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Improving the Quality Conduct and Efficiency of Clinical Trials with Training:
Recommendations for Qualification of Investigators and Delegates

Author names and affiliations

Jimmy Bechtel,¹ Tina Chuck,² Annemarie Forrest,³ Christine Hildebrand,⁴ Janette Panhuis,⁵
Suzanne R. Pattee,⁶ Sabrina Comc-Savic,⁷ Teresa Swezey^{3, 8}

¹Society for Clinical Research Sites, 7250 Parkway Dr, Suite 405, Hannover MD 21076, jimmy.bechtel@myscrs.org; ²The Feinstein Institutes for Medical Research, Northwell Health, 125 Community Dr, Great Neck, NY 11021, tchuck@northwell.edu; ³Clinical Trials Transformation Initiative, PO Box 17969, Durham, NC 27714, annemarie.forrest@duke.edu; ⁴Amici Clinical Research, 34 E Somerset St, Raritan, NJ 08869, christine.hildebrand@amicicr.com; ⁵Population Health Research Institute, 237 Barton St E, Hamilton, ON, Canada L8L 2X2, janette.panhuis@phri.ca; ⁶US Food and Drug Administration, 10903 New Hampshire Ave, White Oak, Bldg. 51, Rm. 3328, Silver Spring, MD 20993, suzanne.pattee@fda.hhs.gov; ⁷The Medicines Company, 8 Sylvan Way, Parsippany, NJ 07054, sabrina.comic-savic@themedco.com; ⁸Department of Population Health Sciences, School of Medicine, Duke University, 215 Morris St, Durham, NC 27701, teresa.swezey@duke.edu.

All authors are considered equal contributors.

Corresponding author: Annemarie Forrest, annemarie.forrest@duke.edu

Keywords

Clinical trials, investigator qualification, good clinical practice, investigator training

Abbreviations

CRO, Contract Research Organization; CTTI, Clinical Trials Transformation Initiative; FDA, Food and Drug Administration; GCP, Good Clinical Practice; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; US, United States.

Abstract

The Clinical Trials Transformation Initiative (CTTI) Investigator Qualification Project addresses the need for a more efficient and effective means of identifying qualified clinical investigators and delegates. Selection of investigators and delegates who are qualified by training and experience to conduct clinical trials is essential to safeguarding protections for study participants and ensuring data quality and integrity. Sponsors generally document investigator qualification through training on the principles of good clinical practice (GCP), as defined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), adopted by regulatory authorities in the United States, Japan and the European Union. Although these GCP principles provide an important foundation for promoting the conduct of quality clinical trials, the industry standard “one-size-fits-all” GCP training may not fully prepare investigators and delegates for conducting quality clinical trials. Routine GCP training alone may not be sufficient to prepare an inexperienced member of a site team, while repeating such training is unlikely to enhance the qualifications of an experienced researcher. The CTTI project team used findings from qualitative research activities, as well as input from an expert meeting with multiple stakeholders, to identify gaps and redundancies in the current training of investigators and their delegates and recommend practical, action-based solutions. CTTI provides recommendations on how to implement a more efficient and effective means of qualification for investigators and delegates, determine whether a site team is a good fit for a particular protocol, and improve the quality of clinical trial conduct.

1 INTRODUCTION

Ensuring clinical investigators and their delegates are qualified to conduct clinical trials is essential to safeguarding protections for study participants and ensuring data quality and integrity. Under United States (US) Food and Drug Administration (FDA) regulations, trial sponsors are responsible for selecting investigators qualified by training and experience [1]. Sponsors generally document investigator qualification through training on the principles of good clinical practice (GCP), as defined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) principles (ICH E6(R2) [1, 2]), adopted by regulatory authorities in the United States, Japan and the European Union. While GCP training is essential, new methodologies can improve the conduct of quality clinical trials, as well as trial efficiency and effectiveness.

