GOOD CLINICAL PRACTICE TRAINING FOR THE CONDUCT OF CLINICAL TRIALS

LITERATURE REVIEW REPORT

Purpose of the Report: In 2013, CTTI’s Good Clinical Practice (GCP) Training Project Team commissioned a literature review of current practices in the implementation of GCP training in order to inform the project. The review was conducted and prepared at the Duke Clinical Research Institute by Amy Kendrick, MSN, and Megan Chobot, MSLS, of the Duke Evidence Synthesis Group, Gillian Sanders, PhD, Director.
METHODS

Literature Search Strategy
To identify relevant published literature, we searched PubMed®, limiting the search to articles published from January 1, 2003, through July 1, 2013. (Appendix A contains the search terms.) We believe that articles published in the past 10 years adequately represent current practices for Good Clinical Practice (GCP) training. An experienced search librarian guided all searches. All articles were imported into an electronic database (EndNote®, Thomson Reuters, Philadelphia, PA).

Inclusion and Exclusion Criteria
The criteria used to screen articles for inclusion/exclusion at both the title-and-abstract and full-text screening stages were:

Inclusion:
- U.S. focused or U.S. component
- Discussed elements of GCP training
- Related to clinical research beyond Phase 1 (so human subjects are being recruited)
- English language
- Published in the past 10 years

Exclusion:
- Discussed only HIPAA (Health Insurance Portability and Accountability Act)
- Focused on building clinician-researcher workforce for the future (for example, generic descriptions about how to ensure there are enough dentists, surgeons, psychiatrists, pediatricians; doing research in the future)

Article Selection
Figure 1 shows the flow of literature through the search and screening process. Using the prespecified inclusion and exclusion criteria described above, two individuals independently reviewed 2,961 titles and abstracts for potential relevance. There were 258 articles included by either reviewer that underwent full-text screening. At the full-text review stage, two individuals independently reviewed the articles and indicated a decision to include or exclude the article for data abstraction. Disagreements on inclusion or exclusion were reconciled by a secondary review or a third-party arbitrator if needed. Thirty-one full-text articles met eligibility criteria and were included for data abstraction. All screening decisions were made and tracked in a Distiller SR database (Evidence Partners Inc., Manotick, ON, Canada).
Figure 1. GCP Training Literature Flow Diagram

2958 citations identified by MEDLINE literature search

3 added from manual searching

2961 citations

2703 abstracts excluded

258 articles passed abstract screening

227 articles excluded:
• 187 were not related to GCP training in research
• 40 had no U.S. GCP training component

31 articles passed full-text screening for data abstraction:
• Qualitative and Survey: 10
• Investigator and Site Staff Training: 7
• Research Networks: 6
• Policy and Guidance: 4
• Online Training Modules: 4
Data Abstraction
The research team created data abstraction forms and evidence table templates for abstracting data. One reviewer abstracted the data, and the second reviewed the completed abstraction form alongside the original article to check for accuracy and completeness. Disagreements were resolved by consensus, or by obtaining a third reviewer’s opinion if consensus could not be reached. To aid in both reproducibility and standardization of data collection, data abstraction instructions were reviewed at each stage of the process.

The elements collected in the data abstraction forms were specified in consultation with the GCP Training project team. These included the type of article, training audience, frequency of training, proof of training, and components of GCP covered in training. We also recorded if data elements were not reported in the article. (Appendix B contains a list of data elements abstracted.)

