ABSTRACT

HODGES, KATHRYN RENA. Certified Principal Investigator (CPI) Certification as a Predictor of the Number of Major and Critical Protocol Deviations in Clinical Trials: Does Certification Make a Difference? (Under the direction of Dr. Duane Akroyd).

There is an increasing demand for qualified clinical principal investigators to help close the translational gap between basic science discovery and the development of human therapeutics. Though programs to train clinical researchers have grown in quantity and diversity, the number of clinical principal investigators (PI) is still too few to meet the development need, and the quality of work of current clinical PIs requires continued improvement. The purpose of this study is to determine if Certified Principal Investigator (CPI) certification can improve the quality of clinical PI work through a certification and subsequent continuing education requirement that has clear parallels to the certification requirement that has proven effective in medical practice.

The study was a quasi-experimental, single-group interrupted time-series research design using quantitative analytic measures. A sample of clinical PIs was selected from the Quintiles Infosario database. Descriptive statistics summarized participant characteristics. A paired sample t-test was used to determine the difference between mean protocol deviations produced before and after participant CPI examination. Hedges’ g was used to estimate the effect size of the mean protocol deviation difference.

In this study population of 976 clinical PIs, 23 participants were consented and 12 participants produced enough data before and after certification for analysis. The results of the paired–samples t-test showed a significant difference in the mean protocol deviation of clinical PIs before taking the CPI exam ($M = .5792$, $SD = .6751$) and after passing the CPI exam ($M = .1250$, $SD = .2560$); $t(2.3325)$, $p < .05$. This study’s results suggested that a
clinical PI’s mean protocol deviation drops an average of 0.4542 major and critical protocol deviations per enrolled clinical trial subject after passing the CPI exam and becoming certified. Hedges’ g for t-tests revealed a large effect size of 0.8588 and demonstrated a strong connection between mean protocol deviations and certification. Future research should include a larger, experimental design that further limits self-selection bias. If further research in this area validates these initial results, both the pharmaceutical industry and pharmaceutical regulatory bodies should consider certification as a requirement to perform the duties of the clinical PI.
Certified Principal Investigator (CPI) Certification as a Predictor of the Number of Major and Critical Protocol Deviations in Clinical Trials: Does Certification Make a Difference?

by
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A dissertation submitted to the Graduate Faculty of
North Carolina State University
in partial fulfillment of the
requirements for the degree of
Doctor of Education

Educational Research and Policy Analysis

Raleigh, North Carolina

2017

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BIOGRAPHY

Rena Hodges was born in Gastonia, NC and raised in Clover, SC. After graduation from Clover High School, she entered Duke University, Durham, NC, from 1987-1991, earning a Bachelor of Arts in Economics. Subsequently, she earned a Master of Medical Science from Emory University, Atlanta, GA, in 1994, a Master of Business Administration from Campbell University, Buies Creek, NC, in 1997, and a Master of Clinical Research from Campbell University in 2006. In 2013, she was admitted to the Doctoral Program in Adult and Community College Education at North Carolina State University, Raleigh, NC.

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CHAPTER 1: INTRODUCTION

The development of human therapeutics demands the successful completion of clinical trials. In the U.S., clinical trials must be conducted by qualified clinical principal investigators (PI). The Food and Drug Administration (FDA) does not specify minimum training for PIs in clinical research, but clinical PIs should have appropriate training and experience to investigate an investigational product (‘‘United States Food and Drug Administration,’’ 2015). Most commonly, PIs are educated at the PhD or professional doctorate level. In clinical research, the most common professional degree for clinical PIs is the doctor of medicine (MD). Although certifications like Certified Principal Investigator (CPI) exist, clinical PIs are not currently required to have them. This study seeks to determine if certified PIs produce higher quality clinical trial data than non-certified PIs.

The phenomenal pace of basic science discovery has outpaced its translation into usable human therapeutics. The quality of clinical PI training and the volume of clinical PIs being trained are partly to blame for this translational gap. In 2003, The National Institutes of Health (NIH) recognized this deficit and produced the NIH Roadmap which called for the creation of innovative clinical PI training programs to address this barrier to development (Zerhouni, 2003). Over the next decade, educational systems developed programs with formal degrees, mentorships, and organized on-the-job training for clinical research students and practicing professionals transitioning to clinical research. These programs followed the medical training model and incorporated experiential learning theory and elements of self-directed learning theory.
Although programs for clinical PI training have grown and diversified, FDA audits have revealed persistent deficits in data quality ("Association of Clinical Research Professionals, Annual Conference," 2010). Since the mid-1990s, clinical PI protocol deviations have been the top FDA audit findings (Getz & Campo, 2013). Sweetman and Doig (2011) found that protocols deviations, though significant in clinical trials, were actually under-reported which can threaten the internal validity of studies. Protocol deviations, especially those classified as major or critical deviations, can affect the usability of data, which impacts both cost and timely delivery of clinical studies, and subject safety. Therefore, protocol deviations are important because they impact data integrity and subject safety, which are two of the primary tenets at the core of Good Clinical Practice (GCP), the standard for clinical trial conduct ("United States Food and Drug Administration," 2015).

Continuing Education (CE) for clinical PIs may be part of the solution for resolving persistent deficits. CE has been shown to improve professional practice, including medical practice (Davis et al., 1999). Since CE is generally required to maintain certification, requiring clinical PIs to become certified would logically require a level of CE that could improve practice. Improved practice could improve data quality by reducing key quality indicators such as major and critical protocol deviations.

Persistent deficits in the quality of data produced by clinical PIs exist in clinical research. Both initial training and CE for clinical PIs are not standardized. This study seeks to determine if clinical PI certification, via the CPI, can positively impact the quality of clinical trial data as determined by the number of major and critical protocol deviations produced by PIs participating in the study.
Statement of the Problem

Even with the increased number and diversity of training programs for PIs in clinical research and the added emphasis on the criticality of clinical PI shortages to conduct clinical studies, there are still not enough PIs to meet development needs (Zerhouni, 2003). Additionally, there has been a significant shift from clinical PIs operating in academic medical centers to physician practices outside of these centers (Lightfoot, Sanford, & Shefrin, 1999). This shift is important because the heaviest concentration of formally trained clinical PIs remains in the pharmaceutical industry and academic medical centers (Lightfoot et al., 1999). These numbers suggest that a high percentage of practicing clinical PIs lack formal training. Although clinical PIs are few in number, the quality of practicing clinical PIs is also concerning. Just as there is no standardized training for clinical PIs, there is also no standardized CE requirement. Notably, the top five FDA investigator audit findings have remained unchanged over the years. (“Association of Clinical Research Professionals, Annual Conference,” 2010). These indicate areas of improvement for clinical PI practice, with a primary one being inadequate training (“Association of Clinical Research Professionals, Annual Conference”).

Like medical practice, the clinical research environment changes rapidly. In clinical medicine, continuing medical education (CME) is required for licensure and certification and effectively promotes changes in medical practice to maintain current standards of patient care. However, practicing clinical PIs are not required to maintain CE in clinical research. In the same way that medical practice is improved through CME, requiring PIs to earn CE
through clinical research certification could improve clinical research practice (Davis et al., 1999).

Certification is a direct way to confirm base level knowledge in any given profession. To maintain certification, follow-on requirements for regular CE are generally required. Therefore, requiring clinical PI certification could ensure a baseline level of experiential and didactic knowledge and a level of knowledge maintenance through regular, follow-on CE.

Though not required for practice in clinical research, the primary certification for clinical PIs is the certified principal investigator (CPI). CPI, which is accredited by the National Commission for Certifying Agencies and awarded by the Association of Clinical Research Professionals (ACRP), is the only accredited certification for clinical PIs. To attain CPI, a clinical PI must have a doctoral level degree and documented clinical research experience and must pass a certification exam (“Association of Clinical Research Professionals, PI Certification,” 2015). Only two studies have been conducted on the CPI to date (Haeusler, 2009; Vulcano, 2012). Although both studies have significant limitations, both studies found a positive difference in certified PIs over non-certified PIs with respect to clinical PI outcomes.

Vulcano (2012) studied both data audits and for cause audits conducted by the FDA at clinical investigator sites. Though Vulcano did not find that statistically fewer for cause audits were performed at sites with certified PIs, he did demonstrate that certified PIs experienced better outcomes in the form of audit result classifications. In Vulcano’s study, certified PIs received more “no action indicated” than “official action indicated” classifications. Vulcano’s work suggests that sites with certified PIs have fewer quality issues
that warrant official action to correct, may have better standard processes for conducting clinical research, and may produce higher quality, cleaner data. In Vulcano’s study, specific audit findings were not analyzed; therefore, no particular findings associated with data quality, like major and critical protocol deviations, were compared between sites with certified PIs and sites without certified PIs. Vulcano’s work lacks specificity of quality drivers but does suggest that CPI may improve overall quality of clinical trial conduct, which warrants further investigation.

Haeusler (2009) demonstrated fewer mean protocol deviations for sites with certified PIs versus sites without certified PIs. Haeusler compared sites with a certified PI only, a certified PI plus a Certified Clinical Research Coordinator (CCRC), a CCRC only, and sites without CPI or CCRC staff. Haeusler found that sites with both CPI and CCRC had the fewest mean protocol deviations, but sites with only CCRC did not have fewer mean protocol deviations than those without CPI and CCRC staff. CPI-only certified sites had fewer mean protocol deviations than any other grouping except the grouping with both CCRC and CPI staff. The study suggests that CPI, not CCRC, contributes to fewer mean protocol deviations. Based on Haeusler’s findings, a more focused study on sites with CPI-only versus no certification is warranted. Additionally, Haeusler included minor protocol deviations in his results, which generally have no impact on data quality and patient safety. When minor protocol deviations are included, they can dilute the significance of the deviations that are actually impactful. Therefore, future studies need to analyze major and critical protocol deviations involving CPI only.
Theoretical Framework

Clinical PI training, like other medical training, includes hands-on experience and an application of the didactic material learned. Experiential learning is the educational theory that best accounts for this type of learning.

Experiential learning theory in the education and training of clinical PIs.

According to Dewey (1938), education should be grounded in a theory of experience. Clinical PI training, like pre-service medical training, incorporates practical performance of skills or practice, exposure to new experiences, and application of didactic material. Clinical research’s ever-changing environment and fast pace create the need for lifelong learning. Dewey’s theory of experience and its two central tenets, continuity and interaction, parallel clinical PI training. Dewey believed that individuals learn from every experience, and this accumulated learned experience influences future experiences, which creates a continuity of experiences. Most clinical PI training incorporates practical performance of skills that allows for exposure to situations that create new experiences and make application of didactic material. This ongoing exposure to new experiences fits well into the central tenet of Dewey’s theory of experience, continuity.

Dewey (1938) describes the second tenet of this theory, interaction, as a way to explain how past experience interacts with present situations to create a present experience. Applied to a clinical PI training context, the tenet of interaction suggests that any situation can be experienced in very different ways based on a clinical PI’s past experiences. Therefore, clinical PI training should account for the vast array of experiential differences and backgrounds that clinical PIs possess. The variety of clinical PI training that has
developed over the years could be interpreted as a result of this need and application of interaction.

Additionally, the direct links between education and work in clinical research are consistent with experiential learning theory (ELT). ELT’s pragmatic approach to learning is what best fits the initial and continuing educational needs of PIs. Experiential learning theorists have attempted to show that experiential learning is not limited to learning facts and skills and then making application of them. Some theorists contends that much more happens when an individual learns something and then applies it to a real world situation. This transformation through reflection was particularly noted by Donald Schon (1983).

Schon’s (1983), reflexive practitioner model introduced knowing-in-action and reflection-in-action to describe the artistry of professional practice. Schon recognized that most professional practice situations are unique and cannot be solved with previously acquired knowledge; thus, professionals had to generate knowledge in the moment. He called this knowing-in-action. Schon also introduced reflection-in-action to describe how professionals reshape what they are doing in real-time to negotiate work situations. Reflection-in-action is different from knowing-in action during which professionals simply move from an indeterminate situation to a determinate situation through the use of past experiences on a current situation. Therefore, knowing-in-action is described as application of knowledge acquired in training, and reflection-in-action occurs during professional practice over a period of time. Clinical PI practice can be described in the language of the reflexive practitioner. Over time, the clinical PI moves from the prescriptive execution of a clinical trial to a deeper understanding of the rationale for the strict regulatory environment
required to ensure the safety and efficacy of an investigational product and to protect clinical trial subjects and the public health at large.

Though Schon (1983) emphasized the importance of knowledge acquired in real-time during professional practice, Kolb (1984) with his experiential learning model further highlighted the importance of experiential learning. Similar to Schon, Kolb determined that experiential learning is not the simple application of didactic learning and rote practice of skills to a set of predetermined experiences. Experiential learning is, instead, highly adaptive and dynamic. Ideas are modified by experiences, and learning is by the process of learning or adaptation, not by outcomes. This process of adaptation in real-time is consistent with Schon’s model of the reflexive practitioner and the concept of reflection-in-action. Kolb’s process of adaptation translates well to clinical PI training and to clinical research as a whole because it mimics the scientific model which utilizes adaptive experimentation based on observation to create new knowledge. Similarly, Kolb describes an adaptive process by which knowledge is continuously created and re-created rather than just acquired and applied.

Understanding why professionals, like clinical PIs, want to participate in learning, particularly CE, is equally important to understand knowledge acquisition in professional practice. Self-directed learning (SDL), as described by Knowles’ (1975) elements of andragogy, applies to the area of continuing clinical PI education. According to Knowles, self-directed learning is the process by which a learner identifies her own learning needs, sets goals and garners resources to meet these needs, executes learning, and then evaluates learning based on desired outcomes. Clinical PIs, as adult learners, choose CE that they
believe will assist them with their practice. Knowles’s theory of self-directed learning assumes that adult learners learn what is required to perform their life’s tasks and that adult learners are task and problem-centered. These assumptions are particularly salient to CE for clinical PIs. As adult learners, clinical PIs use CE to fill knowledge gaps, resolve ongoing problems, and improve professional practice.

The receipt of new knowledge and the application of this knowledge in practice are important to changing clinical PI practice. CE has been the basis for both medical relicensure and re-certification (Cervero, 2001) and can improve medical practice (Davis et al., 1999). The CME required for medical practice certification parallels the CE required for clinical research certification for PIs. Therefore, through CE, PI certification may similarly improve the quality of data produced in clinical research trials.