GCP training of investigators and delegates is usually presented as a “one-size-fits-all” approach, which may not fully prepare investigators and delegates to conduct quality clinical trials. Although training in GCP principles provides an important foundation for the conduct of quality clinical trials, routine GCP training alone is not sufficient to prepare an inexperienced member of a site team, and repeating such training is unlikely to enhance the qualifications of an experienced researcher. Thus, clinical trial sites may waste considerable time and resources attending routine GCP training that does not effectively support clinical trial quality. In fact, the most common deficiencies noted during investigator inspections are directly related to GCP principles [3]. Furthermore, prior studies have identified concerns that clinical research training is time-consuming [4], redundant [5, 6], lacking in specificity [7], and unrelated to research validity [8].

The Clinical Trials Transformation Initiative (CTTI) 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. CTTI recognized the need for a more efficient and effective means of identifying whether investigators and their delegates are qualified to conduct clinical trials. To address this issue, CTTI conducted the Investigator Qualification Project, which was guided by five objectives: 1) develop a framework that defines the conduct of quality clinical trials; 2) describe the impact GCP training has on the conduct of quality clinical trials; 3) identify gaps and redundancies in the current training of investigators in preparation for the conduct of quality clinical trials; 4) identify key learning objectives for training to qualify investigators for the conduct of quality clinical trials; and 5) provide key recommendations to better prepare clinical investigators for the conduct of quality clinical trials.

Using evidence gathered through qualitative interviews with subject matter experts [9] and a multi-stakeholder expert meeting [10], CTTI developed consensus-based recommendations on how to identify qualified site teams while simultaneously reducing inefficiencies in training and better preparing site teams for the conduct of quality clinical trials. These recommendations address how to implement a more efficient and effective means of qualification, determine whether a site team is a good fit for a particular protocol, and improve the quality of clinical trial conduct.

2 MATERIALS AND METHODS

2.1 Qualitative Study

CTTI conducted a qualitative descriptive study using semi-structured interviews with investigators and clinical trial sponsors to 1) describe the characteristics that define the conduct of quality clinical trials and concerns related to the conduct of quality clinical trials; 2) identify critical tasks that lead to the conduct of quality trials; 3) identify key knowledge and skills necessary to perform critical trial tasks with quality; and 4) discover gaps and redundancies in existing clinical trial training, including GCP training on critical tasks. Details of participant eligibility and selection, data collection and analysis, as well as the results of this study, focusing on critical tasks and burdens, redundancies, and gaps in GCP training are described in Swezey et al. [9].

In brief, the majority of respondents' definitions of conduct of quality clinical trials mapped to more than one of the 13 principles of GCP [2]. The top three most frequently mapped principles were 1) compliance with a scientifically sound protocol; 2) accurate reporting, interpretation, and verification of study data; and 3) freely given informed consent from every participant prior to participation. Most respondents also said that the GCP domain "ethics," which is one of seven GCP categories, is central to the conduct of quality clinical trials and serves as the foundation for all GCP principles. Data quality and integrity and quality of informed consent were frequently mentioned concerns.

Similarly, respondents' descriptions of the critical tasks associated with the conduct of quality clinical trials also linked to GCP principles. The top three most frequently named critical tasks were 1) informed consent; 2) protocol compliance; and 3) protecting participants' health and safety, which map to the GCP principles of 1) informed consent freely given from every subject prior to participation; 2) compliance with a scientifically sound protocol; and 3) rights, safety, and well-being of subjects prevail, respectively. Respondents described a variety of knowledge and skills as essential to conducting the top three critical tasks, as well as for the conduct of quality clinical trials in general.

Suggestions for improving GCP training with respect to the top three critical tasks were provided. For example, respondents proposed:

1. better defining what informed consent involves and providing training on writing clearer, more concise consent forms that are easier for participants to understand, and the role of the investigator in the informed consent process;
2. aiding protocol compliance by better defining protocol deviations/violations and clinically significant events and emphasizing training on all aspects of the protocol; and
3. promoting participant safety by clearly defining specific endpoints, adverse events, and monitoring periods, and providing training on how participant data may be used in the future, particularly for topics such as genetic data, as these may impact participant safety and rights for many years after the study has been completed.