We obtained the GCP components by evaluating sample articles for how the training elements are commonly divided and presented. Thus, our list of GCP components included:

- Overview of GCP/International Conference on Harmonisation (ICH)
- Drug development/investigational new drug (IND)
- Institutional review board (IRB)/independent ethics committee (IEC) oversight
- Investigator responsibilities
- Staff training and delegation of responsibilities
- Protocol adherence
- Data management
- Investigational drug (accountability, masking, randomizing)
- Statistics (data and safety monitoring board [DSMB], randomization plans, analysis plans, sample size)
- Informed consent
- Vulnerable populations
- Serious adverse events (SAEs)/adverse events (AEs)
- Monitoring
- Trial records (mandatory files, timeframe to retain)
- Audits and inspections
- Reporting (FDA, sponsor)
- Medical device regulations
Data Synthesis
The set of 31 included articles was sorted, based on a review of their content and structure, into the following 5 categories for further discussion in the Results section:

1. **Qualitative and Survey** (10 survey summaries and qualitative reviews)
2. **Investigator and Site Staff Training** (7 author recommendations)
3. **Research Networks** (6 descriptions of experiences implementing GCP training across a research network)
4. **Policy and Guidance** (4 articles clarifying how regulations are to be interpreted)
5. **Online Training Modules** (4 descriptions of software developed to implement GCP training)

RESULTS

**Qualitative and Survey Articles**
We identified 10 articles\(^1\)\(^-\)\(^{10}\) that were primarily qualitative and survey-based, and this group highlights the variability in implementation of GCP training programs (Table 1). The first such article\(^1\) is based on survey results from 1,479 NIH-funded scientists in 2002. Six articles\(^2\)^\(^-\)^\(^{5}\),\(^8\)\(^-\)\(^{10}\) based on surveys of various groups within the clinical research arena each make a case for a unified and consistent approach to training in research ethics. Another article\(^6\) also highlights the inadequacy of training but expands this idea further by calling for clear research ethics training goals, with measurable outcomes, as a way to facilitate consistency in content and requirements of training programs. Two articles focused their surveys on specific components of GCP training: conflict of interest disclosure to potential subjects\(^4\) and IRB guidelines.\(^7\) These articles also reinforce that GCP training programs vary both in content and audience.

The qualitative and survey-based articles had some limitations. The most recent survey\(^9\) did not capture any details about the content or delivery methods used in GCP training across the 200 NIH-funded institutions they surveyed. The data used in one\(^1\) was 5 years old, and in another\(^4\) the survey was limited because it used a convenience sampling strategy of 300 coordinators attending a professional conference. Further, the surveys did not include information on the frequency of training or what sort of testing/proof of training was required.
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<td>Anderson, 2007¹</td>
<td>Survey: 7,700 researchers</td>
<td>Investigators</td>
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<td>Investigators and site staff</td>
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<td>Site staff</td>
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<td>Kalichman, 2007⁶</td>
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<td>Investigators and site staff</td>
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<td>Kotzer, 2007⁷</td>
<td>Survey: Online, 643 research staff</td>
<td>Investigators and site staff</td>
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<td>Resnik, 2012⁹</td>
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<td>Investigators and site staff</td>
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<td>Steneck, 2007¹⁰</td>
<td>RCR overview</td>
<td>Investigators and site staff</td>
<td>NR</td>
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<td>X</td>
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Abbreviations: ASBH=American Society for Bioethics and Humanities; CITI=Collaborative Institutional Training Initiative; CRC=clinical research coordinator; CTSA=Clinical and Translational Science Award; FDA=Food and Drug Administration; FHI=Family Health International; GCP=good clinical practice; ICH=International Conference on Harmonisation; IEC=independent ethics committee; IRB=institutional review board; NIH=National Institutes of Health; NR=not reported; RCR=responsible conduct of research; SAEs=serious adverse events
Investigator and Site Staff Training Articles

We identified seven articles\textsuperscript{11-17} that discuss the variability of training for investigators and staff (Table 2). These articles, however, are not survey-based, and several of them go into more detail about training strategies for both staff and specific investigator subgroups. Another article\textsuperscript{13} discusses training needs in relation to FDA monitoring for compliance and implications for misconduct. One article\textsuperscript{15} discusses the variety of training programs for consent administrators, making the case that consent training needs to be a priority in order to help mediate health disparities found in recruitment of subjects for clinical research projects. Another\textsuperscript{17} calls for certification to enhance regulatory compliance by investigators, as proposed by Academy of Pharmaceutical Physicians and Investigators (APPI).
Table 2. Summary of Investigator and Site Staff Training Articles