Clearly, medical practice parallels clinical research practice. Yet medical practice has established an effective plan for professional training that clinical research practice has not. Therefore, clinical research practice can benefit from understanding medical CME outcomes and process. Pre-professional training and CME for physicians are informed by experiential learning theory (Dewey, 1938; Schon, 1983; Kolb, 1984) and self-directed learning theory (Knowles, 1975). Davis et al. (1999) showed that CME requirements for medical certification improve medical practice for physicians. From these studies and the evident parallels between medical practice and clinical research practice, this study seeks to determine if certification of clinical PIs impacts the quality of clinical research practice.
**Dependent Variable**

For this study, the dependent variable is the mean protocol deviations for each study participant during the periods of interest. Protocol deviations are defined as per Quintiles Transnational Corporation (Quintiles) standard operating procedure, CS_WI_PM0231 Handling of Protocol Deviations (“Quintiles Transnational Corporation, Handling of Protocol Deviations,” 2013):

- Major Protocol Deviation – deviations from protocol that impact scientific, ethical, regulatory or business integrity and which, if left unattended, could become critical
- Critical Protocol Deviation – deviations from protocol that impact scientific, ethical, regulatory or business integrity and could invalidate acceptability of a study to a manufacturing sponsor or regulatory body or invoke regulatory action

**Independent Variable**

The independent variable is certified PI versus non-certified PI as determined by the criteria set forth and certificate awarded by ACRP.

**Purpose**

The purpose of this research is to add to the body of knowledge on the CPI by investigating whether clinical PI’s produce fewer mean protocol deviations on clinical trials after they attain the CPI credential than before they attain the CPI credential.

**Research Question**

Is there a difference in the mean protocol deviation before and after clinical PI certification?
Significance

The growing demand for human therapeutics requires an increasing number of qualified clinical PIs to conduct clinical trials (Zerhouni, 2003). Clinical PI initial and ongoing education is not standardized, and the regulatory definition of a qualified clinical PI remains vague (“United States Food and Drug Administration,” 2015). Additionally, the complexity of clinical trial design has increased significantly, which has led to lower quality clinical data with subsequent increased trial costs (Getz, 2014). Getz estimated the cost related to procedures in protocols performed but not essential to objectives and endpoints to be between $4 and $6 billion USD each year for pharmaceutical companies running FDA-regulated phase II and phase III trials. Although initiatives such as the SPIRIT 2013 checklist and guidelines (“SPIRIT,” 2013) and adaptive trial design techniques have been developed to simplify protocol design and reduce unnecessary procedures in trials, trial sponsors have been slow to change the complexity of trial design (Getz, 2014). Therefore, trial design continues to drive development costs and fuel the need for better trained clinical PIs who could potentially increase data quality. In addition to increased development costs, complexity of clinical trial design can exacerbate subject safety.

According to Emanuel et al. (2004) the oversight of research has been inadequate to protect research subjects. Further, inadequate educational requirements for clinical PIs is one of the primary structural problems with the current protection system. (Emanuel et al., 2004) Additionally, ineffective safety reporting by PIs, which remains one of the top 5 FDA investigator audit findings, is one of the primary procedural problems with the current

Clinical trial cost as it relates to research protocol complexity and research subject safety as it pertains to PI safety reporting of adverse events, both highlight the significance of appropriate initial and continuing clinical PI training. Although there is a variety of clinical research training programs for PIs, significant quality deficits persist. Additionally, there has been no significant push by the FDA or the pharmaceutical industry to require PIs to maintain clinical research skills and knowledge. A positive difference in clinical trial data quality between PIs who are CPI certified and PIs who are not CPI certified could impact the value of clinical PI certification. Positive results would suggest that PI certification improves data quality, which can reduce clinical trial costs (Getz, 2014) and improve clinical trial subject safety (Emanuel et al., 2004). Therefore, positive findings could change the pharmaceutical industry and regulatory certification standards for clinical PIs.

**Chapter Summary**

CME has been shown to improve medical practice (Davis, et al., 1999). The FDA’s top five clinical investigation site audit findings have remained consistent (“Association of Clinical Research Professionals, Annual Conference,” 2010) despite the growth of degreed programs, non-degreed training, and the availability of certification for clinical PIs. This study uses a quasi-experimental design and attempts to control for many of the confounders present in previous studies. Retrospective studies have shown that investigational sites with certified clinical PIs have fewer protocol deviations (Haeusler, 2009) and have better FDA audit outcomes (Vulcano, 2012) than sites without certified clinical PIs. The data from this
study could potentially determine if the CPI can have a prospective impact on the quality of clinical trial data as demonstrated through a reduction in mean protocol deviations.

**Definitions**

Academy of Clinical Research Professionals (Academy): administers certifications offered by the Association for Clinical Research Professionals. The Academy is an independent affiliate of the Association for Clinical Research Professionals.

Academy of Pharmaceutical Physicians and Investigators (APPI): a professional society for physicians and principal investigators in clinical research. APPI’s mission is to promote and advance excellence and professionalism in pharmaceutical medicine and clinical research, and APPI is affiliated with the Association of Clinical Research Professionals.

Accreditation Council for Graduate Medical Education (ACGME): a private, non-profit organization that reviews and accredits graduate medical education (residency and fellowship) programs, and the institutions that sponsor them, in the United States.

American Board of Medical Specialties (ABMS): a professional board for physicians that works in collaboration with 24 specialty Member Boards to maintain the standards for physician certification. AMBS’s focus is on improving the quality of health care to patients, families, and communities by supporting the continuous professional development of physician specialists.

Association of Clinical Research Professionals (ACRP): a professional society that supports clinical research professionals through membership, training and development, and certification. ACRP’s mission is to promote and maintain high standards and best
practices of clinical research by recognizing those professionals who demonstrate a well-defined competency through valid and reliable certification programs.

Certified Clinical Research Coordinator (CCRC): the certificate awarded to a clinical research coordinator who has met eligibility requirements, demonstrated proficiency of specific knowledge and job-related skills, and passed the standardized Association of Clinical Research Professionals clinical research coordinator certification exam.

Clinical Research Coordinator (CRC): an individual who works at a clinical research site, with study subjects, under the immediate direction of a principal investigator, whose research activities are conducted under GCP guidelines.

Continuing education (CE): education provided for adults after they have left the formal education system, consisting typically of short or part-time courses and often used to support maintenance of professional certification.

Continuing medical education (CME): consists of educational activities which serve to maintain, develop, or increase the knowledge, skills, and professional performance and relationships that medical professionals use to provide services for patients, the public, or the professions.

Certified Principal Investigator (CPI): the certificate awarded to a principal investigator who has met eligibility requirements, demonstrated proficiency of specific knowledge and job-related skills, and passed the standardized Association of Clinical Research Professionals principal investigator certification exam.
Clinical trial: any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes for the purpose of registration to market the intervention.

Clinical Trial Management System (CTMS): a software system used by biotechnology and pharmaceutical industries to manage clinical trials in clinical research.

Contract Research Organization (CRO): an organization that provides support to the pharmaceutical, biotechnology, and medical device industries in the form of research services outsourced on a contract basis.

Critical Protocol Deviation: deviation from protocol that impacts scientific, ethical, regulatory or business integrity and could invalidate acceptability of a study to a manufacturing sponsor or regulatory body, or invoke regulatory action.

Food and Drug Administration (FDA): the United States federal agency responsible for monitoring trading and safety standards in the food and drug industries.

Good Clinical Practice (GCP): an international quality standard for clinical research that governments can transpose into regulations for clinical trials involving human subjects.

Harvard–MIT Division of Health Sciences and Technology- Medical Engineering Medical Physics (HST-MEMP): a unique venture between Harvard University and Massachusetts Institute of Technology that takes students in engineering doctoral programs and provides them didactic courses and clinical rotations in clinical medicine.
Infosario: Quintiles Transnational Incorporated’s proprietary clinical trial management system.

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH): an international council that brings together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration. ICH's mission is to achieve greater harmonisation worldwide to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner.

Institute for Credentialing Excellence (ICE): accredits personnel certifications or certificates.

Institutional Review Board (IRB): a committee established to review and approve research involving human subjects. An IRB’s purpose is to ensure that all human subject research be conducted in accordance with all federal, institutional, and ethical guidelines.

Maintenance of Certification (MOC): the process of physician certification maintenance through one of the 24 approved medical specialty boards of the American Board of Medical Specialties.

Major Protocol Deviation: deviation from protocol that impacts scientific, ethical, regulatory or business integrity and which, if left unattended could become critical.

National Commission for Certifying Agencies (NCCA): is the accreditation body of the Institute for Credentialing Excellence. The NCCA's mission is to ensure the health, welfare and safety of the public through the accreditation of a variety of individual certification programs that assess professional competency.
National Institutes of Health (NIH): the principal United States federal agency within the Department of Health and Human Services overseeing health research.

Principal Investigator (PI): an individual who holds a doctoral-level degree, serves as the principal, sub- or co-investigator; monitors, supervises, or designs clinical trials; and accepts responsibility for the safe and ethical conduct of a clinical trial.

Quintiles Transnational Incorporated (Quintiles): the world’s largest provider of biopharmaceutical development and commercial outsourcing services. Quintiles is a contract research organization focused primarily on Phase II-IV clinical trials and associated laboratory and analytical services.

Quintiles Transnational Incorporated Quality Assurance Department (QA): provides an effective and efficient quality assurance system and counsel for the operational units at Quintiles.

Quintiles Transnational Incorporated Site Identification Department (Site ID): responsible for identifying appropriate clinical principal investigators practicing at clinical investigator sites who can conduct clinical trials efficiently and with appropriate data quality.

Statement of Investigator Form (FDA 1572): an agreement signed by the clinical investigator to provide certain information to the pharmaceutical sponsor and assure that he/she will comply with FDA regulations related to the conduct of a clinical investigation of an investigational drug or biologic.
CHAPTER 2: REVIEW OF THE LITERATURE

Introduction

The purpose of this study is to determine if CPI certification can improve data quality produced in a clinical trial as indicated when measured by a commonly tracked metric used to indicate data quality, protocol deviations. This literature review opens with the regulatory definition of a clinical PI and the roles and responsibilities a clinical PI assumes in a clinical trial. The status of clinical PI training is discussed and training needs, which are driven by increasing volume in clinical trials, increasing complexity of trial design, and the regulatory environment, are explained. Next, the different types of clinical PI training are outlined and the application of experiential learning theory as central to current clinical PI training is described. The literature review then explores how self-directed learning and the transtheoretical model impact a clinical PI’s decision to seek CE and apply learning to practice. The need for more and better trained clinical PIs is then described through NIH investment in clinical research and clinical PI training and persistent FDA clinical PI audit findings. A potential gap in training and CE is discussed as a possible reason for persistent findings. Further, major and critical protocol deviations, which are imperative to this study, are defined. CME is then introduced as a proven means to improve medical practice. The American Board of Medical Specialties and its maintenance of certification process is presented as a recent example of CME certification that improved clinical practice. CPI certification is described and a potential outcomes parallel between the American Board of Medical Specialties maintenance of certification process and CPI is proposed. Lastly, previous research on the CPI is presented and critiqued, setting the stage for this study.
Definition and Responsibilities of a Principal Investigator

Per the FDA in the Code of Federal Regulations, Title 21, Part 312, Subpart D, an investigator is someone qualified by training and experience as an appropriate expert to investigate an investigational product. Subpart D further outlines the responsibilities of a clinical study investigator as reflected in Table 1.

Table 1.

Duties of a Principle Investigator

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<tr>
<th>Duties</th>
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<tr>
<td>Maintain appropriate qualifications</td>
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<tr>
<td>Maintain adequate resources to conduct study</td>
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<td>Provide medical care to study subjects</td>
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<td>Maintain appropriate communication with ethics committees and institutional review boards (IRB)</td>
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<td>Maintain study protocol compliance</td>
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<td>Maintain control of investigational product</td>
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<td>Perform appropriate randomization and unblinding of subjects when needed</td>
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<td>Perform appropriate consent of subjects</td>
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<td>Maintain appropriate records and reports of study</td>
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These investigator responsibilities are consistent with GCP. They are the product of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), and they serve as the standard for the design, conduct, performance, monitoring, auditing, analyses and reporting of clinical trials. These standards assure that the
data and reported results are credible and accurate, and that the rights, integrity and confidentiality of the subjects are protected (“United States Food and Drug Administration,” 2015).

Clinical research relies heavily on the expertise of its PIs. In addition to the primary clinical PI responsibilities outlined by ICH-GCP, some key clinical PIs critique initial trial design and suggest protocol amendments during trial conduct. Key clinical PIs also serve on boards that review interim data and safety signaling. Although some research sites have large support staffs, the clinical PI is ultimately responsible for ensuring that the trial is conducted per protocol, the data collected is accurate, and adverse events are properly reported. The responsibilities are tremendous, yet most clinical investigators have no formal clinical trial training. In a survey of 7300 physicians, Thomson CenterWatch found that only 25% had undergone formal training in clinical trials. Of those surveyed, approximately one-half had no experience in clinical trials. In total, 92% of the inexperienced physicians and 57% of the experienced physicians had no formal training in clinical trials (Space, 2007). Both numbers are staggering as the need for physicians who are willing to participate in clinical trials continues to grow and the clinical research environment utilizes more complex protocol designs, regulatory environments, and operational conduct.

Complexity of the Clinical Research Environment

Protocol design. The complexity of protocol design has increased over the last decade and the reasons are multifaceted (Getz, 2014). Measures of chronic disease mechanism progression and the economic impact of new therapeutics require larger amounts of clinical data. Also, more genetic and biomarker data is being collected to develop
stratified, personalized treatments. Clinical teams collect more data so that information is available for post-hoc analyses if primary and secondary endpoints are not met. Increased data collection can also mitigate the risk of regulatory agencies and payers asking for additional information after a trial is completed and to inform future research. Lastly, clinical scientists and biostatisticians add procedures and increase complexity to better aid their interpretation of data and inform future development decisions. This pile-on effect is particularly apparent as sponsors attempt to make use of burgeoning basic science.

Secondary to advances in basic science research, trials are able to detect more surrogate markers that demonstrate effects of treatment. Researchers use biomarkers to stratify study arms and increase the trial’s ability to detect treatment effects even if only in a subpopulation. This type of analysis often requires complex adaptive designs to screen and randomize subjects. The majority of this differentiation can be built into automated interactive web response systems. However, the subject screening process may have to be altered during trial conduct to ensure that study arms are filled appropriately for proper statistical analysis. This requires that the clinical PI understand the rationale behind these complex designs. From a regulatory perspective, the primary investigator must interact and advocate for each clinical trial’s approval through an IRB. While trial sponsors can assist with the rationale for particular study design, ultimately the primary investigator interacts with the IRB and must advocate clearly for the clinical trial to obtain approval. This clinical PI skillset is particularly important when trial complexity through increased procedures requires numerous protocol amendments. Like protocol procedures to capture more data, amendments have increased substantially over time (Getz et al., 2008).
**Regulatory environment and operational conduct of trials.** Regulatory authorities and IRBs are also very concerned with the trial burden that subjects incur. Subjects should be inconvenienced as little as possible during their participation and guidelines such as SPIRIT 2013 checklist should be developed to assist with this (“SPIRIT,” 2013). Such guidelines, along with more streamlined adaptive designs, work to reduce complexity, but industry uptake of these improvements has been slow (Getz, 2014). So, with increased design complexity and greater regulatory scrutiny comes a greater need for trial monitoring to ensure that the trial is conducted per protocol and that the data gathered is accurate. This level of monitoring or audit requires site support and can consume great amounts of staff and primary investigator time. This burden on the investigative staff and the clinical PI can manifest itself in decreased data quality (Getz, 2014) and ineffective and incomplete safety reporting (Emanuel et al. 2004). Clinical PI training has, therefore, been a focus to improve safety reporting (Emanuel et al., 2004) and data quality (Getz, 2014).