While investigators and sponsors believe that GCP principles generally address the top three critical tasks, they felt that current GCP training is burdensome and repetitive. They suggested that content should focus more on hands-on application of GCP principles in a real-world, skills-

based environment, and training should be more engaging and interactive. Mentorship as well as opportunities to engage in ongoing real-world training were seen as important means of supporting investigators. Respondents also expressed frustration about a lack of research training for physicians, resulting in investigators who are well-trained in medicine, but poorly qualified to lead research. Several investigators proposed that GCP training be conducted less frequently, particularly for non-critical elements, such as historical information, which was viewed as redundant. Other suggestions included standardizing and/or centralizing GCP training.

2.2 Expert Meeting

CTTI convened an expert meeting in December 2017 to discuss the interview findings and the proposed framework of characteristics of a qualified site team, drawing from the expertise of the meeting attendees [10]. Over 50 attendees represented academic medical centers, private practice/research sites, industry (including pharmaceutical, medical device, and contract research organizations [CROs]), government (including the National Institutes of Health and the FDA), and study participant representatives. The experts discussed the current standard practices for investigator qualification and identified the issues that they hoped to resolve or improve as a result of this project. Six key themes emerged during the expert meeting.

1. **When evaluating qualification, look at the whole community, not just the individual.** It is time to expand the focus of qualification beyond the individual investigator. To conduct a quality clinical trial, investigators should be supported by an effective study team and infrastructure appropriate to that trial's specific requirements. Therefore, the focus of qualification should be on evaluating the overall capabilities of a prospective study team and clinical site.
2. **Go beyond "checking the box."** In addition to didactic, lecture style training on GCP content, training in role-specific skills is needed for all members of the study team. Additional modes of learning, such as just-in-time training, learning through doing, mentorship, and peer-to-peer training can be highly effective in supporting continuous improvement for investigators and delegates. Site personnel should actively engage in the learning process by identifying specific learning needs and seeking additional support and training, as needed.
3. **Incorporate the voice of study participants.** All training needs to evolve to be more participant-centric and include factors that matter to study participants.
4. **Incentives are powerful.** An accreditation process would motivate improvement while allowing sites to meet standards in their own way. It would also allow sponsors to more readily identify sites that are prepared and qualified for the quality of trial conduct.
5. **Communication is key.** Early communication between sites, sponsors, and CROs can help improve preparedness to conduct a trial. Inviting sites to review the study protocol during the selection process will enable them to provide feedback that can make the protocol more feasible and applicable to real-world practice. Once a clinical trial begins, communication within and between sites can promote shared learning, address issues, and advance the education of everyone involved in conducting the trial.

- 6. Build in quality measures.** Once new training modalities are implemented, quality measures are needed to determine if the training is working well and driving measurable improvements in the quality of trial conduct.

In addition to these themes, meeting attendees discussed solutions to inform the development of project recommendations and tools [11].

2.3 Development of Recommendations and Resources

After the project team determined that the evidence-gathering objectives had been met and no major gaps in evidence remained, the team followed a systematic development process to craft a series of project recommendations and resources for all clinical trial stakeholders [11]. As with all its projects, CTTI aimed to develop recommendations that are actionable, concise, consensus-driven, and easily accessible by an external audience.

To this end, the project team followed an iterative development process. First, team members used the data from the interviews and input from the expert meeting to draft and propose project recommendations and tools. Next, the project team sought and incorporated input from the Executive Committee Champion, CTTI leadership, CTTI members, and an ad hoc committee comprised of change agents independent of the project team. Refinement of the recommendations and resources continued until all groups reached consensus. Finally, the CTTI Executive Committee approved the recommendations and resources.

3 RECOMMENDATIONS AND DISCUSSION

3.1 Recommendations

Successful clinical trials consist of a well-designed protocol, robust site-based research infrastructure, and well-qualified site teams. Therefore, these recommendations on investigator qualification should be used in conjunction with CTTI's Quality by Design recommendations [12] on protocol development and CTTI's Investigator Community recommendations [13] for a holistic approach to conducting quality clinical trials.

The recommendations presented below are divided into two stakeholder groups: 1) sponsors and CROs, and 2) investigators and their delegates.

3.1.1 Expand qualification beyond GCP training

GCP principles are critical to the reliability and accuracy of trial data and the protection of human subjects. However, repetitive didactic presentation of GCP principles is unlikely to either adequately prepare an inexperienced member of a site team or add value to the practice of an experienced researcher.