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<td>Beresin, 2003</td>
<td>Investigators</td>
<td>Classroom</td>
<td>NR</td>
<td>None</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<td>Chen, 2003</td>
<td>Investigators and staff</td>
<td>Classroom, paper-based</td>
<td>NR</td>
<td>None</td>
<td>X</td>
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<td>Hamrell, 2010</td>
<td>Investigators and staff</td>
<td>Online and paper-based</td>
<td>NR</td>
<td>None</td>
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<td>Jha, 2010</td>
<td>Site staff</td>
<td>Paper-based</td>
<td>NR</td>
<td>Certificate</td>
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<td>Larson, 2009</td>
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<td>Classroom</td>
<td>NR</td>
<td>Test</td>
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<td>Trembath, 2011</td>
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<td>Vulcano, 2012</td>
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<td>NR</td>
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<td>Certificate</td>
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Abbreviations: FDA=Food and Drug Administration; GCP=good clinical practice; ICH=International Conference on Harmonisation; IEC=independent ethics committee; IRB=institutional review board; NR=not reported; SAEs=serious adverse events
**Research Network Articles**

We identified six articles\textsuperscript{18-23} with discussions of implementing GCP training across research networks (Table 3). Two of these\textsuperscript{18,23} discuss experiences in the Practice-Based Research Network (PBRN) when instituting GCP training across research sites. One\textsuperscript{18} reports that a variety of training methods allow training to be more flexible to adapt to community-based researchers. This article suggests discussing with IRBs how to define the appropriate levels of training needed for site staff by taking into consideration the lower risk emphasis of PBRN research (surveys, practice improvement, or behavioral interventions).

Two articles\textsuperscript{19,20} discuss processes implemented by the Academy of Family Physicians National Research Network (AAFP-NRN) in instituting GCP training across their research sites. In one of these,\textsuperscript{20} the initial emphasis is to provide classroom training during weekend site initiation visits. Written materials are also provided so that as site staffing changes and responsibilities are delegated, the site staff can update their own training. In the other,\textsuperscript{19} the Collaborative Institutional Training Initiative (CITI) training modules, either online or paper-based, are presented as an alternative method to ensure that a consistent GCP training message is achieved and certified at least every 3 years.

One article\textsuperscript{21} details the online GCP training developed for the military research network, as mandated by the Human Use Regulatory Affairs Advisor (HURAA). For this network, the online aspect is easy to universally implement, and there is a testing requirement at the end of the training to document that content was delivered and processed by the individual. Another article\textsuperscript{22} provides details about the content and experience of the National Institute of Drug Abuse (NIDA) when instituting GCP training across their research network. While that network had no testing or certification requirements, the content is comprehensive and is provided in all three possible modalities: classroom, online, and paper-based self-study. The article also discusses NIDA’s quality assurance and monitoring initiative and suggests that it be left to the study’s principal investigator to determine the training content and frequency based on each site’s performance.
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<td>Dolor, 2008¹⁸</td>
<td>Investigators and site staff</td>
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<td>NR</td>
<td>Test + certificate</td>
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<td>3 years (minimum)</td>
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<td>Hu, 2004²¹</td>
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<td>Online</td>
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Abbreviations: AAFP-NRN=Academy of Family Physicians National Research Network; FDA=Food and Drug Administration; GCP=good clinical practice; HURAA=human use regulatory affairs advisor; ICH=International Conference on Harmonisation; IEC=independent ethics committee; IRB=institutional review board; NIDA=National Institute on Drug Abuse; NR=not reported; PBRN=Practice-Based Research Network; SAEs=serious adverse events
Policy and Guidance Articles
Among the four articles\textsuperscript{24-27} we identified that are policy or guidance documents, three are from U.S. government entities: FDA,\textsuperscript{24} Department of Health and Human Services (DHHS),\textsuperscript{25} and Office for Human Research Protections (OHRP)\textsuperscript{27} (Table 4). Articles that discuss the FDA and DHHS each reinforce that it is ultimately the investigator’s responsibility to ensure that their staff is adequately trained and that responsibilities have been delegated appropriately. Another article\textsuperscript{26} presents a competence statement from the Academy of Physicians in Clinical Research (APCR). This article asserts that after an investigator receives certification in clinical research, which is available through the APCR, the investigator should be deemed exempt from additional research training—provided that the research they are participating in is within his or her area of clinical expertise.
Table 4. Summary of Policy and Guidance Articles