It seems reasonable, therefore, that those who participate in initial and continuing clinical research training can move through these complexities with greater success and produce higher data quality as evidenced by fewer major and critical protocol deviations.

**Types of Clinical PI Training**

The FDA’s definition of who can serve in the clinical PI role remains vague. Therefore, an individual serving as a PI could have formal and ongoing training, a cursory knowledge of clinical PI responsibilities through a 30 minute training session presented at an investigator meeting, or any variation in-between. It should then come as no surprise that both basic scientists and clinicians with mutual research interests often fall haphazardly into
clinical research without a firm knowledge of the responsibilities that come with it. More recently, formalized cross-training was developed through dual degrees, namely MD-PhD programs, creating the physician scientist. These programs were intended to produce individuals who could interpret basic science into impactful human therapeutics. Though this model would seem ideal, unexpected forces such as financial realities and exponential growth of basic science knowledge have de-railed its ability to live up to expectations.

Kaushansky (2003) notes that only 10-20% of clinical PIs in the U.S are MD-PhD trained physician-scientists, and the remaining percentage has come to clinical research through other avenues and later in their careers. Further, Lader et al. (2004) found that 75% of physicians in the U.S. practice outside of a hospital setting; whereas, Daye et al. (2015) found that 81% of U.S. MD-PhD program alumni were employed in academia, research institutes, or industry. Further, since the 1980s, U.S. physicians report that direct patient care activities have increased while research activities have decreased. (Daye et al., 2015) Therefore, it is not surprising that the demand for more patient care and the demand for more trained clinical PIs has spurred the growth of both degreed and non-degreed programs intended to educate practicing professionals on clinical trial conduct to meet the needs of development.

**Degrees to train clinical PIs.**

**MD-PhD and MD.** MD-PhD programs generally require the student to spend 3 to 5 more years in training than either single degree. This is becoming a financial burden (Sung et al. 2003). The Association of American Medical Colleges reported in 2010 that medical students incurred over $160,000 in debt. Essentially, the debt could increase by 50 to 100%
with the increased years of training and study for those pursuing dual degrees. Not only is the increased debt for a dual degree problematic, but students also see this as time that could be better spent working clinically to pay their debt down. MD-PhD students describe faculty mentorship as an instrumental part of their training and development; however, even faculty have little time to conduct their own research because of clinical pressures to see patients and earn revenue instead of working with study subjects. This pressure has worsened with the explosive growth of managed care organizations (Kaushansky, 2003). Consequently, time for mentorship becomes less of a priority. The lack of physician scientist role models results in a decrease in the recruitment of capable and motivated students into clinical research (Sung et al.).

Although the MD-PhD is trained to excel as both a scientist and a clinician, the breadth of knowledge that must be acquired and maintained over time to remain current in these rapidly changing, cutting edge environments is too great. Although MD-PhD graduates can provide leadership to bridge the language differences between scientists and clinicians, they cannot be expected to know the intricacies of scientific techniques or have the skill of clinical practice that either a full-time scientist or a fulltime clinician enjoys.

Based on MD-PhDs production barriers and the limitations of these individuals even after program completion, the education of future clinical researchers must change to meet the needs of research. Some unique programs have developed over the years to meet this need, but future training should focus on a team-oriented clinical researcher model rather than an individual one. Clinical researchers of the future will be an integral part of a research
team specialized in a particular area with a working knowledge of other areas and an ability to communicate effectively with team members.

With the team approach to clinical research in mind, several top ranked research institutions integrated cross-training into their standard biological science and medical doctor curriculum. One of the more well-known programs is the Harvard/MIT joint venture known as the Harvard–MIT Division of Health Sciences and Technology (HST) – Medical Engineering Medical Physics (MEMP) model (Gray & Bonventre, 2002). The HST has a unique MD program that focuses on medical innovation and boasts a greater percentage of graduates earning MD-PhD dual degrees, 40%, versus other schools with dual degrees whose figures are often less than 10% of the graduating medical school class. Understanding that even these numbers would not keep up with the need for qualified clinical researchers, the MEMP program was developed. It takes students seeking PhDs in engineering and the physical sciences with an interest in resolving human health problems and jointly enrolls them into HST, creating the HST-MEMP Program students (Gray & Bonventre, 2002).

The HST-MEMP students receive a set of seven preclinical courses that are taken alongside the HST students. This is followed by six weeks of concentrated clinical didactic training and then six weeks of clinical training in the hospital with the HST medical students. During this time, HST-MEMP students are expected to perform at the level of third year medical students. Later in their PhD training, the HST-MEMP students construct a one-month preceptorship under a clinical adviser. These preceptorships can result in various activities such as the design and launch of a pilot clinical study (Gray & Bonventre, 2002).
The HST-MEMP program produces graduates in six years, which is consistent among other graduates in collaborating departments at Harvard and MIT. From 1981-1995, the Program could confirm that 25% of its alumni were directly involved in moving scientific discovery into the clinical arena. This demonstrates that non-MD researchers can contribute to clinical research (Gray & Bonventre, 2002).

In 2005, the Howard Hughes Medical Institute provided $400,000 to $1 million each to selected research institutions through its Med into Grad initiative (Hutson, 2009). The initiative was intended to support innovative graduate programs that integrated clinical knowledge into PhD biomedical training to prepare researchers to work at the interface of biological sciences and clinical medicine. Baylor College of Medicine and Cleveland Clinic Case Western Reserve University used this funding to develop new PhD programs in translational biology and molecular medicine. These programs produced graduates within five years (Smith, Jarrett & Bierer, 2013).

An alternative to dual degrees is an integration of clinical research into the standard medical school curriculum. All medical students interested in clinical research may not desire a dual degree, so some medical educators have suggested a middle ground approach in which the fourth year of medical training includes a clinical research curriculum. This curriculum would extend into residency training and would allow the new physician to test her interest in the field while giving her the practical knowledge to pursue a career in research if it is good fit (Miller, 2001). A similar approach is found in Burge & Hill (2014). The Residency Research Network of Texas sponsored a summer program for medical students designed to teach research processes in family medicine while yielding data for ongoing research studies.
The program included two weeks of didactic training in research design and medical writing and four weeks of trial conduct training.

**MS, MPH and MSCR.** As acknowledged, the need for researchers exceeds the number of new professionals who are jointly trained. Some universities have attempted to bridge this gap by offering clinical research degrees to currently practicing clinicians that focus more on the conduct and design of clinical trials. Wake Forest University offers an MS in epidemiology and health services research in which graduates gain basic understanding of biostatistics, outcomes research, epidemiology, and public health issues (Moskowitz & Thompson, 2001). Similarly, the University of Puerto Rico offers a postdoctoral master of science in clinical research degree and a graduate certificate program in clinical research. The master of science in clinical research program is only offered to individuals with doctorate levels degrees, such as MD, DO, DMD and PhD, and requires intensive didactic classes with a mentored research project (Estape, Rodriguez & Scott, 2005).

Master’s degree programs have also been effective. Kapoor, Wu and Banks (2011) studied the funding support granted to 25 fellows at Brigham and Women’s Hospital. Those fellows who earned a master’s in public health while performing their fellowship were more successful in obtaining research funding within the three years post fellowship (77%) than fellows who completed a short seven-week research course during fellowship (0%).

**Certificate programs.** Certificate programs exist for practicing clinicians who do not wish to complete formal degrees but acknowledge that they need training in clinical study conduct. The University of Colorado offers a 22 credit hour, one-year certificate mentoring program intended to develop basic proficiency and skill in conducting clinical research
In addition to its MSCR degree, The University of Puerto Rico offers a certificate program that includes a one-year didactic component intended to increase skills and knowledge in clinical research (Estape et al. 2005).

Shorter, more intensive certificate programs are also available for new MD investigators. These programs are often institution specific and for specific therapeutic areas such as oncology that are heavily engaged in clinical research. One such example is the eight-day certificate program offered by the Southwest Oncology Group in San Antonio, TX. This program puts new researchers through an intensive didactic curriculum in statistical principles, data collection and analysis, critical decision-making, and protocol development guidelines (Nahleh et al., 2006).

**Mentorship.** Strong mentorships have been shown to be the key predictor of academic success and persistence in research for investigators (Flemming, Burnham, & Huskins, 2012). Studies have been conducted to determine desired traits and competencies for mentors. Using focus groups, literature review, mentor training curricula review, mentor evaluation form reviews and expert panel consultation, Abedin et al. (2012) proposed a set of general and clinical research-specific mentor competencies. The NIH has proposed a list of seven benchmark recommendations for mentoring research trainees (Fleming et al., 2012). Burnham, Schiro and Flemming (2001), through information obtained from focus groups comprised of NIH directors and research mentors, proposed alleviating common barriers and providing greater support for mentors. These included increased compensation for mentoring, greater access to core labs, assistance with grant and manuscript preparation, membership in mentor academies, mentor awards, mentor training, promotion, and peer support.
Individual professional societies have also sought to improve mentorship in their therapeutic areas. The National Heart Blood and Lung Institute organized a workshop to assess ways to attract and properly train advanced fellows to pursue research careers in lung disease. Recommendations from the workshop included to increase research exposure in early education starting in high school and to increase awareness of physician-scientist role models in the lung community (Choi et al., 2009).

Examples of applied mentorship in clinical research can also be found. Marinac and Gerkovich (2012) describe a much shorter but effective approach to mentoring. The Focused Investigator Training program is a five-day development boot camp for mid-career doctorate of pharmacy professionals. The program formed proposal groups of four mentors and two mentees to review detailed research proposals and provide active feedback through small group sessions, lectures, and panel discussions. The Focused Investigator Training program increased attendee self-efficacy for obtaining external research funding based on the attendees own previous success.

**Standardized certification.** Regardless of the types of training clinical researchers may have, there remains a desire that each has a standard level of knowledge and that this level of knowledge is maintained through CE. In the U.S., certification is not mandatory. The Academy of Pharmaceutical Physicians and Investigators, as consolidated under ACRP, has a goal to become the industry standard for investigator certification; however, only a fraction, approximately 10%, of clinical researchers are certified in the U.S. This statistic will likely remain low unless requirements are stipulated by the government or the pharmaceutical and device industries apply selective pressure favoring certified investigators (Space, 2007).
Although the educational routes to become and function as a clinical PI are extremely varied, most clinical PI training, like most physician medical training, include a component of hands-on experience and application of the didactic material learned. The educational theory that best accounts for this type of learning is Experiential Learning Theory.

**Experiential Learning Theory in the Education and Training of Clinical PIs**

Experiential learning theory is clearly applied in the field of clinical research; therefore experiential learning theory can inform improvements in both initial and ongoing training for clinical PIs. It was Dewey (1938) who suggested that education should be grounded in a theory of experience.

**Dewey.** Dewey’s (1938) theory of experience and its two central tenets, continuity and interaction, are found in clinical PI training. Continuity is the idea that individuals are affected by their experience and rely more on experience than on pre-wired instinct. Dewey believed that individuals learn something from every experience, whether positive or negative, and this accumulated learned experience influences future experiences, which creates a continuity of experiences. Most clinical PI training incorporates some form of practical performance of skills or practice that allows for the exposure to situations that create new experiences and make application of didactic material.

Dewey’s (1938) tenet of interaction is more elusive but can also be found in clinical PI training. Interaction furthers the tenet of continuity and explains how past experience interacts with present situations to create a present experience. That is, current experience can be understood as a function of past experiences which interact with the present situation to create clinical PIs experiences. Therefore, any situation can be experienced in different
ways based on a clinical PI’s past experiences. Thus, clinical PI training planners do well to understand the past experiences of clinical PIs to develop better educational situations that cater to these experiences.

Because of its pace and complexity, clinical research lends itself to some fundamental premises of experiential learning theory, namely lifelong learning and direct linkages between education and work. Likewise, the vocationalist feel and pragmatic approach of experiential learning theory fit well with the initial and continuing educational needs of clinical PIs. Some existing programs have parts that even mimic the past roles of apprenticeships and internships. This type of training is not uncommon in the professions and does seem to be a part of clinical PI training. Charles Sawyer, MD, of the Memorial Sloan-Kettering Cancer Center stated that formal programs dedicated to clinical investigation are a new phenomenon and that a clinical PI’s most valuable training is gained through actual research projects (Morrison, 2008). Jodi Segal, MD, from the Johns Hopkins University School of Medicine, suggested that on-the-job training alone can qualify a clinician to function as a clinical PI (Morrison, 2008). Even the formal education components of clinical PI training are driven by innovations in industry and the pressure industry imposes on educational institutions to meet the demand for professionals who are fit-for-purpose to analyze and synthesize information and progress the body of knowledge.

Many higher institutions of learning have conformed to this industry or economic pressure, which has led to criticism of experiential learning theory. Critics believe that the theory in practice seems too pragmatic for the academic mind and somehow diminishes true learning through its anti-intellectual and vocationalist skew (Kolb, 1984). Theorists have
attempted to show that experiential learning is not limited to learning facts and skills and then applying them. Instead, much more happens when an individual learns something and then applies it to a real-world situation. This transformation through reflection was noted by Kurt Lewin, Jean Piaget and Donald Schon.

**Lewin, Piaget and Schon.** Lewin’s (1951) Experiential Learning Model emphasized the tension between concrete and abstract concepts and between observations and action (cited in Hickcox, 1990). In a clinical research example, Lewin’s model begins with the clinical PI having a concrete experience in a clinical research environment. The clinical PI then collects data and makes observations about the experience. The PI reflects upon the experience and considers new concepts and new generalizations of previously accepted facts and ways of working. Then the PI applies or tests the new concepts and generalizations on a new experience.

Piaget (1970) used his Model of Learning and Cognitive Development to show that, from infancy to adulthood, an individual moves from a concrete to an abstract view of the world and from an egocentric to a reflective way of knowing. Additionally, this development occurs via a cycle of interaction between the individual and the environment. From a clinical PI perspective, the abstract is the unknown of discovery. The PI moves to a Piaget’s reflective way of knowing by taking the unknown or what is suspected or hypothesized, and referencing it to what is known to formulate new knowledge.

Schon (1983) introduced knowing-in-action and reflection-in-action to describe professional artistry in his model of the reflective practitioner. Cervero (1992) discusses Schon’s work and explains that most situations in professional practice are unique and cannot
be solved using knowing-in-action. Instead, professionals have to reflect while acting, which reshapes what they are doing in real-time. This allows the practitioner to move from an indeterminate situation to a determinate situation by applying past experiences to a current situation. Therefore, knowing-in-action is described as an application of knowledge acquired in school; whereas, reflection-in-action occurs over time in professional practice. From a clinical PI perspective, the actual conduct of clinical trials over time allows movement from the rote execution of a clinical protocol to an understanding of the necessity for the prescriptive nature of a protocol to then extrapolate the safety and efficacy of an investigational product and move the clinical PI to reflection-in-action.

