECOMMENDATIONS & RESOURCES

I. Recommendations for Developing Site-Based Research Infrastructure & Staff

Site investigators must have foundational knowledge to carry out their roles[1] but also require supportive infrastructure and well-trained staff to conduct high-quality clinical trials while effectively managing workload and other burdens. Regardless of whether investigators are embedded within large academic or private health systems, or work in smaller community/private-practice settings, internal support for their research activities (and in the case of larger systems, broader institutional support) is critical for success.

Recommendations for Investigative Sites

1. **Hire and retain well-trained, experienced research coordinators and other essential staff.**

   Research coordinators perform many essential study activities delegated by the investigator. Other key roles/areas of expertise provided by site staff may include the following responsibilities, although each role does not necessarily need to be fulfilled by an individual dedicated exclusively to that function:

   - Sub-investigator(s)
   - Regulatory affairs expertise
   - Administrative support
   - Data/informatics and IT support
   - Budget and contracting knowledge
   - Research pharmacists (for inpatient trials)
   - Patient recruitment expertise

2. **Provide continuous training for research staff.**

   Research sites must value and support training for study personnel. Targeted training specific to clinical research must include all staff involved in clinical research activities, not solely the investigator. Participation is paramount and can be achieved through online training courses, professionally provided training, onsite mentoring, and participation in professional organizations.

3. **Guide clinical research practice at the site with standard operating procedures (SOPs) and systems.**

   Systems (e.g., electronic health records; clinical trials management systems) and written SOPs for supporting research can help ensure compliance and consistent, high-quality execution of clinical trials. Sites may find it helpful to organize study-related procedures and tasks according to the following trial milestones:

   - Pre-study (preparation for ultimate site selection)
   - Study start-up (IRB approval, budget finalization, coordination of research team members, pre-selection of potentially eligible patients, etc.)

[1] CTTI's Investigator Qualification Project: https://ctti-clinicaltrials.org/our-work/investigators-and-sites/investigator-qualification/

- Study execution (site initiation, patient recruitment, data entry collection, adverse event reporting, clinical event reporting, maintenance of investigational product for drug therapy trials, study-related visits and procedures, and sign-off procedures)
- Study close-out and preparation for the U.S. Food and Drug Administration (FDA) inspection

Recommendations for Sponsors, CROs, and Health Systems/Private Practices

1. **Recognize principal investigators, co-investigators, and research coordinators as key contributors to product development.**

   Sponsors, clinical research organizations (CROs), and health systems/private practices, as well as their delegates, should formally acknowledge site investigators and staff who conduct clinical research. This may include approaches such as thanking site staff personally or recognizing contributions of site staff and study participants via websites, in television ads, or in regular communications, publications, and presentations. When appropriate, site investigators should be offered the opportunity to participate as co-authors on publications.

2. **Provide opportunities for investigators and site staff remain engaged in between trials.**

   Inactivity in between trials presents challenges and opportunities. Sponsors, CROs, and health systems/private practice should actively support investigators and site staff in between trials by providing developmental opportunities via attendance at clinical trial-related conferences, continual medical education certified trainings, and engagement with professional society and trade associations.

II. Recommendations for Optimizing Trial Execution and Conduct

Investigators and site staff should include operational considerations as part of overall preparations for conducting a successful trial. Sponsors should follow CTTI Quality by Design and Recruitment Project recommendations to minimize trial execution challenges.

Recommendations for Sponsors

1. **Create enrollable study protocols and ensure effective recruitment planning.**

   According to the CTTI Quality by Design and Recruitment Project recommendations, attention to minimizing recruitment challenges *at the trial design and protocol development stages* is essential. This can be achieved by engaging all stakeholders as equal partners in the process, ensuring the relevance of the scientific question to stakeholders, limiting protocol complexity to reduce the burden of participation, developing realistic eligibility criteria, and limiting collection of data to only those needed to maintain patient safety and answer the scientific question.[2,3]

2. **Follow FDA safety reporting requirements.**

   The FDA's requirements for reporting safety issues and adverse events impose critically important obligations, as well as burdens, on site investigators. Creating, reviewing, and dispatching adverse event (AE) reports can require significant time and effort, despite FDA efforts to minimize sponsor and site burdens in this area.[4,5] Following referenced federal guidance and CTTI recommendations will lessen associated regulatory safety reporting workload.