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<tr>
<td>Anderson, 2011&lt;sup&gt;24&lt;/sup&gt; FDA</td>
<td>Investigators and staff</td>
<td>Paper-based</td>
<td>NR</td>
<td>None</td>
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<td>U.S. Department of Health and Human Services, 2009&lt;sup&gt;25&lt;/sup&gt; DHHS</td>
<td>Investigators</td>
<td>Non-binding guidance document</td>
<td>NR</td>
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<td>Koren, 2011&lt;sup&gt;26&lt;/sup&gt; APCR</td>
<td>Investigators</td>
<td>NR</td>
<td>Once certified, never need to repeat</td>
<td>Certificate</td>
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<td>Schwetz, 2007&lt;sup&gt;27&lt;/sup&gt; OHRP</td>
<td>Investigators and staff</td>
<td>Classroom, paper-based, online</td>
<td>NR</td>
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Abbreviations: APCR=Academy of Physicians in Clinical Research; DHHS=Department of Health and Human Services; FDA=Food and Drug Administration; GCP=good clinical practice; ICH=International Conference on Harmonisation; IEC=independent ethics committee; IRB=institutional review board; NR=not reported; OHRP=Office for Human Research Protections; SAEs=serious adverse events
Online Training Module Articles

We identified four articles\textsuperscript{28-31} that discuss a specific online GCP training package or system (Table 5). The package with the most components\textsuperscript{29} was developed with the University of Miami and provides training to users at academic institutions, government agencies, and commercial organizations in the United States and around the world. They have added recertification modules to streamline training when IRBs require recertification within a specific timeframe.

Two of the four articles discuss the training system developed by Family Health International (FHI)\textsuperscript{30,31}. This system was created to help address international training needs, especially in underserved areas of the world, where FHI does much of their research. The components are streamlined and made available on a CD as well as paper-based to be accessible in areas that may not have internet access or abundant computer availability. Materials for the FHI training were tested in five countries (India, Kenya, Zimbabwe, Philippines, and United States) and have been translated into many languages, allowing a multinational study to deliver the same training content in a variety of languages.

A system developed by the University of Pittsburgh\textsuperscript{28} contains items determined to be the most essential for their research staff. Functionality of this system includes links within a module quiz to instructional material that lets users learn why their answer was incorrect. When the user must repeat the training module, subsequent quiz questions can be pulled randomly from a group of similar questions.
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<tr>
<td>Barnes, 2006&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Investigators and staff</td>
<td>University of Pittsburgh: Online</td>
<td>NR</td>
<td>Test + certificate</td>
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<td>Braunschweiger, 2007&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Investigators and staff</td>
<td>CITI Program: Online</td>
<td>NR</td>
<td>Test + certificate</td>
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<td>Merritt, 2010&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Investigators and staff</td>
<td>FHI: Online and paper-based</td>
<td>NR</td>
<td>Certificate</td>
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<td>Rivera, 2005&lt;sup&gt;31&lt;/sup&gt;</td>
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<td>FHI: Online and paper-based</td>
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Abbreviations: CITI=Collaborative Institutional Training Initiative; FDA=Food and Drug Administration; FHI=Family Health International; GCP=good clinical practice; ICH=International Conference on Harmonisation; IEC=independent ethics committee; IRB=institutional review board; NR=not reported; SAEs=serious adverse events
LITERATURE REVIEW SUMMARY