**Kolb.** Informed by both Lewin and Piaget’s learning models, Kolb (1984) developed a new experiential learning model that included learning styles and continuums. The continuums reflect how a task is approached and the emotional response surrounding a task. Kolb determined that experiential learning is not the static application of learned facts and skills to experiences. Instead it is highly adaptive and dynamic. Ideas are not fixed but are constantly being modified by experiences; thus, learning is not defined by outcomes but by the process of learning or adaptation.

This adaptive process models the scientific method, which represents the very core of clinical research and clinical PI training. The scientific model progresses the body of knowledge through observation and experimentation. Similarly, the adaptive process in experiential learning emphasizes that knowledge is continuously created and re-created rather than just acquired and applied. Knowledge is the result of transformed experiences (Kolb, 1984).
Much as Dewey (1938) believed that training should be customized based on a learner’s past experiences, Kolb (1984) believed that training should be based on a learner’s preferred, single learning style. Kolb explains that learning style is influenced by factors such as social environment, educational experiences, or basic cognitive structure and is the product of two pairs of variables that describe a learner’s orientation towards learning. Kolb’s product was the learning styles inventory, a nine item self-description questionnaire that fits learners into one of four basic learning modes: concrete experience (CE), reflective observation (RO), abstract conceptualization (AC) and active experimentation (AE).

Plovnick (1975) used the learning styles inventory in his study of the relationship between learning styles and specialty choices made by senior medical students. His results found that primary care physicians fell into the CE/AE quadrant (accommodating), specialty physicians fell into the AC/AE quadrant (converging), psychiatrists specifically fell into the CE/RO quadrant (diverging), and those physicians going into academia and research fell into the AC/RO quadrant (assimilating). These types of differentiations become important as clinical PI ranks become more diverse. For example, specialty physicians who are often recruited as clinical PIs, are considered convergers. Because convergers learn best by doing through coaching and hand-on experimentation, training methods should include interactive rather than passive instruction. Conversely, academic and research physicians whose primary function is often research, are assimilators. Because assimilators learn best through a combination of watching and thinking through concepts, training methods should include lectures followed by demonstrations. Although current clinical PI training places a great emphasis on experiential learning, the type and delivery of this learning, per Kolb’s
experiential learning model and learning styles inventory, can impact the quality of this training. In addition to adapting training to learning styles, it is important to understand why and under what conditions clinical PIs want to participate in learning and which factors are instrumental to implementing change and incorporate learning into actual practice. Self-directed learning and the transtheoretical model apply to these areas of continuing clinical PI education.

**Self-Directed Learning Theory**

According to Knowles (1975), self-directed learning occurs when a learner identifies her own learning needs, sets goals and garners resources to meet these needs, executes learning, and then evaluates learning based on desired outcomes. Clinical PIs choosing CE, much like physicians choosing CME, choose learning activities they believe will assist them with their practice. Houle (1961) describes this in terms of orientation of the learner and Knowles described this in terms of andragogy as applied to self-directed learning.

**Houle.** Cyril Houle (1961) categorized learners as one of three types:

- Goal-oriented – participates in learning to achieve an end goal
- Activity-oriented – participates in learning for social reasons
- Learning-oriented – participates in learning for the sake of learning

Because CE can be time-consuming and may not always be reimbursed, a clinical PI constantly tries to achieve an end goal, thus he is goal-oriented.

**Knowles.** Malcolm Knowles (1975) outlined assumptions of self-direction in adult learners:

- Adult learners grow in capacity and need to be self-directing
• Experiences are rich resources for learning
• Learners learn what is required to perform their life’s tasks
• Learner is task and problem-centered oriented
• Learner is motivated by internal incentives such as a desire to achievement

Clinical PIs use CE in a very pragmatic way to fill knowledge gaps and to resolve ongoing problems that they have.

An important step to changing clinical PI practice is the receipt of new knowledge and the application of this knowledge in practice; however, other factors, such as motivation and learner self-efficacy, are integral for CE to actually change the way a clinical PI practices.

**Transtheoretical Model**

Prochaska and DiClemente’s (1983) transtheoretical model informed Williams, Kessler and Williams’ (2014) research on the importance of both motivation and self-efficacy on the intent to implement CME. The transtheoretical model consists of four constructs: stages of change, decisional balance, self-efficacy, and processes of change. The stages of change construct represents motivation ranging from pre-contemplative to a state of maintenance in which the behavior has occurred. Williams, Kessler and Williams found that there is a significant relationship between one’s belief in the capability to change, self-efficacy, and the intent to change. They also found that self-efficacy in the practice environment predicts high level of motivation to change. Motivation, then, predicts intent to change practice patterns based on knowledge obtained via CE.
There are not enough clinical researchers who have self-selected and entered formal programs to learn the profession to fill the demand for clinical researchers. A literature search of educational programs for clinical PIs reveals that many institutions of higher learning, professional organizations and clinical organizations attempt to alleviate this deficit through a variety of degrees, training programs and certifications. Additionally, the manner in which clinical PIs are trained may not be conducive to maximize productivity or maintain this much needed skillset. Lack of ongoing training (such as that provided by CE) and experience may explain some of this deficit. Essentially, exposure does not equal knowledge. Knowledge results from the transformation of experiences (Kolb, 1984). So, the need for more and better trained clinical PIs, although recognized, goes largely unmet.

**Need for More and Better Trained Clinical PIs**

The need for clinical PIs is ever-growing as the pace of discovery increases through technology and knowledge sharing. Modern medicine has extended average life spans. Our ability to diagnose and treat diseases at earlier stages has contributed to this. This benefit of modern medicine also brings with it later stage, more complicated, chronic disease and new disease that only presents in later life. Better diagnostics are needed to identify disease in earlier states. In addition, new therapeutics are needed to treat chronic, later stage disease and disease in aged populations. The 5-year doubling of the NIH budget from 1987-2003 (Zerhouni, 2003) and increasing research and development budgets in industry reveal support for biomedical research to address these problems. The exponential growth in basic science discoveries is grossly outpacing the ability to move promising treatments to regulatory submission and market; therefore, the return on investment has not been realized. As a
consequence, patients suffer needlessly while an inefficient system continues to under-produce. It is generally agreed that this requires innovative training programs to meet this need for more clinical PIs (Zerhouni, 2003). According to the literature, a variety of training programs have emerged to try and meet this need. Therefore, it is perplexing that primary FDA audit findings continue to demonstrate a lack of clinical PI compliance with some of the basic principles of ICH-GCP.

**Primary FDA audit findings.** The top five FDA inspection findings for clinical PIs were revealed at the Association of Clinical Research Professionals, Annual Conference in 2010 ("Association of Clinical Research Professionals, Annual Conference," 2010):

- Failure to follow protocol
- Failure to keep adequate and accurate records
- Failure to account for disposition of investigational product
- Deficiencies with informed consent form or process
- Failure to report adverse events and changes in research to sponsor, IRB or EC

These top FDA PI audit findings are also protocol deviations that would be classified as major or critical deviations and would therefore impact the quality of data produced by clinical PIs.

This presentation also noted that the top five FDA inspection findings for clinical PIs have not changed significantly in recent years for the following reasons:

- Investigational sites rely on individual site staff performance to ensure compliance rather than establishing systems and processes that lead to quality outcomes
• New investigators join the industry each year and may not have a sufficient understanding of their roles and responsibilities

• Experienced clinical PIs lack ongoing training, especially in light of constantly changing competitive and regulatory environments

An integral part, namely CE in the area of clinical trial conduct, may be missing, which may explain the failure of expanded avenues of clinical PI education to impact these results. It seems evident that without adequate maintenance of training, even basic clinical PI tasks are overlooked. If clinical PIs do not stay up-to-date on their responsibilities and current research trends, they may not consistently produce quality data which comes from knowing and carrying out their responsibilities with a high degree of fidelity. Failure to do this can make important data unusable.

Based on the current, diverse clinical PI training available and persistent FDA clinical PI audit findings, research on CE certification as a potential solution for the performance gap in clinical research is imperative.

**Major and critical protocol deviations.** Clinical PI protocol deviations are a key finding in FDA audits and can serve as a surrogate marker for data quality. In FDA guidance for industry ("United States Food and Drug Administration, Guidance for Industry," 2013), the FDA adopted the definitions from ICH E3 for protocol deviations and important protocol deviations. This guide states that protocol deviations are defined as any change, divergence, or departure from the study design or procedures defined in the study protocol. The guidance defines an important protocol deviation as a deviation that might significantly affect the completeness, accuracy and/or reliability of the study or that might significantly affect the
subject’s rights, safety, or well-being. Quintiles standard operating procedure, CS_WI_PM0231 Handling of Protocol Deviations (“Quintiles Transnational Corporation, Handling of Protocol Deviations,” 2013), uses similar verbiage to describe protocol deviations:

- **Minor Protocol Deviation** – deviations from accepted procedures that will not adversely affect subject/data
- **Major Protocol Deviation** – deviations from protocol that impact scientific, ethical, regulatory or business integrity and which, if left unattended could become critical
- **Critical Protocol Deviation** – deviations from protocol that impact scientific, ethical, regulatory or business integrity and could invalidate acceptability of a study to a manufacturing sponsor or regulatory body, or invoke regulatory action

Because both major and critical protocol deviations can impact the integrity of a study, they are the most important to consider in measuring protocol compliance and data quality.

Quintiles further categorizes protocol deviations into 14 categories within its Infosario database as reflected in Table 2.
Table 2.

Quintiles’ Categorization of Protocol Deviations

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<tr>
<th>Protocol Deviation Categories</th>
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<tr>
<td>Informed consent</td>
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<td>Eligibility and entry criteria</td>
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<td>Concomitant medication criteria</td>
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<tr>
<td>Laboratory assessment criteria</td>
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<tr>
<td>Study procedures criteria</td>
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<tr>
<td>Serious adverse event criteria</td>
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<td>Randomization criteria</td>
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<tr>
<td>Visit schedule criteria</td>
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<tr>
<td>Investigational product compliance</td>
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<tr>
<td>Efficacy criteria</td>
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<tr>
<td>Administrative criteria</td>
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<tr>
<td>Source document criteria</td>
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<tr>
<td>Regulatory or ethics approvals criteria</td>
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<tr>
<td>Other criteria</td>
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With the growing diversity of clinical PI training programs available, it is surprising that the same data quality issues continue to arise, as evidenced by FDA PI audits. A possible etiology is that no specific training is required; therefore, most practicing clinical PIs have not been formally or even informally trained and have very cursory knowledge of their responsibilities. However, it may be that formally training the volume of clinical PIs to meet the current need is not feasible. Such requirements could significantly slow the development of human therapeutics. A lack of CE to update and improve practice over the lifetime of a
clinical PI is another etiology for persistent data quality issues. This deficit would apply to all those serving in the clinical PI role, trained and untrained. In other areas of medicine, physicians have attempted to improve practice and stay updated on new information through CME, often as required to maintain licensure and certification.

**Continuing Medical Education**

The primary purpose of CME for physicians is to improve medical practice. Although a substantial amount of education is required to become a practicing physician, knowledge and skills must be maintained and expanded over the course of a career which can run 40 to 50 years. Because discovery in human therapeutics is ever increasing, CME has remained the vehicle by which physicians stay abreast of changes (Cervero, 2001). According to Cervero (1992) CE in the professions has a distinct advantage over the other stages of professional education as it comes at a time when professionals are aware of the need to do things better.

**Prevalence, acceptance and requirement for medical practice.** Systems of CME for physicians started in the 1960s, and by the 1970s, CME was being used as a basis for both re-licensure and re-certification. The 1980s brought more comprehensive CME programs, and professional medical societies developed systems of accreditation for CME providers (Cervero, 2001). In the 1990s, programs expanded but were predominantly didactic and devoted mainly to updating physicians on the latest treatments and developments. As litigation became more common in medical practice, regulatory bodies increasingly used CME completion as the method of choice to demonstrate accountability. Additionally, state medical boards expanded their use of CME as a basis for re-licensure (Cervero, 2001). CME
has undoubtedly become the default for accountability and basis for certification and licensure, but some question whether CME improves medical practice.

**Basis for improved medical practice.** Davis et al. (1999) showed that CME can improve professional practice; however, didactic delivery alone is not responsible for improved performance. Instead, Davis et al. found that interactive CME that allows for participant activity and skills practice affects change in performance. Therefore, improved performance may hinge on the type of CME. Robertson, Umble and Cervero (2003) corroborated these results in their evaluation of research syntheses and demonstrated that CME can improve performance, but the improvement driven by the type of CME, namely CME that is interactive, ongoing, contextually relevant, and based on needs assessment impacts practice. Legare et al. (2015) evaluated the objectives of 110 accredited CME activities offered to physicians and other health professionals in Canada using Bloom’s taxonomy (Bloom et al., 1956). They found that the majority were not designed to promote practice change because they focused on the cognitive domain, particularly on knowledge and comprehension, rather than on the psychomotor or affective domains. Cervero, Rottet and Dimmock (1986) determined that other variables, in addition to the type of program, can impact performance change. These were:

- Attitudes of the individual professional pertaining to adoption of innovations
- Nature of the proposed change and the likelihood that it would be implemented
- The social system in which the professional practices and if the desired performance change is reflective of how colleagues practice
The AMA reiterated its commitment in 2001 to continuous practice improvement by stating that physicians have an ethical obligation to not only continue their studies but also to apply this knowledge (Aparicio & Willis, 2005). With the intent to improve medical practice, the AMA added two new learning platforms, performance improvement and internet point of care, to the existing CME framework. These platforms were intended to better represent the way physicians learn and apply what they learn.

The performance improvement platform was intended to break down the barriers that existed between the quality improvement community and CME and draws from Edward Deming’s model for quality improvement: plan, do, study, act (PDSA) (Aparicio & Willis, 2005). Under the performance improvement platform, physicians establish a performance baseline by tracking and analyzing data according to reference criteria, performing an intervention, and tracking changes over time. Performance improvement credit is given for evaluating the results of the intervention and properly interpreting the data. Building quality improvement into required CME is also being considered outside the U.S. Czabanowska et al. (2012) describe a Quality Improvement Competencies Framework that includes 35 competencies with six domains, one of which is continuing professional education.

The point of care platform is intended to capitalize on the effectiveness of self-directed learning. The physician identifies a gap between her knowledge and the desired level of competence. The physician then claims credit for investigating the information via search queries, selects relevant sources, and then describes the application to practice. This platform allows physicians to learn in the context of patient care and directly apply learning to their work (Aparicio & Willis, 2005).
These new platforms have had a mixed reception in the U.S. Particularly, the discipline of quality improvement is largely unfamiliar to physicians. However, greater integration of CME and quality improvement could position CME to actually accomplish its purpose, improved medical practice and improved patient outcomes. Shojania, Silver and Levinson (2012) recommend four levels of integration of quality improvement into CME:

- Highlight clinical areas with quality problems in traditional CME
- Explicitly add quality improvement content in CME specific clinical topics
- Supplement CME with post-event deliverables
- Embed CME in larger quality improvement initiatives

According to the literature, the right types of CME improve medical practice. Therefore, it would stand to reason that modalities, like certification that require CME, would improve medical practice. A recent example that supports this idea comes from the American Board of Medical Specialties and its maintenance of certification process.