CTTI's recommendations on GCP Training for Investigators [14] describe how to optimize GCP training for members of a site team who may need education about applying GCP elements to conduct quality protocols. Investigators and delegates who regularly demonstrate proficiency in applying GCP elements may be exempted from further GCP training requirements, while still benefiting from protocol-specific training.

Recommendation	Investigators / Delegates	Sponsors	CROs
Move away from repetitive GCP training as the one-size-fits-all approach to qualifying investigators and their delegates for the conduct of clinical trials.		✓	✓
Develop educational programming that is tailored to your protocol and the members of your site team.		✓	✓
Recognize that completion of GCP training alone is insufficient to fully prepare for the conduct of a quality clinical trial.	✓		
Evaluate the site team's preparedness to conduct clinical research before seeking selection as a trial site. To support the recommendations and guide this assessment, CTTI has developed a framework of characteristics describing attributes that can be modified through learning and training [15] (Figure 1).	✓		

3.1.2 Identify the unique learning requirements of each trial and site

The knowledge, skills, and experience required for investigators and their delegates will vary with each trial. Different study phases, disease states, trial designs, study participant populations, and clinical settings should guide unique training requirements for each protocol.

Recommendation	Investigators / Delegates	Sponsors	CROs
At the beginning of the site selection process, provide the draft or completed protocol to potential site teams so that investigators can assess their ability to conduct the protocol and identify any learning requirements. This transparency is crucial to establishing a collaborative approach to identifying qualified investigators and their delegates.		✓	✓
Before the start of the trial, allow site teams to review the protocol and provide feedback on potential feasibility issues or concerns, so that problems can be addressed prior to initiation. In addition, site teams who have previously reviewed a protocol will better understand the protocol requirements once the study begins. This exchange of information is a critical part of the learning necessary for each new protocol and engages the site team in a way that didactic instruction does not.		✓	✓
Complete thorough pre-study visits. To support the recommendations, CTTI has developed a framework of characteristics to help guide the assessment and selection of sites [15].		✓	✓
To prepare for a specific trial, request the protocol—even if only in draft—as soon as a sponsor or CRO contacts the site for possible selection, and assess whether the site and its delegates are adequately qualified and prepared to conduct the trial.	✓		
Discuss the assessment findings openly with the sponsor to close any gaps in preparedness. Such transparency and collaboration can help to ensure that the educational resources provided by the sponsor are customized to support the site team’s efforts to meet the specific needs of a protocol and conduct a quality trial.	✓		

3.1.3 Take a targeted approach to qualification

A targeted, risk-based approach to qualification identifies potential risks in protocol execution and focuses targeted, applied learning solutions toward high-risk areas. Risk analyses may be improved by considering the potential challenges associated with a particular protocol as well as the most common deviations that have occurred on protocols similar in design or therapeutic area.

Recommendation	Investigators / Delegates	Sponsors	CROs
Critically evaluate the skills, knowledge, and experience of site teams before selecting sites and formulating learning requirements.		✓	✓
Discuss the evaluation of the site openly with investigators. Transparency surrounding the sponsor's assessment of a site team's ability to conduct a particular protocol is critical for identifying educational needs and creating appropriate training to ensure that investigators and their delegates are truly qualified.		✓	✓
Consider reallocating resources to identifying qualified investigators and their delegates as needed. Investing time and effort toward site selection and preparation can preempt quality issues and avoid the need to invest additional resources to fix them.		✓	✓
Evaluate investigator and delegate performance on past protocols and develop policies, procedures, or educational programming to improve the conduct of future clinical trials. For example, reviewing common protocol deviations may allow investigators to create strategies to avoid such deficiencies. Analyses of recruitment and enrollment efforts may identify tactics that have worked, as well as areas that need improvement. Once addressed, focus on closing gaps that come up on a trial-by-trial basis.	✓		
Share any findings with sponsors and CROs during the site selection process to guide effective preparation of the site team.	✓		

3.1.4 Improve Educational Offerings

To ensure that investigators and their delegates are qualified, educational programming should focus on the learning requirements of the specific trial and address potential high risks in protocol execution as well as the gaps in knowledge and skills identified during site assessment. Educational programming should be created with adult learners in mind and take into account individual study roles of site team members.

