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CPI™ Certification as Predictor of Clinical Investigators' Regulatory Compliance

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Abstract

Hospitals, research sponsors, institutional review boards, and other stakeholders do not have data to support a universal "test" to ensure that a clinical investigator is not only adequately trained in the International Conference on Harmonization Good Clinical Practices but can implement those principles into practice. Many stakeholders have created their own training programs of vastly different content and quality with little to no reciprocity. This has led to waste in the industry as well as qualified investigators having to retake basic courses because of the lack of reciprocity or globally accepted mark. In addition, investigators who may not be as well versed as they should be often are left to continue in their role because of the lack of efficacy evaluation of what training they received. The Certified Physician Investigator (CPI™) certification put forth by the Academy of Pharmaceutical Physicians and Investigators is poised to be that standard yet is not widely accepted as it is relatively new, and thus its effectiveness as a predictor of regulatory compliance needs to be studied.

Keywords

CPI, certification, Good Clinical Practices, GCP, training, principal investigator, clinical investigator, Academy of Pharmaceutical Physicians and Investigators, APPI, FDA, audit

Clinical investigators are required by regulations and ethics boards to have training in the ethics and regulations of clinical research. Although this is required per se, there are widely inconsistent definitions and criteria of what that training should entail. Currently, accepted thresholds of adequate training range from verbal attestations ("I did research in my residency," which may mean they simply collected data for another investigator), to searching online for research regulations (what this author calls "trained by Google"), to completing a potpourri of online modules, to attending a 15-minute "GCP refresher" session on the International Conference on Harmonization (ICH) Good Clinical Practices (GCP) at an investigator meeting for a given protocol, to attending 3 days of classroom education (with or without post-classroom mentoring), or even to achieving full academic degrees specific to the conduct of clinical research. There is no hypothetical "blood test" to determine if an investigator has received adequate training, and thus the stakeholders need to look elsewhere.

In other branches of medicine, stakeholders turn to various medical boards to "certify" an individual as adequately trained to perform specific duties. Although certification alone does not make an individual perform better, it is a mark established by a peer group that an individual has both the knowledge needed and the ability to apply that knowledge in real-world settings and in complex scenarios involving conflicting laws and ethics. This "board certification" concept has been around for more than 100 years and is widely and often unquestionably accepted among professionals, institutions, payers, and regulators. Certification by a medical board is often required prior to privileging by hospitals to conduct related duties in a hospital or outpatient setting. Insurance payors also rely on board certification to be listed on provider panels. This general acceptance by stakeholders prevents each stakeholder from having to create his or her own examination models.

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In the absence of a generally accepted board certification specific to being a clinical investigator (ie, not having an additional privileging category of "Clinical Investigator"), hospitals are left to assume in-depth knowledge of research ethics and regulation as part of a physician's general medical qualifications. HCPro, a consulting company many hospitals use to delineate privileging requirements, has recently written a white paper on how to create a separate privileging category for investigators ("Practice Area 415: Clinical Investigator"[1]), but this has not yet been widely adopted. Unlike other subspecialties that require separate privileging, the ability to conduct research is generally an "automatic right to be taken away" as opposed to "an additional privilege to be earned." In addition, sponsors of clinical research and institutional review boards (IRBs) often independently develop their own in-house training and certification that is often not reciprocated, thus resulting in duplicated resources between the sponsors as well as lost investigator resources because of repeating coursework that is not reciprocated between sponsors.

In 2005, 3 organizations had certification programs exclusively for physician investigators: the Drug Information Association (DIA) with CCI (Certified Clinical Investigator), the American Academy of Pharmaceutical Physicians (AAPP) with CPI (Certified Physician Investigator), and the Association of Clinical Research Professionals (ACRP) with CCRI (Certified Clinical Research Investigator). Through a series of transactions in and around 2006, the 3 programs consolidated to form a single certification program for clinical investigators, known as the Certified Physician Investigator, or CPI™.[2] This program was overseen by a newly created entity called the Academy of Pharmaceutical Physicians and Investigators (APPI). The APPI succeeded the AAPP and thus maintained its seat on the American Medical Association's House of Delegates. The APPI's CPI certification as a Physician Investigator follows the same pathway as similar agencies in the American Board of Medical Specialties in that recipients must receive the peer-defined necessary education, gain the necessary experience, and pass an examination based on current job analysis and psychometric principles. Certification is then maintained through periodic retest and/or through receiving ongoing continuing education relevant to the field of practice. To have the CPI examination accredited by the Institute for Credentialing Excellence/National Commission for Certifying Agencies (NCCA), the CPI exam was moved in 2010 to be operated by the Academy of Clinical Research Professionals, which runs ACRP's other 2 accredited examinations in the clinical research industry for clinical research coordinators (CCRCs) and clinical research associates (CCRAs).