*Maintenance of certification.* According to Cook et al. (2015), there is evidence that physicians’ knowledge and skill decrease over time and that once-in-a-lifetime certification could not ensure competency throughout a career. The American Board of Medical Specialties approved the maintenance of certification process in 2000 based on the following evidence (Lipner, Hess, & Phillips, 2013):

- Physician ability to independently and accurately self-assess is poor
- Greater clinical experience does not always lead to better outcomes of care
- Less than 30% of physicians examine their own performance data to improve practice
The purpose of the maintenance of certification process is to support physician knowledge, skills and quality care through self-directed assessment and quality improvement activities. There is growing evidence that shows an association between maintenance of certification activities and clinical quality measures. Maintenance of certification is comprised of four parts:

- Professional standing – maintenance of active licensure
- Life-long learning – self-assessment and self-study modules
- Cognitive expertise – passing an exam
- Practice performance – completion of a quality improvement project

In their study of physician perceptions of the maintenance of certification process, Cook et al. note that physicians accept the concept of specialty recertification is a good idea but want to make the process more efficient given the already heavy administrative demands on their time.

The individual professional medical specialty boards have further supported maintenance of certification by differentiating between their members who are and who are not compliant with MOC. Teirstein (2014) notes that in 2014, the American Board of Internal Medicine began differentiating their members by listing them as certified and meeting MOC requirements or as certified and not meeting MOC requirements. The American Board of Internal Medicine has mandated maintenance of certification for newly certifying physicians, and maintenance of certification has become a differentiator between established physicians for job attainment and retention (Teirstein, 2014). Further, the literature on the effectiveness of the maintenance of certification process is not conclusive, although specialty boards have
accepted them as beneficial (Teirstein, 2014). In their literature summary of 78 articles on the effectiveness of maintenance of certification, Lipner, Hess and Phillips (2013) found that board certified physicians do provide better patient care, but the difference is modest and not unequivocal. Though marginal benefit is presumed, member specialty boards of the American Board of Medical Specialties, whose members account for almost 90% of practicing physicians in the U.S. (Lipner, Hess, & Phillips, 2013), accept maintenance of certification, making it the new professional demonstration for public accountability and transparency (Cook et al., 2015).

Many parallels can be drawn between specialty board maintenance of certification and the CPI. CPI has the potential for improving practice in clinical research as it requires CE.

**CPI**

The ACRP defines a CPI as a clinical PI who has met eligibility requirements, demonstrated proficiency of specific knowledge and job-related skills, and passed the standardized Academy of Clinical Research Professionals PI Certification Exam. CE for CPI is earned on a point system. For a clinical PI to maintain CPI, she must earn and report 24 points or retake and pass the certification exam every two years. Points must be earned in the following categories:

- Minimum of eight points from participation in research-related CE programs
- Minimum of twelve points from continuing involvement (CI) activities
- Remaining four points may be supplemented through CE and/or CI activities

CE points are earned through instructional activities in two topics areas, research and healthcare, where the certificant is the learner. Examples within the research topic area are trial management, regulatory issues and GCP. Examples within the healthcare topic area are pharmacology, oncology and medical devices. CI points are earned through participation in research in a capacity other than learning. Examples include research meeting attendance, serving in or volunteering in a research setting, presentation of research information, and providing trial oversight (“Association of Clinical Research Professionals, PI Certification,” 2015).

Clinical PI certification, much like specialty board maintenance of certification, is in its infancy. The first CPI was awarded in 2005, and it is estimated that less than 10% of U.S. PIs are certified (Space, 2007). Unlike specialty board maintenance of certification, however, CPI has not had the support of a specialty board because one does not yet exist for clinical research. Indeed, the Accreditation Council for Graduate Medical Education does not recognize clinical investigation as one of its 26 specialty areas (Morrison, 2008). Additionally, interested stakeholders, such as pharmaceutical companies, the FDA, and contract research organizations, have not mandated it. This lack of support may exist in part because the certification has not been adequately researched. Like specialty board maintenance of certification, CPI has been studied for effectiveness, but there are only two studies: the first, a retrospective study of protocol adherence between clinical PIs with CPI and clinical PIs without CPI and the second, a retrospective comparison in number and outcomes of FDA audits between clinical PIs with CPI and clinical PIs without CPI.
**As a predictor for regulatory compliance.** Vulcano (2012) used results of FDA inspections from 2007 to 2009 and compared certified PIs to non-certified PIs by volume of both data audits and for cause audits and in subsequent outcomes of these audits. Results showed that certified PIs are just as likely to have for cause audits, but their inspections outcomes were significantly better.

Although this study suggests a differentiation in the quality of work between certified PIs and non-certified PIs, the audit parameters are broad and may stray from the primary FDA audit findings that effect data quality. Therefore, future research on the CPI should use more defined parameters, such as major protocol deviations, to judge data quality between certified PIs and non-certified PIs.

**As a predictor for protocol compliance.** Haeusler (2009) performed retrospective analysis of protocol adherence in four multicenter trials in the U.S. In this study, Haeusler collected the volume of protocol deviations per randomized subject per site. These were differentiated based on sites that had personnel participating on the trials with CPI plus CCRC certifications, CPI only, CCRC only, and non-certified. Protocol deviations were used as a proxy for quality data. Results showed that the CPI plus CCRC and CPI only groups demonstrated significantly lower protocol deviations and thus higher data quality.

Although this study included the CPI certification specifically, the study’s conclusions are confounded by other clinical research certifications. Another limitation of the study is its inclusion of minor protocol deviations that generally have no impact on data quality and patient safety. It is, therefore, desirable in future research on the CPI to include
only parameters that effect quality and patient safety, such as major and critical protocol deviations, and to attempt to control for confounders such as other research certified staff.

**Summary of Literature Review**

This literature review uncovered a significant gap between clinical PI training and clinical PI performance as evidenced by FDA audit findings that contribute to data quality. It is improbable and potentially not feasible to formally train the volume of clinical PIs needed in human therapeutics development. Therefore, CE, as demonstrated by CME in this literature review, may be the key to improving clinical PI performance on key data quality metrics like major and critical protocol deviations. The standardization of this CE would likely require association with and be a requirement for certification like CPI. Experiential learning theory, which describes how professional adults learn, and self-directed learning theory, which describes why adult learners learn, form the foundation of this study and serve as the rationale for why CE, as required by certification, might be the solution to close the gap between clinical PI training and clinical PI performance.
CHAPTER THREE: METHODOLOGY

Chapter three describes the methodology used in the study. The research design, population, sampling method and methods of data collection are outlined. The independent and dependent variables are defined. The methods of data analysis for the research question are described. The purpose of this study is to determine if the CPI certification is a predictor of major and critical protocol deviations in clinical trials. Prior to the initiation of this study, the research proposal was submitted to the Institutional Review Board of North Carolina State University. It received an Exempt status approval.

Research Question

Is there a difference in the mean protocol deviation before and after clinical PI certification?

Research Design

To answer the research question, a quasi-experimental, single-group interrupted time-series design (Creswell, 2014) was used as depicted in Figure 1. The mean protocol deviation was calculated for each study participant from protocol deviations produced retrospectively, from May 1, 2014 to April 30, 2016. This mean protocol deviation was compared to the mean protocol deviation for each study participant prospectively from October 11, 2016 to March 22, 2017.

Treatment Group  O-----X-----O

*Figure 1.* Quasi-experimental, single-group interrupted time-series design (Creswell, 2014). X = treatment (CPI). O = observation (mean protocol deviation).
Population and Sample

Physicians in Quintiles databases who conducted clinical trials with Quintiles since May 1, 2014 and who plan to conduct clinical trials with Quintiles through March 22, 2017 in the United States was the population of interest. All of the participants who were sampled were conducting trials through Quintiles for indications in 3 primary therapeutic areas: gastroenterology, rheumatology and oncology. PIs conducting studies in these specialties were selected because data for these types of trials is available from May 2014 and is expected to continue through ongoing trials through March 2017, which is the time period that was selected for this study. Therefore, selecting PIs who conduct trials in the therapeutic areas of gastroenterology, rheumatology and oncology was intended to ensure adequate data for analysis. A sample of participants from the population were selected based on certain inclusion and exclusion criteria.

Inclusion Criteria

Degreed status and experience. Participants were standardized based on their degree and level of experience. Standardization helped to avoid outliers whose level of experience and educational background alone could affect their performance in the study.

Each participant had to be a U.S. MD or Doctor of Osteopathy (DO) as verified by their curricula vitae (CV). CV are provided as a supplement to the Statement of Investigator form (FDA 1572) and the Quintiles Infosario database. If participant degree status could not be verified by their CV, PIs were also be verified by their State Medical Board. A doctoral degree is a requirement set forth by ACRP for participants to be eligible to take the CPI exam. This study attempts to draw parallels between medical doctor practice improvement as
it pertains to certification and CME maintenance and potential clinical PI practice improvement as it pertains to clinical PI certification and CE maintenance. Therefore, only medical doctors, MD and DO, were included.

Each participant must have worked as a clinical PI for at least two years of the most recent five years as verified by their CV which is provided as supplement to FDA Form 1572 and the Quintiles Infosario database. This is a requirement set forth by ACRP for participants to be eligible to take the CPI exam.

**PI record with Quintiles.** For the successful conduct of the study, PIs must have had no regulatory actions pending against them that would prohibit them from participation in future studies with Quintiles and must have successfully recruited subjects into clinical trials that are managed by Quintiles. Each participant must have been in good standing with the Quintiles Quality Assurance (QA) Department and able to conduct clinical trials as verified by the Quintiles Infosario database. QA clearance is required by Quintiles for a clinical PI to conduct studies with Quintiles.

This study relied on future recruitment for data; therefore, the PIs who were selected had to have a history of successful subject recruitment for clinical trials that are managed by Quintiles. Each participant must have had proven recruitment metrics per the Quintiles Site Identification Department as verified by the Quintiles Infosario database. Each PI must have met or exceeded clinical trial subject recruitment quotas for the last two clinical trials that were conducted with Quintiles.
Each participant must have conducted clinical trials with Quintiles from May 1, 2014 onward as verified by the Quintiles Infosario database. This allowed for a comparison of past major and critical protocol deviations with future deviations.

**Study timelines.** To be included in the study, participants needed to commit to the study timelines for taking the CPI exam.

Each participant had to meet all criteria to be eligible for the CPI exam by June 30, 2016, and had to be willing and available to take the exam during the administration window, which was September 8, 2016 through October 1, 2016. This was verified using the CV provided as a supplement to FDA Form 1572, the Quintiles Infosario database, and by the PI at the time of screening.

**Exclusion Criteria**

**Prior formal research training.** Participants who have previous, ongoing and planned clinical research training and certification may be predisposed to have higher data quality than participants who do not have this prior experience, which could, in turn, impact the results of the study. Therefore, participants who were currently enrolled in or had previously completed a clinical research education program that met the ACRP standards as a substitute for one year of the two years of required employment experience as a PI to be eligible for the CPI exam were excluded. This was verified by the CV that was provided as a supplement to FDA Form 1572 and by the PI at the time of screening. Similarly, a participant was excluded if he or she stated an intent to simultaneously enroll in a clinical research education program that meets the ACRP standards as a substitute for one year of the two
years of required employment experience to be eligible for the CPI exam. This was verified by the PI at time of screening.

Participants were excluded if they had an MD/DO-PhD, MD/DO-MPH or MD/DO-MSCR dual-degree as verified by the CV provided as supplement to FDA Form 1572.

Participants were excluded if they were currently certified, had previously been certified or had previously failed the CPI exam as verified by the ACRP database.

**Commitment to data production.** Each participant had to commit to continue their clinical trial practice so that data could be produced for the study.

Participants were excluded if they had known impediments that might jeopardize sufficient enrolment in clinical trials. Such impediments included prolonged absences from work in the form of sabbaticals, planned pregnancies, and prolonged vacations as verified by the PI at the time of the screening. Participants were not excluded for vacations of two weeks or less at a time and absences due to normal clinical or research conference attendance.

**Study Procedure**

Prescreening using information in Quintiles and ACRP’s databases were performed to narrow the number of participants contacted for screening. Remaining criteria were verified with potential participants at telephone and email screenings. Both prescreening via databases and screening via email and telephone were conducted after IRB approval. In total, 500 potential participants were prescreened. Screening ended when 40 participants were identified.

ACRP estimates that 10% of participants will withdraw from the exam cycle and not take the exam. Therefore, Figure 2 shows that 4 withdrawals, or 10% of the participants are
expected to withdraw. ACRP also estimates that up to 45% of the participants will fail to pass the exam. Therefore, Figure 2 further shows that 16 participants are expected to fail. The 20 participants who are expected to pass the exam will become evaluable participants from which data will be collected.

To account for the possibility of a non-normal distribution of data and to show a significant effect, if one does exist, a large enough sample size was chosen to allow for parametric testing (Harris, 1995). Twenty evaluable meets the minimum threshold for parametric testing (Harris, 1995).

Based on known test failure and withdrawal rates, 40 participants were expected to result in 20 evaluable participants. Quintiles training modules for GCP were offered to improve participants’ pass rate. Additionally, access to CPI practice exams were provided to participants. These training modules and practice exams were the primary risk mitigations to reduce the projected participant test failure rate. There was no way to confirm the amount of preparation each participant made for the exam. Close email communication with participants between consent and testing was the primary risk mitigation to reduce the projected withdrawal rate.

Figure 2. Projected study procedure. Actual study procedure is located on page 68.
**Instrumentation**

CPI is the only accredited certification for clinical PIs and is accredited by the National Commission for Certifying Agencies (NCCPA). The NCCPA is the accreditation body of the Institute for Credentialing Excellence which accredits personnel certifications or certificates. The CPI originates from and is administered by the Academy of Clinical Research Professionals and is awarded by the Association for Clinical Research Professionals.

The CPI exam is administered twice annually, once in the spring and once in the fall. Applications for the CPI exam must be received and accepted before the testing cycle. For this study, participants had to apply and be accepted by August 15, 2016, to sit for the Fall 2016 testing cycle, which was September 8, 2016 through October 1, 2016. To be eligible for the CPI exam, participants had to meet the criteria described in Table 3 (“Association of Clinical Research Professionals, PI Certification,” 2015). Exams are administered by Prometric Test Centers in over 600 locations across the U.S. Because the exam is computer based, participants knew when they finished testing if they passed or failed. This was a preliminary result. ACRP typically verifies preliminary results within 30 calendar days of testing (“PI Certification”).
Table 3.