In 2013, CTTI’s Good Clinical Practice (GCP) Training Project Team commissioned a literature review of current practices in the implementation of GCP training in order to inform the project. A variety of GCP training curricula and methodologies have been developed. Some of these implement training for local research investigators and staff, and others have started at the university level to invoke standards for faculty and staff. Several government agencies (such as NIH, FDA, OHRP, and National Institute of Allergy and Infectious Diseases) also have developed various GCP training modules.

In reviewing the 31 articles identified in this literature search, we noted several recurrent concepts:

- GCP training is an important way to try to safeguard the integrity of clinical research.
- In the past 10 years, a variety of training programs have been developed. The varied content of these training efforts has challenged the GCP training message and at times has slowed the initiation of clinical studies.
- Clarifying GCP training goals and increasing guidance for the research community will help to streamline GCP training practices.
- Online GCP training has the benefits of flexibility and convenience, and researchers who want classroom or face-to-face training can apply their time together to concentrate on protocol-specific items.
- GCP training usually includes the following components:
  - IRB/IEC oversight
  - Investigator responsibilities
  - Staff training and delegation of responsibilities
  - Protocol adherence
  - Data management
  - Informed consent
  - Vulnerable populations
  - SAEs/AEs
  - Monitoring
- We found little information about the optimum frequency for GCP training and only a few mentions of testing or proof of training (i.e., documentation).

An agreement on a core GCP training curriculum appears to be something the research community seeks in order to streamline the research process while enhancing the GCP training message. The upfront investment of time in a core GCP curriculum will ultimately be a resource saver.
REFERENCES


10. Steneck NH, Bulger RE. The history, purpose, and future of instruction in the responsible conduct of research. Acad Med. 2007;82:829-34.


## Appendix A. Search Strategy

**Topic:** Good Clinical Practice Training  
**Date:** July 1, 2013  
**Database:** PubMed

<table>
<thead>
<tr>
<th>Set #</th>
<th>Terms</th>
<th>Results</th>
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<td>&quot;Education&quot;[majr] OR &quot;staff development&quot;[tiab] OR &quot;training&quot;[tiab]</td>
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</tr>
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<td>4</td>
<td>Limits: English, last 10 years</td>
<td>2958</td>
</tr>
</tbody>
</table>
Appendix B. Sample Data Abstraction Form

- Type of article (*radial button, choose one*)
  - Current GCP Training Practices
  - Recommendations for GCP Training in Future
  - Both

- GCP component (*check all that apply*)
  - Overview of GCP/ICH
  - Drug Development
  - IRB/IEC Oversight
  - Investigator Responsibilities
  - Staff Training/Delegation
  - Protocol Adherence
  - Data Management
  - Investigational Drug
  - Statistics: Design, Analysis
  - Informed Consent
  - Vulnerable Populations
  - Serious Adverse Events/Adverse Events
  - Monitoring
  - Trial Records
  - Audits and Inspections
  - Reporting (FDA, Sponsor)
  - Medical Device
    - Other (specify)
  - Other (specify)

- Type of training (*check all that apply*)
  - Class/instructor led
  - Self-study (online)
  - Self-study (paper-based)
  - Other (specify)

- Frequency of training (*radial button, choose one*)
  - 6 months
  - 1 year
  - 2 years
  - Other (specify)
  - Not Reported

- Participants (*check all that apply*)
  - Investigators
  - Site Staff (specify)

- Proof of Completion (*check all that apply*)
  - Test
  - Certificate
  - None
  - Other (specify)

- Verification of Data Overread/Confirmation