In contrast to the wide and often unquestioned acceptance of other medical specialties, CPI certification is not yet widely adopted as a requirement by research sponsors, hospitals, IRBs, and research institutions. Part of the reason may be the newness of the examination and thus the lack of evidence validating this new certification as a mark attesting that the investigator was adequately trained. Nearly all of the literature attesting to the quality of the varying certification products is not evidence based but merely anecdotal or advertising. The first known evidentiary article, published by a commercial sponsor in 2009, presented a retrospective analysis of its database of over 1400 randomized participants across 4 multicenter clinical trials consisting of 101 investigators, 29% of whom were CPI certified. This analysis revealed that, in comparison to sites where neither the research coordinator nor the investigator was certified, protocol deviations were significantly lower in sites where the investigator was CPI certified, particularly when the lead coordinator was also certified (CCRC) by the Academy of Clinical Research Professionals.[3]

Although lack of adherence to a clinical trial protocol remains in the top deficiency areas of clinical investigators, other areas would be investigated in a comprehensive Food and Drug Administration (FDA) inspection. Therefore, to further research the validity of CPI certification as a predictor of regulatory compliance, it was desired to look beyond protocol deviations as a sole determinant and investigate all areas of FDA compliance. This study evaluated the difference in FDA inspection outcomes between CPI certified investigators and those who are not CPI certified. If validated as a tool, sponsors, hospitals, and other stakeholders could rely on the CPI certification as a differentiator in regulatory compliance (as determined by FDA inspections) and thereby save the duplication of resources needed to individually create and maintain their own certification as well as keep the certification of investigators independent to avoid any accusations of conflicting interest.

This study evaluated 3 hypotheses. The first hypothesis (hypothesis 1) was that CPI certified investigators did not have as many "for-cause" inspections from the FDA as those who were not CPI certified. The subsequent 2 hypotheses pertained to the difference of outcomes of FDA inspections between CPI certified investigators and noncertified investigators, regardless of cause. Hypothesis 2 was that CPI certified investigators received the most favorable outcome ("no action indicated") more often than investigators who were not CPI certified. Hypothesis 3 asked if CPI certified investigators received the least favorable outcome ("official action indicated") less often than investigators who were not CPI certified.

Method

The analysis is based on the combination of 2 databases. The first is the Clinical Investigators Inspection List (CLIIL),[4] which is the FDA database on clinical inspections compiled

since 1977 and available under the Freedom of Information Act (FOIA). This database offers some basic demographic information about the investigator and shows the abbreviated results of the audit in 1 of 3 classifications. The first classification, "no action indicated" (NAI), means that no objectionable conditions or practices were found during the inspection. The second classification is "voluntary action indicated" (VAI), meaning some objectionable conditions were found but the problems do not justify further regulatory action, and any corrective action is left to the investigator to take voluntarily. The third classification is "official action indicated" (OAI), meaning objectionable conditions were found and regulatory and/or administrative sanctions by the FDA are indicated. The second database used is the CPI certification database obtained from the APPI.[5]

Because CPI certification of physician investigators did not exist until recently, the analysis could not use the entire CLIIL database of more than 16,000 investigations and was thus limited to inspections conducted during the past 3 calendar years of data (2007-2009). The April 2010 version of the CLIIL database was used under the assumption that the FDA input all data for 2009 (note: this assumption cannot be verified by the author). The CPI certification database supplied by the APPI was current as of August 2010. Investigators in the APPI database were matched to investigators in the CLIIL database. Matching was defined as having the same first name, last name, and city/state fields in both databases. As physicians may have multiple addresses, 2 cities within 50 miles of each other in the same state were considered the same location and thus a match.

Once the databases were linked, descriptive statistics were used to evaluate the 3 hypotheses with simple chi-squared statistical tests using Microsoft Excel (Microsoft, Redmond, Washington).

Results

Hypothesis 1: CPI certified investigators do not have as many "for-cause" audits from the FDA as those who are not certified.

There are 2 FDA inspection types: data audit (DA) and for cause (FC). A data audit is an inspection that focuses on verification of study data. A for-cause inspection focuses on the conduct of the study by the clinical investigator[3] and usually results from a complaint or other anomaly brought to the FDA's attention. Table 1 compares audit types between CPI certified investigators and noncertified investigators. Noncertified investigators received for-cause inspections 20.3% of the time, with the remaining 79.7% being data audits. CPI certified investigators received for-cause inspections only 10.4% of the time, with the remaining 89.6% being data audits. Although the percentage of for-cause inspections of noncertified investigators was nearly twice the percentage of for-cause inspections of CPI certified investigators, the chi-squared test revealed that the increased likelihood of non-CPI certified investigators receiving a for-cause audit did not achieve statistical significance ($\chi^2 = 2.891$, $P = .089$).