Recommendations for Investigative Sites and Health Systems/Private Practices

1. **Determine whether the study protocol is suitable for your site.**

   Investigators, site staff, and associated health systems should review and assess the study protocol for basic feasibility[5] and prepare for possible challenges. **Above all, investigators and health systems/private practices should be selective in taking on trials, and decline studies that are a poor fit for their site.** They should also:

   - Engage reviewers with diverse perspectives to review protocols;
   - Communicate concerns to the study sponsor regarding time commitments, logistics, or other issues;
   - Request any needed clarifications regarding trial design; and
   - Develop realistic estimates of time/resource needs and anticipate likely delays due to patient recruitment or other reasons.

[2] CTTI's Recruitment Project at: https://ctti-clinicaltrials.org/our-work/quality/recruitment-2/
[3] CTTI's Quality by Design (QbD) Project at: https://ctti-clinicaltrials.org/our-work/quality/quality-by-design/
[4] FDA Draft Guidance, *Safety Assessment for IND Safety Reporting*, Guidance for Industry, Dec 2015 [5] CTTI's IND Safety Reporting Project at: https://ctti-clinicaltrials.org/our-work/ethics-and-human-research-protection/safety-reporting/

2. Manage recruitment effectively.

To ensure successful, sustainable study recruitment, investigators and staff should:

- Seek out potential patient perspectives on study participation;
- Communicate with study sponsors about any concerns related to recruitment (eligibility criteria, study burden, etc.);
- Discuss any challenges in screening or recruiting participants with site staff and the associated health system to identify strategies to overcome these;
- Develop a recruitment plan prior to study execution;
- Recruit patients from one's own practice and other areas and develop a referral system (local physicians, community centers, religious centers, health centers, etc.);
- Experiment with different recruitment strategies and track results; and
- Create realistic estimates for recruitment rates.

III. Recommendations for Site Budget and Contract Negotiations

Issues related to contracts and budgets present challenges for site investigators and sponsors. Stakeholders often have differing perspectives regarding the adequacy and accuracy of budget allocations, the fairness of budget and contract negotiations, the optimal schedule of payments, and the methods by which fair market value (FMV) is determined and applied to budget estimates and projections.

Recommendations for Investigative Sites

Investigators and site personnel should focus on four critical areas related to negotiating and executing budgets and contracts, addressing payment delays, and managing cash flow (see Table 1 for details):

1. **Review the study protocol and create cost assessments.**
   When negotiating the study budget, site research staff should review the study protocol/schedule of assessments, create their own cost assessments and supply justifications.

2. **Ensure that staff understand key contract components.**
   Well-trained site research staff (e.g., investigator, coordinator, or financial/office manager) should all understand key components of contract terms and/or delegate to a more qualified individual (e.g., outsource this activity; work with an attorney).

3. **Plan for and address delayed/outstanding payments.**
   Develop specific strategies to address delayed and/or outstanding payments.

4. **Manage site cash flow concerns.**
   Identify and incorporate strategies to manage site cash flow concerns.

Recommendations for Sponsors and CROs

1. **Use master agreements whenever possible.**
   Master agreements can greatly expedite the process of contracting across multiple studies and provide clarity to sponsors, CROs, and investigative sites. Sponsors should consider greater use of master agreements and the creation of a template set of key administrative elements for site contracts and associated research.

2. **Foster transparency about fair market value (FMV) determination.**
   Sponsors and CROs should provide sites with a transparent accounting of how FMV is determined. FMV calculation (benchmarked averaged estimate of procedure costs and associated reimbursement) often is not fully understood by sites and can become a source of mistrust. Better articulation from sponsors and CROs on FMV calculation may foster improved dialog and smoother contract negotiations between sponsors, CROs, and investigative sites.

IV: Recommendations for Investigators Interested in Conducting Additional Studies

A large proportion of site investigators indicate that they want to conduct additional trials but do not know how to access opportunities for doing so.[2] Interested investigators should:

1. Make use of investigator/trial matchmaking systems.

Investigators should consider using the multiple professional societies, trade associations, and companies that provide matchmaking services. These online systems match sponsors and CROs with qualified investigators and sites around the world.

2. Contact sponsors and CROs directly.

Many sponsors and CROs have online registration portals for investigators interested in conducting their clinical trials. Investigators should consider completing online profiles for sponsors and CROs conducting studies in their therapeutic area of expertise.