Active learning encompasses a broad range of unstructured and structured (or informal and formal) approaches to increasing knowledge and skills. Training is one type of active learning that imparts information through a structured, learner-centered approach with measurable outcomes. Site-based learning activities may include mentoring programs, job-shadowing programs, virtual or in-person knowledge-sharing networks, and mock run-throughs of study participant visits and protocol procedures. CTTI has compiled a compendium of existing

mentoring programs and knowledge-sharing networks¹ to illustrate how these activities are being implemented in practice [16].

Recommendation	Investigators / Delegates	Sponsors	CROs
Recognize the value of learning approaches that go beyond traditional training methods, and consider establishing knowledge-sharing networks for specific trials that provide forums for information exchange and peer support.		✓	✓
Accept documentation of the completion of previous relevant training, and/or the continued application of knowledge and skills during the conduct of clinical trials as evidence of the qualification of investigators and their delegates.		✓	✓
Consider the previous application of required skills when tailoring protocol-specific educational programming to meet individual learning needs.		✓	✓
Apply adult learning approaches when developing educational programming particularly at Investigator Meetings and Site Initiation Visits. Consider using practical hands-on training rather than, or in addition to, traditional didactic lecture style review of protocol content.		✓	✓
Clearly define gaps in knowledge and skills when considering the learning requirements for a study, and develop or recommend existing educational programming to address these gaps.		✓	✓
Create role-, topic- and protocol-specific education goals that communicate what is new, unique, and difficult about the study.		✓	✓
Recognize that different members of the site team may benefit from different types of education and experience in pursuit of the same learning goal.		✓	✓
Consider how to best meet the learning needs of site personnel, including through approaches other than traditional training.	✓		
Seek out educational offerings that meet content-specific learning goals and suit individual learning styles. Time the completion of educational programming to coincide with conducting trial activities that require the knowledge and skills learned.	✓		

¹ A knowledge-sharing network is a collection of individuals and teams who come together across organizational, spatial, and disciplinary boundaries to create and share a body of knowledge.

Recommendation	Investigators / Delegates	Sponsors	CROs
Encourage more experienced members of the site team to participate in mentoring programs with less experienced members.	✓		
Document learning activities, as well as the successful application of knowledge and skills pertinent to each person's role in conducting trials, to serve as a record demonstrating qualifications for the conduct of clinical trials.	✓		

3.1.5 Additional Resources

CTTI prepared a variety of resources to assist in the evaluation and documentation of qualification for investigators and their delegates. These companion resources include CTTI's Investigator Qualification Framework [15], a Quick Reference Guide to Documenting Qualification for Investigators and Their Delegates [17], and a documentation template [18].

3.2 Discussion

Clinical trial education and training are not given the same emphasis as medical education and training of clinical professionals, such as physicians and nurses. Research training typically occurs ad hoc, as investigators enter the research community and implement clinical trials. As a result, investigators vary widely in their backgrounds and training needs.

The CTTI project team recommendations focus on the findings that a successful approach to learning cannot be one-size-fits-all; rather it should be fit-for-purpose, risk-based, focused on application, and inclusive of non-training modalities, such as mentoring. To avoid the burden associated with repetitive clinical trial training, sponsors may recognize previous training and alternate qualification activities and methods.

Effective clinical trial training should meet real on-the-job needs and change the behavior of study personnel. It is important for sponsors and CROs to assess the need for training that extends beyond knowledge of GCP principles to include other areas important for the quality of trial conduct (e.g., quality management and project management). Learning professionals can assist sponsors and CROs with risk and needs assessments; address potential issues with format, delivery, content, communication, and evaluation of clinical trial training; and advise on best practices for reviewing and revising trainings.

Investigators with little experience may need a comprehensive, more time-intensive type of GCP training that provides opportunities for them to practice and apply what they have learned. Experienced investigators may only need a version of GCP training that teaches new best practices or reviews scenarios specific to a particular protocol. A test-out option could allow personnel to avoid repeating material they have already mastered. All investigators and their delegates can benefit from customized training that addresses aspects of a study that are at high risk for protocol deviations.