Table 1. Cause of Audits (Percentage) of Certified vs Noncertified Investigators

	Data Analysis, No. (%)	For Cause, No. (%)
CPI™ certified (n = 77)	69 (89.6)	8 (10.4)
Not certified (n = 1441)	1149 (79.7)	292 (20.3)

CPI™, Certified Physician Investigator.

Table 2. Percentage Breakdown of Food and Drug Administration Clinical Investigator Audit Results

Outcome	CPI™ Certified (n = 77), %	Not CPI™ Certified (n = 1441), %
NAI	50.6	35.1
VAI	49.4	53.0
OAI	0	11.9

CPI™, Certified Physician Investigator; NAI, no action indicated; OAI, official action indicated; VAI, voluntary action indicated.

Hypothesis 2: CPI certified investigators are more likely to receive the most favorable outcome in FDA audits (NAI) than noncertified investigators.

Hypothesis 3: CPI certified investigators are less likely to receive the least favorable outcome in FDA audits (OAI) than noncertified investigators.

Table 2 displays the results of FDA investigations over the 3-year study period. Slightly more than 50% of inspections of CPI certified investigators yielded NAI codes as opposed to only 35.1% of non-CPI certified investigators. Likewise, no inspection of a CPI certified investigator yielded an OAI, whereas nearly 12% of non-CPI certified investigators had problems significant enough to warrant that level of enforcement.

A chi-squared test was performed to determine whether CPI certification was an indicator of receiving the most desired outcome of NAI. The results show clear separation between the groups ($\chi^2 = 7.719$, $df = 1$, $P = .005$), indicating that investigators with CPI certification are more likely to receive the most desired outcome of an FDA inspection. Likewise, a second chi-squared test was performed to determine whether CPI certification was an indicator of avoiding the least desired outcome of OAI. Again, the results showed clear separation between the groups ($\chi^2 = 10.371$, $P = .001$), indicating that investigators

with CPI certification are less likely to receive the least desired outcome of an FDA inspection.

Discussion

The results show that although CPI certified investigators are currently just as subject to for-cause inspections from the FDA as those not certified, CPI certified investigators have better inspection outcomes. This is consistent with the other peer-reviewed and more targeted studies on this issue and adheres to the general assumption that adequate training is effective. Although CPI certification did strongly predict more favorable FDA inspection outcomes, it does not imply that it is the exclusive differentiator; many noncertified investigators are doing extremely well on FDA inspections. It is likely that many sites that have adequately invested in ensuring the proper training of investigators simply have not required or desired investigators to take the CPI examination because sponsors and most government regulators neither require nor pay a quality differential based on the mark. Although other variables may contribute to a more compliant investigator, there has been no universal methodology studied to date to detect the underlying differentiator in performance between investigators. Therefore, scientific studies such as the one presented here are necessary to validate the APPI's CPI certification as a valid predictor of regulatory compliance.

This analysis was dependent on the matching of individual physicians across 2 databases. There are 2 potential faults in the matching process: (1) resources prohibited matching those physicians practicing in multiple states (such as those near a state line or moved from one state to another during the 3-year study period), and therefore these individuals may not have been identified as a match, and (2) 2 or more physicians with the same first name, last name, and city/state may have been identified as a match. The chance of either of these to occur is rare and therefore not expected to have any significant impact on the results.

Several issues make these findings relevant. First, it provides stakeholders, predominately research sponsors, hospitals, and IRBs, an independent predictor of regulatory compliance that is easily verified by simply viewing the investigator's name on the APPI website registry. Using the results could lead to significant savings in the investigator qualification process. Sponsors, IRBs, hospitals, regulators, and other stakeholders could use the mark as an assurance that the investigator has obtained basic training in the Good Clinical Practices and thus does not need to repeat multiple trainings, saving both stakeholder and investigator resources that could be put to better use. Essentially, a CPI certified investigator would not have to demonstrate any additional competency in GCPs to IRBs, sponsors, or hospitals, whereas investigators who are not CPI certified would be obligated to demonstrate their training by completing each sponsor's, IRB's, and/or hospital's training courses.

Overall, this study concludes that although a CPI certified investigator may not be less likely to receive a for-cause FDA inspection, the CPI certification is a valid differentiator in predicting regulatory compliance as investigators obtaining CPI certification perform better on FDA inspections than those investigators who are not CPI certified.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The author has volunteered for various boards and committees for the Association of Clinical Research Professionals (an organization having business affiliations with the Academy of Pharmaceutical Physicians and Investigators) but receives no compensation for those volunteer roles.

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