**Eligibility Criteria for the CPI Exam**

<table>
<thead>
<tr>
<th>Education</th>
<th>Employment</th>
<th>Perform Essential PI Duties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doctoral level</td>
<td>Employed as a PI at least two of the most recent five years</td>
<td>Responsible for the safe and ethical conduct of a clinical trial</td>
</tr>
<tr>
<td>degree</td>
<td></td>
<td>Evaluates the study proposal and decides on participation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Facilitates or verifies formal approvals according to regulatory requirements, ICH GCP</td>
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<td></td>
<td></td>
<td>Ensures that all site initiation activities are performed to start and conduct the study</td>
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<tr>
<td></td>
<td></td>
<td>Participates in the selection of trial subjects according to the recruitment strategy</td>
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<td></td>
<td></td>
<td>Performs or supervises the conduct of study-related procedures and monitors the safety of the trial subjects and investigational staff</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Collects accurate and verifiable data and other essential study documents</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ensures compliance with regulatory requirements and ICH GCP, the protocol and the handling of the investigational product</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Communicates with subjects, sponsor’s personnel, and IRB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ensures adequate close-out of the study</td>
</tr>
</tbody>
</table>
For this study, ACRP verified all participants’ exam results no later than October 7, 2016. The testing fee of $525 was reduced to $152 by ACRP for participants. The practice exam fee of $100 was reduced to $27 by ACRP for participants. These reduced fees were paid through a combination of awarded grants by North Carolina State University and the researcher.

**Study Variables**

- **Dependent variable.** The dependent variable was the mean protocol deviations calculated from May 1, 2014 to April 30, 2016 and from October 11, 2016 to March 22, 2017 for each study participant.

- **Independent variable.** The independent variable was clinical PI before certification (0) compared to clinical PI after certification (1).

**Data Collection**

Protocol deviations produced and clinical trial subjects enrolled by the study participants were downloaded from Quintiles Infosario database in the form of Microsoft Excel (Excel) spreadsheets. At time of enrollment in the study, each participant was assigned an identification number. The protocol deviations report contained minor, major and critical protocol deviations generated by each participant. Data was sorted to remove minor protocol because they do not generally impact data quality. The data was further sorted to include only protocol deviations generated during the periods of interest. A recruitment report was run for each participant. This report was sorted for active clinical trial subjects during the periods of interest.
The major and critical protocol deviations were added together and divided by the number of clinical trial subjects recruited by each clinical PI and active during the periods of interest. This created the dependent variable, which created the mean protocol deviations for each participant for each period of interest. The mean protocol deviation for each period of interest was entered into a new Excel spreadsheet adjacent to each participant’s identification number. The mean protocol deviations were loaded to SAS, via Excel, for analysis. Quintiles granted permission to use its standard operating procedure, CS_WI_PM0231 Handling of Protocol Deviations (“Quintiles Transnational Corporation, Handling of Protocol Deviations,” 2013), to define major and critical protocol deviations for the study. These definitions are as follows:

- **Major Protocol Deviation** – deviations from protocol that impact scientific, ethical, regulatory or business integrity and which, if left unattended could become critical

- **Critical Protocol Deviation** – deviations from protocol that impact scientific, ethical, regulatory or business integrity and could invalidate acceptability of a study to a manufacturing sponsor or regulatory body, or invoke regulatory action

These definitions for protocol deviations are consistent with the FDA guidance for industry (“United States Food and Drug Administration, Guidance for Industry,” 2013) which states that protocol deviations are defined as any change, divergence, or departure from the study design or procedures defined in the study protocol. This guidance defines an important protocol deviation as a deviation that might significantly affect the completeness, accuracy
and/or reliability of the study or that might significantly affect the subject’s rights, safety, or well-being.

**Validity**

**Internal threats to validity.** A selection threat was present in that participants could be selected that already had a predisposition to improve their performance as related to protocol deviations. To help mitigate this, the study excluded those who had shown more formal interest in honing their research skills, such as dual degreed professionals, those who had taken the CPI exam in past and had either failed the exam or passed and let their certification lapse, and those who had an educational background that would exempt one year of clinical PI experience in lieu of this education received.

A mortality threat was present in that participants could leave clinical research during the prospective portion of the data collection. This prospective data collection timeline was set at a minimal number of months (approximately 5 months) to reduce this chance. Also, past recruitment performance is no guarantee of future recruitment performance. There was a risk that participants would not generate data during the post-exam period of interest and therefore would not be evaluable.

**External threats to validity.** Participants selected for the study conducted clinical trials within a limited number of therapeutic areas: gastroenterology, rheumatology and oncology. This selection was meant to limit the variation of types and disease indications of clinical trials that these PIs would encounter. Said another way, by keeping with the same therapeutic areas that focus on clinical trials with similar indications and similar complexities, the effect of the treatment (the CPI exam) can be better assessed. However, it is
possible to have more or less of an effect in other therapeutic areas that would participate in either more or less complex clinical trials in completely different indications. Additionally, all participants had experience conducting clinical trials with a contract research organization, Quintiles. This in and of itself may be a differentiator in the motivation and baseline skill of the clinical PI. Therefore, an interaction of selection, treatment and setting threat existed because results may not be generalizable to clinical PIs in other therapeutic areas and clinical PIs that have not had experience with contract research organizations. To mitigate this threat, claims beyond these therapeutic areas and experience interacting with contract research organizations were not made.

**Threats to statistical conclusion validity.** Statistical power was lowered based on sample size. The desired number of participants was twenty. Withdrawal rates were higher than anticipated and decreased the number of participants below the desired number of twenty. Failure rates were lower than anticipated which helped increase sample size; however, this did not compensate for the higher withdrawal rates. With lower sample sizes, an effect that truly existed was harder to determine. Hedges’ g was calculated to determine if the effect was small, medium or large. To mitigate the threat of a higher than projected failure rate, participants were offered ACRP CPI practice exams and Quintiles training modules that focused on the content of the exam as outlined by the ACRP. To mitigate the threat of a higher than projected withdrawal rate, participants were actively engaged by email between the time of consent and the time of the exam.
Analysis

Data analysis was performed using SAS. The independent variable was categorical (certified clinical PI versus non-certified clinical PI), and the dependent variable was continuous (mean protocol deviations).

Demographic Data

Demographic data collection was used to describe participant characteristics. These included the following:

- Medical specialty
- Medical degree type

Demographic data was collected via a CV that was provided as supplement to FDA Form 1572 and Quintiles Infosario database and which was verified with the clinical PI at time of screening.

Descriptive Statistics

Means, standard deviations and ranges were calculated and reported for the following:

- Years of medical practice experience post completion of residency
- Years of clinical trial research experience in the clinical PI role
- Clinical trial subjects enrolled by participants, major and critical protocol deviations produced by participants and mean protocol deviations produced by participants for each period of interest
Data for descriptive statistics was collected via the CV that was provided as supplement to FDA Form 1572 and Quintiles Infosario database and which was verified with the clinical PI at time of screening.

**Inferential Statistics**

Because the standard deviation of the population of clinical PIs that fit the inclusion and exclusion criteria of the study is unknown, paired-samples t-tests were used to draw conclusions about this population. Although t-tests can be used in studies with small sample sizes as low as three, any detected effect size would be large (de Winter, 2013). The effect size of this study’s treatment (CPI) was not estimated. Therefore, a larger sample size was attempted to help power the study to demonstrate if a moderate to large effect size was present.

**Research Question**

Is there a difference in the mean protocol deviation before and after clinical PI certification?

Paired-samples t-tests were used to compare the mean protocol deviations of the study participants from May 1, 2014 to April 30, 2016 and those from October 11, 2016 to March 22, 2017. This provided a before and after analysis of the treatment intervention using each participant as his own control. Effect size was calculated using Hedges’ g calculation for t-test.

**Delimitations**

Ideally, clinical PIs should be evaluated while performing the same clinical trials, as each trial has its own oddities and level of complexity and therefore risk of protocol
deviations. This was not feasible from a scheduling perspective given time constraints on the study and the timing of clinical trials being managed by Quintiles. To help mitigate this, only data from clinical trials in the same therapeutic areas, gastroenterology, rheumatology and oncology were included. Therefore, it is likely that the clinical trials data included in the analysis came from studies of similar complexities and similar indications within the same therapeutic area.

It was not feasible via the databases used to match the participants in each group by years of medical practice experience and years of research experience. Matching these characteristics would eliminate the risk of one participant being significantly more experienced than another. To mitigate this, participants were compared against themselves and thus served as their own control.

The approximate five-month data collection time period was selected due to the time constraints of the researcher. Ideally, participants would be followed at the one-year time point, the two-year, first recertification time point, and the four-year, second recertification time point. Effect size of the CPI if it exists could be best substantiated through this long-term follow-up.

Limitations

The first limitation of the study is the fact that all clinical PI participants had a working relationship with Quintiles. An argument could be made that this fact alone predisposes these clinical PIs to be more astute in clinical research regulations and responsibilities than clinical PIs without this affiliation. Therefore, the generalizability to a clinical PI population outside of Quintiles is more limited. Generalizability is also limited by
the homogeneity of the clinical trials that the participants were conducting. The results may not apply to therapeutic areas outside of gastroenterology, rheumatology and oncology.

It is possible participants might improve their protocol compliance for no other reason than their data is being monitored. This could falsely increase the effect size.

**Chapter Summary**

This study used a quasi-experimental design. Performance metrics and major and critical protocol deviations were compared before and after CPI credentialing. The dependent variable was the mean protocol deviations produced by the participants during the periods of interest. The independent variable was clinical PIs before and after certification. The study population included US physicians in Quintiles’ databases conducting clinical trials in the same therapeutic areas with at least two years’ experience in clinical trial conduct in the last five years of work history. Demographic data was used to describe the sample randomized and to summarize participant characteristics. Descriptive statistics, means, standard deviations, and ranges, were used to show the distribution and the dispersion of the sample data. Inferential statistics, paired-samples t-tests and Hedges’ g calculation for t-tests, were used to show the effect of CPI on protocol deviations.
CHAPTER FOUR: RESULTS

This study attempted to determine if parallels can be drawn from what has been demonstrated in medical practice to clinical research practice. The certification and the subsequent continuing education that is required to maintain certification has been shown to improve medical practice (Davis et al., 1999). The CPI is the accredited certification for clinical PIs. This study sought to determine if certification can demonstrate improved clinical research practice using a key practice quality indicator, major and critical protocol deviations. This chapter presents the results of the analysis described in the preceding chapter. The research question was:

Is there a difference in the mean protocol deviation before and after clinical PI certification?

This chapter is comprised of four sections. The first section describes the participant response rate and number of participants used in the analysis. The second section presents professional and experiential characteristics of the participants. The third section contains the results of participant mean protocol deviations for the two time periods of interest, May 1, 2014 to April 30, 2016 and October 11, 2016 to March 22, 2017. The final section of this chapter presents the analysis of the research question using paired-samples t-tests to demonstrate the effect of treatment (CPI certification) on participants’ mean protocol deviation.

Response Rate and Evaluable Participants

The study population was comprised of 976 clinical PIs within the Quintiles’ Infosario database who were contacted for participation. Twenty-three demonstrated interest
in participation in the study. Of these 23, all passed screening and were consented for participation, resulting in a 2.4% response rate of the population. Of the 23 consented, 20 registered for the CPI exam, equating to a registration rate of 87%. After exam registration, 5 participants withdrew before the exam or were withdrawn because they were unable to sit for the exam during the designated exam cycle. This resulted in an exam withdrawal rate of 25%, which was higher than ACRP’s historic exam withdrawal rate of 10%. Fifteen participants completed the exam, and of these, 14 participants (93.3%) passed the exam. There was one exam failure. This pass rate was substantially higher than ACRP’s historic pass rate of 55%. Of the 14 participants who passed the exam, two participants did not produce adequate data for analysis during the study timelines. Therefore, 12 participants, representing 1.2% of the study population, produced adequate data for analysis. The actual study procedure is depicted in Figure 3.

Figure 3. Actual study procedure.
Participant Characteristics

Professional. All participants held the degree of Doctor of Medicine, MD. Primary medical specialties, as depicted in Table 4, varied but were concentrated in gastroenterology and rheumatology.

Table 4.

Participants by Medical Specialty

<table>
<thead>
<tr>
<th>Medical Specialty</th>
<th>Participants in Specialty</th>
<th>Medical Specialty Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroenterology</td>
<td>4</td>
<td>33.33</td>
</tr>
<tr>
<td>Rheumatology</td>
<td>4</td>
<td>33.33</td>
</tr>
<tr>
<td>Other</td>
<td>4*</td>
<td>33.33</td>
</tr>
</tbody>
</table>

Note. n = 12. *Other medical specialties included Oncology, Internal Medicine, Nephrology and Endocrinology.

Experience. All participants were experienced in medical practice and in clinical research practice. All participants claimed over 10 years of medical practice experience, and 75% of participants claimed over 10 years of clinical research practice experience. The participants’ medical and clinical research practice experience is depicted in Table 5.
Table 5.

*Participant Medical and Clinical Research Practice Experience. Means, Standard Deviations and Ranges for Participants’ Years of Practice Experience*

<table>
<thead>
<tr>
<th>Participant Number</th>
<th>Years Medical Practice</th>
<th>Years Clinical Research Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>31</td>
<td>11</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>27</td>
<td>25</td>
</tr>
<tr>
<td>9</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>10</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>11</td>
<td>25</td>
<td>14</td>
</tr>
<tr>
<td>12</td>
<td>28</td>
<td>12</td>
</tr>
<tr>
<td>M</td>
<td>22.75</td>
<td>14.83</td>
</tr>
<tr>
<td>SD</td>
<td>7.39</td>
<td>7.95</td>
</tr>
<tr>
<td>Min</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Max</td>
<td>35</td>
<td>33</td>
</tr>
</tbody>
</table>

Note. n = 12.

Research experience was found to be a statistically significant predictor of mean protocol deviations; however, this effect was a neutral one in that it was present both before and after certification. Research experience was explored using both the mean and standard deviation for years of research experience. This is depicted in Tables 6 and 7.
Table 6.

Results Two-Sample t-tests for Mean Protocol Deviations Pre-Certification and Post-Certification and Years of Research Experience Using Mean of Years of Research Experience as a Cut-off

<table>
<thead>
<tr>
<th>Variable</th>
<th>M</th>
<th>SD</th>
<th>n</th>
<th>95% CI for Mean Difference</th>
<th>t</th>
<th>df</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean PD – Research Experience Pre-Cert</td>
<td>4.04</td>
<td>5.89</td>
<td>24</td>
<td>[1.55 6.53]</td>
<td>3.5140*</td>
<td>22</td>
</tr>
<tr>
<td>Mean PD – Research Experience Post-Cert</td>
<td>3.81</td>
<td>6.02</td>
<td>24</td>
<td>[1.27 6.36]</td>
<td>3.7604**</td>
<td>22</td>
</tr>
</tbody>
</table>

Note. * p < .01. ** p < .01. Pre-Certification period was from May 1, 2014 to April 30, 2016 and Post-Certification period was from October 11, 2016 to March 22, 2017. Research Experience was divided into two groups, 1-13 years of experience and 14-33 years of experience.

Table 7.