4 CONCLUSIONS

These recommendations describe a new approach to identifying and preparing investigators and their delegates to be qualified to perform clinical research. The recommendations were informed by CTTI's interviews, expert meeting, the experience and expertise of the CTTI project team members, and feedback from CTTI Steering and Executive Committee members [19]. This approach moves beyond repetitive GCP training as a one-size-fits-all solution to qualification towards targeted and effective educational programming. Sponsors and CROs, investigators, and other research professionals may benefit from shifting their perception of qualification activities from necessary but low value to an opportunity for improved quality and efficiency. This new approach proposes to recognize the value of previous training and experience that supports the transfer of skills between studies. Instead of repetitive educational material, gaps in knowledge or skills can be identified and addressed using adult learning methods to deliver risk-based, fit-for-purpose training. Improved training can enrich understanding of how GCP principles apply to the conduct of a specific clinical trial and enhance successful implementation of quality principles in a specific setting.

While qualification of investigators and their delegates is a critical component of site success, training activities are not the sole factor underlying investigator or site success in conducting quality clinical trials. Success of a clinical trial also depends on a "recruitable" protocol that asks an important medical question and is feasible to conduct. A strong organizational research infrastructure at trial sites is also critical to success (Figure 2). CTTI's work on Quality by Design and Strengthening the Investigator Site Community describe these topics in depth elsewhere [20, 21].

CTTI hopes that these recommendations can foster a culture of collaboration among sponsors, CROs, and site teams in preparing investigators and their delegates to conduct quality clinical trials. This cultural shift can engage sites to be active contributors in identifying their learning needs in order to successfully implement protocols. Adoption of these recommendations can help to enable improved clinical trial quality and efficiency, as well as greater protections for study participants.

Improving training and implementing more effective methodologies for adult learning can help to enable the qualification of investigators and delegates and enhance the clinical trial enterprise. Rather than continuing to execute a didactic, one-size-fits-all approach to training investigators and documenting qualification, sponsors and CROs can adopt a multifaceted approach to investigator qualification that combines training in the real-world application of GCP principles with role and protocol-specific training. Facilitating a new approach to investigator qualification can enable investigators and their delegates to conduct quality clinical trials, which will in turn help to further assure protections for study participants, and quality and integrity of data.

5 FIGURES WITH CAPTIONS

Figure 1: Framework of Characteristics of a Qualified Site Team

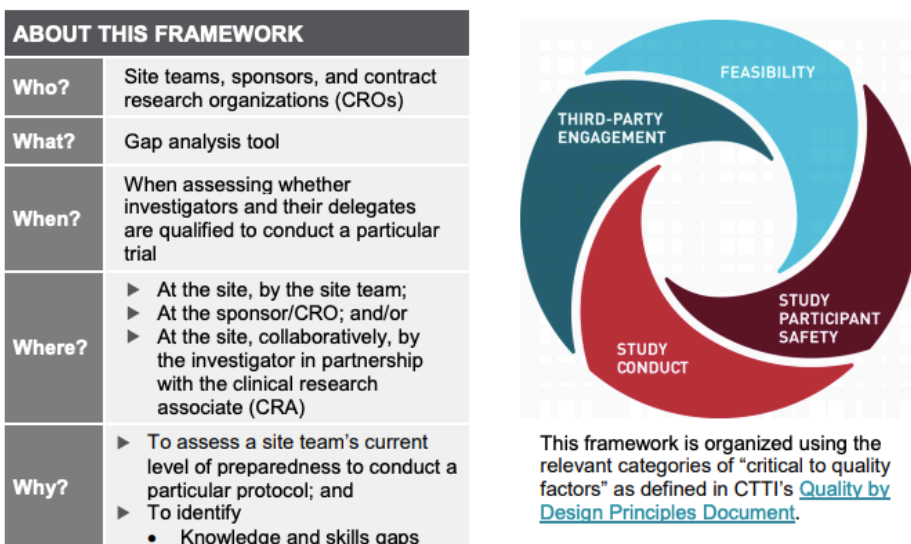


Figure 2: Components of Investigator Success



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