Table 1. Recommendations for Site Budget and Contract Negotiations

Critical Area	Recommendations for Investigative Sites
Executing budget negotiation	• Determine site personnel time • Assess startup costs, fee schedule, overhead, and any associated administrative costs (e.g., document storage or capital equipment) • Communicate with others at site regarding fees (e.g., principal investigator (PI), study coordinator, pharmacy, or radiology) • Leverage lessons learned from previous trials • Question sponsor proactively about FMV calculations relative to individual sites
Executing contract negotiations	• Implement master agreements to expedite contract negotiations • Clarify contract terms and supply justification • Identify and/or escalate any terms that are “deal breakers” and propose alternative language • Communicate with stakeholders at site regarding contract terms (e.g., PI, study coordinator, or financial department) • Leverage “lessons learned” from previous trials/contract negotiations • Proactively direct questions and contract concerns to sponsor
Addressing delayed/ outstanding payments	• Identify a primary point of contact for follow-up on payment issues • Follow a budget for the duration of the study (e.g., are there annual costs to invoice?) • Ensure that staff are familiar with and trained on budget line items, invoicing practices, payment methods, schedules, and timing • Leverage “lessons learned” from previous trials • Proactively communicate any concerns to sponsor
Managing site cash flow	• Negotiate a payment frequency that meets your site’s financial needs (e.g., monthly or quarterly) • Be aware of what can legitimately be included as an invoiced item and invoice for all relevant administrative costs • Identify and negotiate for inclusion in contract a payment trigger controlled by the site that will lead to faster payments (e.g., completion of data entry into electronic data capture system without queries; faster scheduling of monitor visits; completion of payment log; sponsor signature on budget amendment) • Ensure that budget realistically covers all site costs • Identify whether extra personnel (not originally budgeted) were needed during the trial and communicate to sponsor for consideration • Identify sponsor-related delays of payment that need to be escalated • Ensure that budget is updated with any protocol amendment(s)

Chart 1. Recommendations for Identifying and Developing New Investigators

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Recommendations for Identifying and Developing New Investigators

Medical schools, industry sponsors, clinical research organization (CROs), and physicians themselves should use active measures to identify, initiate, and train site investigators. Likewise, sponsors and CROs should provide structured opportunities for these new investigators to become involved in their clinical studies.

WHEN TASKED WITH THE INITIATION AND DEVELOPMENT OF INVESTIGATORS, STAKEHOLDERS SHOULD CONSIDER THE FOLLOWING PATHWAYS:

ACADEMIC MEDICAL EDUCATION & TRAINING

Many productive site investigators are introduced to clinical research during medical school or residency training. **Medical schools and training institutes** can foster future investigators and site staff by adopting some or all of the following measures:

- Create training programs that focus specifically on clinical research design and conduct (including certification and master's degree programs)
- Offer research training fellowships with specific experiences in site-based research activities
- Host lecture series/Grand Rounds on clinical research topics
- Formalize apprenticeship training programs working under experienced site investigators
- Include physician training in budget and contract negotiations for site-based research activities
- Incentivize and reward academic physicians for participating as site investigators for clinical trials
- Develop training programs for community/private-practice sites, as well as for sites affiliated with academic medical centers

ADDITIONAL TRAINING OPPORTUNITIES

Sponsor, CROs, Health Systems/Private Practices, Trade Associations, and Professional Societies should continue and extend existing efforts to initiate and encourage new investigators by:

- Forging new relationships and partnerships with site investigators
- Encouraging use of online training and educational curricula
- Exploring potential for working with physicians who work with unique, diverse patient populations, including members of under-served communities
- Providing new investigators opportunities for clinical trial experiences
- Avoiding oversaturation of sites with repeated requests to participate in trials
- Implementing "reward for quality" programs

PHYSICIAN APPRENTICESHIP/ DEVELOPMENT OPPORTUNITIES

- **Professional societies** and **trade organizations** should sponsor continuing education programs in site-based research activities
- **Research site staff** should be encouraged to attend conferences hosted by sponsors, CROs, industry, and/or professional and trade organizations focused on clinical research
- Provide validated certificate programs focused on Good Clinical Practice (GCP) training

Physicians interested in becoming site investigators can engage in observational or participatory training outside of medical school. Opportunities include:

- Serving as a clinical trial sub-investigator
- Shadowing experienced Investigators
- Participating on an institutional review board (IRB)

ABOUT THE RECOMMENDATIONS

- These recommendations are based on results from CTTI's Investigator Community project.
- CTTI's Executive Committee approved on September 25, 2017.
- Funding for this work was made possible, in part, by the Food and Drug Administration through grant R18FD005292, views expressed in written materials or publications and by speakers and moderators 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 organization imply endorsement by the United States Government. Partial funding was also provided by pooled membership fees from CTTI's member organizations.
- All of CTTI's official recommendations are publicly available. Use of the recommendations is encouraged with appropriate citation.

ABOUT CTTI

The Clinical Trials Transformation Initiative (CTTI)—co-founded by Duke University and FDA—is a public-private partnership whose mission is to develop and drive adoption of 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 therapeutic prevention and treatment options.