Results Two-Sample t-tests for Mean Protocol Deviations Pre-Certification and Post-Certification and Years of Research Experience Using Standard Deviation of Years of Research Experience as a Cut-off

<table>
<thead>
<tr>
<th>Variable</th>
<th>M</th>
<th>SD</th>
<th>n</th>
<th>95% CI for Mean Difference</th>
<th>t</th>
<th>df</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean PD - Research Experience Pre-Cert</td>
<td>5.29</td>
<td>7.23</td>
<td>24</td>
<td>[2.24 8.34]</td>
<td>4.1784*</td>
<td>22</td>
</tr>
<tr>
<td>Mean PD – Research Experience Post-Cert</td>
<td>5.06</td>
<td>7.38</td>
<td>24</td>
<td>[1.95 8.18]</td>
<td>4.3939**</td>
<td>22</td>
</tr>
</tbody>
</table>

Note. * p < .001. ** p < .001. Pre-Certification period was from May 1, 2014 to April 30, 2016 and Post-Certification period was from October 11, 2016 to March 22, 2017. Research Experience was divided into four groups, 1-8 years of experience, 9-17 years of experience, 18-26 years of experience and 27-33 years of experience.

Participant Mean Protocol Deviations

The comparison of mean protocol deviations before and after participant certification represented the dependent variable for the study. To calculate the mean protocol deviations,
the major and critical protocol deviations were collected for each participant for the two periods of interest, May 1, 2014 to April 30, 2016 and October 11, 2016 to March 22, 2017. These deviations were then divided by the number of clinical trial subjects enrolled and followed by each participant during the same two periods of interest.

Table 8.

*Participant Mean Protocol Deviations Pre-Certification and Post-Certification*

<table>
<thead>
<tr>
<th>Participant Number</th>
<th>Protocol Deviations Pre-Cert</th>
<th>Subjects Recruited Pre-Cert (# Trials)</th>
<th>Mean Protocol Deviation Pre-Cert</th>
<th>Protocol Deviations Post-Cert</th>
<th>Subjects Recruited Post-Cert (# Trials)</th>
<th>Mean Protocol Deviation Post-Cert</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58</td>
<td>24(7)</td>
<td>2.42</td>
<td>0</td>
<td>4(3)</td>
<td>0.00</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>4(2)</td>
<td>0.00</td>
<td>0</td>
<td>4(2)</td>
<td>0.00</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>31(1)</td>
<td>0.58</td>
<td>0</td>
<td>39(1)</td>
<td>0.00</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>13(4)</td>
<td>0.00</td>
<td>0</td>
<td>17(5)</td>
<td>0.00</td>
</tr>
<tr>
<td>5</td>
<td>18</td>
<td>28(5)</td>
<td>0.64</td>
<td>0</td>
<td>3(2)</td>
<td>0.00</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>6(1)</td>
<td>0.00</td>
<td>0</td>
<td>10(1)</td>
<td>0.00</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>2(1)</td>
<td>1.00</td>
<td>9</td>
<td>11(5)</td>
<td>0.82</td>
</tr>
<tr>
<td>8</td>
<td>6</td>
<td>13(2)</td>
<td>0.46</td>
<td>4</td>
<td>14(3)</td>
<td>0.29</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
<td>1(1)</td>
<td>0.00</td>
<td>0</td>
<td>7(1)</td>
<td>0.00</td>
</tr>
<tr>
<td>10</td>
<td>38</td>
<td>53(5)</td>
<td>0.72</td>
<td>9</td>
<td>23(5)</td>
<td>0.39</td>
</tr>
<tr>
<td>11</td>
<td>15</td>
<td>20(6)</td>
<td>0.75</td>
<td>0</td>
<td>17(1)</td>
<td>0.00</td>
</tr>
<tr>
<td>12</td>
<td>11</td>
<td>29(8)</td>
<td>0.38</td>
<td>0</td>
<td>39(6)</td>
<td>0.00</td>
</tr>
</tbody>
</table>

*Note. n = 12. Pre-Certification period was from May 1, 2014 to April 30, 2016 and Post-Certification period was from October 11, 2016 to March 22, 2017.*
Table 9.

Means, Standard Deviations and Ranges for Clinical Trial Subjects Enrolled by Participants, Major and Critical Protocol Deviations Produced by Participants and Mean Protocol Deviations Produced by Participants for Each Period of Interest

<table>
<thead>
<tr>
<th>Variable</th>
<th>$M$</th>
<th>$SD$</th>
<th>$Min$</th>
<th>$Max$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects Pre-Cert</td>
<td>18.67</td>
<td>15.33</td>
<td>1</td>
<td>53</td>
</tr>
<tr>
<td>PDs Pre-Cert</td>
<td>13.83</td>
<td>17.95</td>
<td>0</td>
<td>58</td>
</tr>
<tr>
<td>Mean PDs Pre-Cert</td>
<td>0.58</td>
<td>0.68</td>
<td>0</td>
<td>2.42</td>
</tr>
<tr>
<td>Subjects Post-Cert</td>
<td>15.67</td>
<td>12.47</td>
<td>3</td>
<td>39</td>
</tr>
<tr>
<td>PDs Post-Cert</td>
<td>1.83</td>
<td>3.54</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Mean PDs Post-Cert</td>
<td>0.13</td>
<td>0.26</td>
<td>0</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Note. $N = 12$. Pre-Certification period was from May 1, 2014 to April 30, 2016 and Post-Certification period was from October 11, 2016 to March 22, 2017.

These values are shown as the mean protocol deviations, pre-certification and post-certification, in Table 8. Table 9 presents descriptive statistics for this data.

**Analysis of the Research Question**

As indicated in Table 6, twelve participants were analyzed. The paired-samples t-test was used to compare the mean protocol deviations of the study participants from May 1, 2014 to April 30, 2016, before certification, to the mean protocol deviations of the study participants from October 11, 2016 to March 22, 2017, after certification.

The results in Table 10 demonstrate a statistically significant difference in mean protocol deviations of participants before and after taking the CPI exam. The results suggest that a clinical PI’s mean protocol deviation drops an average of 0.4542 major and critical protocol deviations per enrolled clinical trial subject after passing the CPI exam. Hedges’ $g$ for t-tests was calculated to estimate the magnitude of the mean difference. Using the accepted interpretation of 0.2 representing a small effect, 0.5 representing a medium effect
and 0.8 representing a large effect (Hedges & Olkin, 1985), the effect size was found to be large at 0.8588.

Table 10.

Results of Paired-Samples t-test and Descriptive Statistics for Mean Protocol Deviations Pre-Certification and Post-Certification

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pre-Cert</th>
<th>Post-Cert</th>
<th>95% CI for Mean Difference</th>
<th>t</th>
<th>df</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>n</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>.5792</td>
<td>.6751</td>
<td>.1250 .2560</td>
<td>.0256 .8827</td>
<td>2.3325* 11</td>
</tr>
</tbody>
</table>

Note. * p < .05. Pre-Certification period was from May 1, 2014 to April 30, 2016 and Post-Certification period was from October 11, 2016 to March 22, 2017.

Chapter Summary

This study sought to determine if CPI certification could reduce the number of major and critical protocol deviations produced by clinical PIs and thus improve the quality of data produced in clinical trials. A paired-samples t-test was conducted to compare the mean protocol deviation of clinical PIs before taking the CPI exam to the mean protocol deviation of clinical PIs after passing the CPI exam. The results of the paired–samples t-test showed a significant difference in the mean protocol deviation of clinical PIs before taking the CPI exam (M = .5792, SD = .6751) and after passing the CPI exam (M = .1250, SD = .2560); t (2.3325), p < .05. This study’s results suggest that a clinical PI’s mean protocol deviation drops an average of 0.4542 major and critical protocol deviations per enrolled clinical trial subject after passing the CPI exam and becoming certified. Participant years of research
experience was found to be a statistically significant predictor of protocol deviations but was
determined to be a neutral effect because it was present both before and after certification.
CHAPTER FIVE: SUMMARY, CONCLUSIONS, & RECOMMENDATIONS

Chapter Five provides a summary of the previous chapters. It describes how this research ties to educational theory and impacts industry, regulatory policy, patients, and clinical PIs. The limitations of this research along with additional research opportunities of the Certified Principal Investigator (CPI) are discussed. Lastly, opportunities for outcomes research of other credentialing using a similar study design is highlighted.

Basic science discovery has been progressing at a pace that has exceeded our ability to translate its benefits into usable human therapeutics. This translational gap was formally recognized in the NIH Roadmap, which identified clinical PI training as one of several key drivers to close this gap (Zerhouni, 2003). Since this time, various types of clinical PI programs have been developed to meet this need. These programs have ranged from certificate level to graduate degrees but have failed to produce both the volume of clinical PIs needed and the quality of data that would be expected of a more trained clinical PI labor force. This has been best demonstrated in the persistent data quality findings in FDA audits (“Association of Clinical Research Professionals, Annual Conference,” 2010).

To increase the numbers of clinical PIs, the pharmaceutical industry has looked beyond the academic medical centers where most of the formally trained clinical PIs reside (Lightfoot, Sanford, & Shefrin, 1999) to physician practices outside these centers. There has been a significant shift in clinical research work to physician practices outside of academic medical centers (Lightfoot et al.). This suggests that an increasingly higher number of practicing PIs lack formal clinical research training, as currently the FDA does not provide a standardized initial training requirement or continuing education requirement for clinical PI
practice. The FDA allows the pharmaceutical industry leeway to interpret their broad requirement that a clinical PI must have appropriate training and experience to investigate an investigational product (“United States Food and Drug Administration,” 2015).

Both clinical PI training and medical training share a common theoretical framework in experiential learning theory. Because of its pace and complexity, clinical research fits comfortably with two fundamental premises of experiential learning theory, namely lifelong learning and direct links between education and work. Similarly, the pragmatism of experiential learning theory fits well with the initial and continuing educational needs of clinical PIs. Dewey’s (1938) theory of experience and its two tenets of continuity and interaction parallel clinical PI training and medical training. The ever-changing environment of medical and clinical research practice constantly exposes clinical practitioners to new experiences. These new experiences influence future experiences that form the continuity of experiences that Dewey describes. Also, Dewey’s tenet of interaction suggests that education and training should account for the full array of experiential differences and backgrounds that medical and clinical PIs possess. Schon’s (1983) reflexive practitioner model describes the art of professional practice in terms of knowing-in-action and reflection-in-action. Cervero (1992) uses Schon’s work and explains how most situations in professional practice cannot be solved using knowing-in-action because they are unique. Professionals must reflect while acting, which reshapes what they are doing in real-time. Clinical PIs, therefore, move from the rote execution of a clinical protocol (knowing-in-action) to an understanding of the necessity of the prescriptive nature of a protocol to extrapolate the safety and efficacy of an investigational product (reflection-in-action).
Reflection-in-action describes an adaptive process by which clinical PIs learn. Kolb (1984) described this adaptive and dynamic learning using his experiential learning model. Kolb determined that experiential learning is not the static application of learned facts and skills to experiences. Ideas are constantly being modified by experiences. Therefore, learning is defined by the process of adaptation and not by outcomes. Kolb’s model parallels the scientific method which uses adaptive experimentation based on observation to create new knowledge.

The need and desire for knowledge acquisition for those in medical and clinical research practice are also informed by the self-directed learning theory of Houle (1961) and Knowles (1975), particularly Knowles’s elements of andragogy. Medical and clinical research practitioners, as adult learners, choose learning that fills knowledge gaps, resolves ongoing problems, and improves professional practice.

The acquisition and application of new knowledge are important to changing clinical practice. Continuing education has been shown to improve medical practice (Davis et al., 1999). Continuing education is also the accepted basis of medical re-licensure and re-certification (Cervero, 2001). The parallels between medical practice and clinical research practice are evident. Just as pre-professional training and continuing medical education for physicians are informed by experiential learning theory (Dewey, 1938; Kolb, 1984; Schon, 1983) and self-directed learning theory (Knowles, 1975), so too should this theory apply to clinical research practice. Additionally, as certification and subsequent continuing medical education have improved medical practice (Davis et al., 1999), it is reasonable to suggest that certification and subsequent continuing education can improve clinical research practice.
In summary, the results of this study demonstrate that clinical PIs will choose educational opportunities that they believe will satisfy gaps in knowledge and further their ability to be competitive in the research environment. Though this study offered the CPI exam free of charge, the clinical PIs who participated had to prepare for the exam and schedule time away from their busy clinical practice or their personal life to participate. This demonstrated a belief that this effort would derive them benefit in their clinical research practice. This motivation to learn ties directly to Houle’s (1961) goal-oriented learner category. Similarly, it ties to Knowles’s (1975) assumption of self-direction in adult learners, namely the assumption that learners learn what is required to perform their life’s tasks. Extrapolated from this self-directed baseline is the expectation that credentialing and subsequent continuing education specific to clinical research will improve the participant’s quality of practice. This expectation is inevitably paralleled to what the participants’ have experienced in the continuing medical education that is required for their medical licensure and what Davis et al. (1999) demonstrated was effective to improve medical practice. This self-direction to pursue avenues that are more straightforward and expeditious to accomplish practice improvement and a competitive edge becomes even more logical to nurture given the constraints that other educational paths impose on busy medical professionals.

It is often not feasible for clinical PIs to attend formal training such as a degree or instructor lead-training, which takes them away from their medical practice. However, PI certification and its associated more flexible, ongoing and required continuing education, may be a practical alternative to accomplish three important goals: expanding the number of clinicians participating in clinical research, improving the quality of data produced by
clinical PIs, and improving study safety for subjects participating in clinical trials through proper clinical PI adherence to approved study protocols.

The certified principal investigator (CPI) remains the only accredited certification for clinical PIs. Two retrospective studies have resulted in findings that suggest clinical PIs with CPI outperform clinical PIs without CPI in the areas of protocol deviations (Haeusler, 2009) and FDA audit outcomes (Vulcano, 2012).

This research furthers the theories of experiential learning and self-direction by affirming that they are applicable in a similar, but distinct discipline to medical practice, namely clinical research practice. Additionally, this research reaffirms that certification and continuing education can improve professional practice outcomes.

Clinical research practice, even more than medical practice, resides in the “swampy lowland” that Schon (1983) described. Although accepted research practice and techniques are used in clinical research, clinical PIs are charged with uncovering new knowledge in real time; knowledge that exceeds Schon’s “high, hard ground” that follows what is taught in training and considered to be evidenced-based and applicable to clinical settings.

Kolb’s (1984) process of adaptation is also even more applicable in clinical research practice than in medical practice. Clinical research generates new knowledge that must be adapted to the current body of knowledge or discredit what is known to be true in the present time. This adaptation equates to learning rather than learning equating to the actual outcomes of clinical trials.

This research corroborates the self-directed learning theory of Knowles (1975) and his elements of andragogy. The pace of change in clinical research practice is faster than
medical practice. Clinical PIs must become life-long learners to improve their practice and out of necessity, be driven to activities and learning that fill knowledge gaps and resolve ongoing problems.

Cervero’s (2001) work, related to the medical practice environment, is also reaffirmed by the results of this research. Since continuing education is the accepted basis of medical re-licensure and re-certification, clinical PI certification with its required CE for maintenance could become the standard for clinical research practice. The positive outcomes in mean protocol deviations after certification corroborate Davis et al. (1999) findings that continuing medical education that is required for medical licensure is effective in improving medical practice.

The purpose of this research is to add to the body of knowledge on the CPI by investigating whether clinical PIs produce fewer mean protocol deviations on clinical trials after they attain the CPI certification than before they attain the CPI credential. Protocol deviations are an important measure of data quality and have been identified by the FDA as a recurrent audit finding that impacts not only the usability of clinical trial data but also clinical trial subject safety (Getz & Campo, 2013). The study utilized a prospective, quasi-experimental research design using quantitative methods of data analysis. The population included 976 clinical PIs practicing in the United States and present in Quintiles’ databases. The primary objective for this study was to determine if attaining the CPI certification would decrease the mean protocol deviations produced by clinical PIs. This chapter presents a summary and discussion of the results, contributions to the literature on the CPI certification, limitations of the study, and proposes additional research.
Conclusions and Discussion

Mean protocol deviation was defined as the number of major and critical protocol deviations produced by study participants during the periods of interest divided by the number of clinical trial subjects enrolled and actively followed by study participants during the same periods of interest. Similar to Haeusler (2009), this study demonstrated that clinical PIs with CPI certification produced fewer mean protocol deviations than clinical PIs without CPI certification. However, this study was able to show this effect prospectively using each participant as his own control; whereas, Haeusler looked retrospectively at data comparing credentialed clinical PIs to non-credentialed clinical PIs. Also unlike Haeusler, this study focused solely on the protocol deviations, major and critical, that can significantly impact data quality and clinical trial subject safety. This focus on the protocol deviations that matter most makes the positive findings of this study even more impactful. Participant years of research experience was considered as a possible confounder to these positive results. Indeed participant years of research experience was found to be a statistically significant predictor of mean protocol deviations. However, this finding was thought to be neutral to the study’s endpoint of mean protocol deviations after certification as it was shown to be statically significant both before and after certification.

This study had no comparability to Vulcano (2012) as a different endpoint (FDA audit outcomes) was used for that study. However, this study, like Vulcano’s study, showed that CPI certification does seem to have a positive impact on clinical study conduct.

The literature shows that continuing medical education improves medical (CME) practice (Davis et al., 1999) and that CME is the accepted basis for medical re-licensure and
re-certification (Cervero, 2001). This study suggests that there is an impact to clinical PI data quality after initial certification but does not demonstrate that this is related to continuing education. Additional data collection through the time of re-certification would be required to demonstrate this. However, it is reasonable to assume that like medical practice, clinical research practice would show a similar pattern of practice improvement.

**Implications for Policy and Practice**

Improving the quality and quantity of clinical PIs is integral to closing the translational gap between basic science discovery and human therapeutics. Our current degreed programs have not produced the volume of clinical PIs necessary to perform the volume of work required to help close this gap. Simultaneously, the medical professionals who are working as clinical PIs are making the same errors year after year as evidenced by FDA audit findings (Getz & Campo, 2013). These errors have a negative impact in two substantial ways. Firstly, there is a loss of valuable data that carries with it a significant cost in development time and research and development budget. Secondly, there is greater risk to trial subject safety and increased subject trial burden. Certification and its associated continuing education is an accepted means by which the medical profession stays abreast of the developments in its rapidly changing environment. Certification may be more accepted, easier to acquire, and offer more flexibility to maintain than longer, formal programs in clinical research. It has been shown that continuing education improves professional practice, including medical practice (Davis et al., 1999). Therefore, certification and continuing education could be a primary driver in expanding the number of qualified clinical PIs, improving their ability to produce quality data faster, and increasing clinical trial subject
safety. This study suggests that CPI certification could impact protocol deviations, which is a key data quality indicator.

**Implications for clinical PIs.** CPI certification could offer a reasonable alternative to clinical PIs who cannot afford the time away from medical practice or the financial burden to complete a formal, degreed, clinical research program to demonstrate competency in this specialty. Experienced clinical PIs may see additional certification requirements as a burden, as just another credential requiring maintenance. During the execution of the study, several clinical PIs did express this sentiment. However, most of the clinical PIs contacted expressed sentiment consistent with what Cook et al. (2015) found. Cook et al. found that there is evidence that physicians’ knowledge and skill decrease over time and that once-in-a-lifetime certification or training could not ensure competency throughout a career. Clinical PIs, as practicing physicians, are familiar with the maintenance of certification required by the American Board of Medical Specialties and understand that the need for maintenance of certification is based on the following evidence (Lipner, Hess, & Phillips, 2013):

- Physician ability to independently and accurately self-assess is poor
- Greater clinical experience does not always lead to better outcomes of care
- Less than 30% of physicians examine their own performance data to improve practice

Maintenance of certification in clinical practice with its intent to improve clinical quality measures directly parallels certification in clinical research practice with its intent to improve clinical trial data and safety quality measures. In their study of physician perceptions of the maintenance of certification process, Cook, et al. (2015) note that physicians accept
the concept of specialty recertification as a good idea. This is consistent with the anecdotal responses from the population sampled in this study.

Some clinical PIs who responded positively to being solicited for the study also saw certification as a way to differentiate themselves from their peers. This is consistent with how the individual professional medical specialty boards in clinical practice have further supported maintenance of certification by differentiating between their members who are and who are not compliant with maintenance of certification. Some clinical PIs predict a similar differentiation on the horizon for clinical research practice between those who are certified and those who are not.

Many parallels can be drawn between specialty board maintenance of certification and the continuing education associated with CPI. As with specialty board certification, even clinical PIs who have been trained formally could benefit from improved practice through the continuing education required by certification maintenance. Additionally, improved clinical research practice through CPI certification, could benefit clinical PIs through work efficiencies. A greater understanding of current clinical research practice trends could lead to more efficiently run studies, resulting in greater clinical trial volume and increased revenue for clinical PI practices. Equally important is the care of the clinical PI’s subjects. A greater understanding of current clinical research practice trends could improve protocol compliance and appropriate safety reporting. Increased compliance results in lower risks for the clinical PI’s subjects, who often are also their patients outside of clinical trials.

**Implications for the pharmaceutical industry.** Increasing the quantity of clinical PIs who can produce quality data is critical to the efficient enrollment of clinical trials and in
the timely production of quality data (Zerhouni, 2003). Clinical trial protocol design has become more complex over the last decade (Getz, 2014), requiring clinical PIs to stay abreast of current trends in diagnostics and treatments and requiring them to follow more complex procedures within protocols. This increased complexity brings with it higher risk for subject safety and therefore greater scrutiny from regulatory authorities and ethics committees. This burden can result in decreased data quality and incomplete safety reporting (Emanuel et al., 2004). Preparing clinical PIs for this additional burden begins with baseline training and requires continuing education to stay abreast of updates and changes in the regulatory environment and changes in procedures associated with the conduct of clinical trials. In summary, delays in clinical trial timelines due to an inability to recruit an adequate number of qualified clinical PIs or due to error-ridden, unusable data, can result in unsafe conditions for subjects and failed clinical trials, which may further result in a waste of substantial research and development budget. CPI certification could offer a solution to improve the industry’s data quality issues, improve subject safety, and reduce the overall development timeline and budget for human therapeutics.

**Implications for the regulatory agency.** Regulatory agencies, such as the FDA, are tasked with ensuring that the investigational products that are approved for marketing are safe and efficacious and that undue risk and burden are not placed on clinical trial subjects. This is balanced against the amount of basic science that needs to be translated into human therapeutics to satisfy the needs of patients in a timely fashion. Emanuel et al. (2004) found that this burden can result in incomplete safety reporting. Increasing the quantity and quality of clinical PIs increases the timeliness of eventual approval of new drug applications for
marketing. Additionally, well-trained clinical PIs who are compliant with approved protocols protect subject safety through proper safety reporting of adverse events. Well-trained clinical PIs also decrease trial burden by producing quality data that does not need to be repeated due to protocol deviations.

The FDA is aware of the requirements placed on physicians in clinical practice and how medical specialty boards differentiate between those who are maintaining certification and those who are not. The FDA could consider a similar differentiation between certified and non-certified PIs. Teirstein (2014) notes that in 2014, the American Board of Internal Medicine began differentiating their members by listing them as certified and meeting maintenance of certification requirements or as certified and not meeting maintenance of certification requirements. Maintenance of certification has become a differentiator between established physicians for job attainment and retention (Teirstein). Further, member specialty boards of the American Board of Medical Specialties, whose members account for almost 90% of practicing physicians in the U.S. (Lipner, Hess, & Phillips, 2013), accept maintenance of certification, making it the new professional demonstration for public accountability and transparency (Cook et al., 2015). Similarly, the CPI certification could support the FDA’s continuing effort to improve the timely delivery of safe and efficacious human therapeutics whilst demonstrating accountability and transparency to the public.

**Implications for patients.** The expeditious development of safe human therapeutics is a priority of patients. As diagnostic tools continue to improve clinicians’ ability to accurately diagnose disease in a timely fashion, the demand to then adequately treat disease is increased. A more complex disease process often requires more complex clinical trial
protocols. Though complex protocols are often necessary, they can lead to increased subject burden related to time required to participate and the volume and invasiveness of procedures in the clinical trial. The complexity of protocol design has increased over the last decade, and the reasons are multifaceted (Getz, 2014). Larger amounts of clinical data, often genetic and biomarker data, is being collected to develop stratified, personalized treatments. Additionally, more data in the form of samples and diagnostic procedures is required for post-hoc analyses if primary and secondary endpoints are not met and also to inform future research. The complexity that this pile-on effect causes can lead to safety concerns when clinical trials are poorly executed by clinical PIs who do not fully understand their oversight and safety reporting responsibilities. CPI certification and its associated continuing education could improve the clinical PI’s ability to properly conduct complex protocols and improve clinical trial subject safety.

In addition to safety, access to clinical research opportunities is of concern to patients. Even with the increased number and diversity of training programs for PIs in clinical research, there are still not enough PIs to meet development needs (Zerhouni, 2003). There has been a significant shift from clinical PIs operating in academic medical centers to physician practices outside of these centers (Lightfoot, Sanford, & Shefrin, 1999) which has somewhat improved access. However, the heaviest concentration of formally trained clinical PIs remains in the pharmaceutical industry and academic medical centers (Lightfoot et al., 1999). Therefore, a higher percentage of practicing clinical PIs lack formal training. A priority must be to ensure that this improved access is accompanied by competent clinical research practice. CPI certification and subsequent continuing education may be the best way
to support this growing segment of clinical PI practice and improve patient access to clinical research.

In summary, increasing the quality and quantity of clinical PIs through CPI certification and continuing education could improve patient access to trials and increase subject safety through greater protocol compliance.

Limitations

This study had several limitations. All participants had a working relationship with Quintiles and may therefore be more skilled clinical researchers than clinical PIs without this affiliation. Additionally, PIs were selected from trials running in several therapeutic areas. The results cannot be generalized outside of the specialties studied and should not even be generalized for those specialties represented secondary to the small sample size from each specialty. Generalizability of the study results is also limited for a clinical PI population unaffiliated with Quintiles.

The study sample size was small. Secondary to the researcher’s position within Quintiles, it was believed to be unethical to heavily solicit participants to participate in the trial. An abundance of caution was used here to ensure that no clinical PI felt obligated to participate for fear that it would impact their ability to be selected for studies with Quintiles. Had this not been a concern, more aggressive recruitment techniques could have been employed and would have likely resulted in a greater sample size for analysis.

The study was a quasi-experimental design. Though participants had never registered for or previously taken the CPI exam and had no advanced degree in research, they still self-selected to participate when solicited. Participants could therefore be predisposed to be more
motivated and higher performing than the general clinical PI population in the Quintiles’ databases. Additionally, participants might have improved their protocol compliance for no other reason than their data was being monitored. Both instances could favorably influence the results.

Though the effect size between means evaluated proved to be large, the sample size was less than desired, and the time for data collection, 5 months, could have been longer. These, too, were limitations. A greater sample size and extended study timeline could have affected the study results in either direction.

**Suggestions for Future Research**

This prospective study provided some needed outcomes data for the CPI. Future research should include a larger, experimental design that further limits self-selection bias like that outlined in Figures 4 and 5.

*Figure 4. Proposed study procedure.*
The ideal study would involve participants affiliated with multiple CROs, like Quintiles, and those unaffiliated with CROs. The ideal study would stratify clinical PIs by particular clinical trials and by years of clinical PI practice experience so that trial complexity and experience are not confounding factors. Participants in future trials should be followed long-term to determine if the apparent short-term effect on mean protocol deviations is sustained. Recommended long-term follow-up could include analysis at one year, two years (first recertification cycle) and four years (second recertification cycle). To ethically recruit a larger trial, the recruiter should have no perceived ability by the clinical PIs to affect future trial work with pharmaceutical companies or CROs. In other words, the participant clinical PIs should not feel compelled to enroll in the study through fear that future clinical trial work could be denied.

Treatment Group  R-----X-----O

Control Group   R----------O

Figure 5. Experimental, posttest-only control group design for primary research question (Creswell, 2014). R = random assignment. X = treatment (CPI). O = observation (mean protocol deviation).

The pharmaceutical industry utilizes multiple credentials that are not mandatory to acquire or maintain a position but that are viewed as differentiators when candidates are considered for employment or promotion. The following are just a few of these:

- CCRA – certified clinical research associate
• CCRC – certified clinical research coordinator
• PMP – project management professional
• RAC – regulatory affairs certification

The same type of outcomes research could be conducted for these credentials to determine if professionals holding them produce higher quality work. Within a CRO or pharmaceutical company, metrics that could serve as surrogate markers for quality are collected for the clinical research associates, site research coordinators, project managers, and regulatory affairs specialists who hold these credentials. Some of these credentials, such as PMP, are earned by professionals in many industries. These industries, such as information technology and construction, are beyond this investigator’s scope of knowledge, but likely they too collect metrics to evaluate their own professionals.

Summary

Both the quality and quantity of clinical PIs needs to increase to efficiently translate the volume of basic science discovery into usable therapeutics for patients. The education of clinical PIs is an integral step in realizing this goal. Experiential learning theory has informed clinical medical training and practice, and clinical research practice has evident parallels to clinical medical practice. Continuing medical education has been shown to improve medical practice (Davis et al., 1999). This study suggests that certification, with its continuing education maintenance requirement, may improve clinical research practice.

The data presented in this study suggest that CPI certification decreases mean major and critical protocol deviations and therefore improves data quality in clinical trials. Also, it is possible that CPI certification along with the maintenance-focused continuing education it
would require, could expand the number of qualified clinical PIs and improve the quality of work of currently practicing clinical PIs. Certification of PIs should be considered as a means of expanding the number of clinical PIs and improving the quality of data produced by clinical PIs. If further research in this area validates these initial results, both industry and regulatory bodies should consider certification as a requirement to perform the duties of the clinical PI.

**Concluding Statement**

Though additional research is needed, the relationship between CPI certification and improved clinical research practice does seem to parallel that of clinical medicine. If improvements are to be made that expedite the translation of basic science into human therapeutics, clinical research training will play a significant part. CPI certification, along with the required continuing education to maintain credentialing, may prove to be an integral part in the way that we deliver human therapeutics to the patients who need them in the future.
REFERENCES


