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RESEARCH ARTICLE

Certification in good clinical practice and clinical trial quality: A retrospective analysis of protocol adherence in four multicenter trials in the USA

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Abstract

Background: The value of training in Good Clinical Practice (GCP) for clinical research professionals is unknown. The objective of this study was to assess the impact of formal training in GCP on the quality of clinical trials.

Methods: Retrospective analysis of data collected from four multicenter trials conducted in the US in 2008. Certification as Physician Investigator (CPI) or Clinical Research Coordinator (CCRC) was used as proof of formal training in GCP. Protocol adherence was used as a proxy for the quality of clinical trials and quantified by the number of protocol deviations. The primary variable for analysis was the number of protocol deviations per randomized subject and site.

Results: A total of 1,418 subjects were randomized by 101 investigators (29% CPI) and 109 clinical research coordinators (29% CCRC), with 520 protocol deviations. Compared to "no certification", the Odds Ratios (OR) for the incidence of protocol deviations were OR = 1.20 (95% Confidence Interval [0.852–1.688]; p NS) for "CCRC-only", OR = 0.70 ([0.513–0.953]; p = 0.0256) for "CPI-only", and OR = 0.37 ([0.273–0.507]; p < 0.0001) for "CCRC + CPI".

Conclusions: This pilot study showed that formal training in GCP has the potential to improve protocol adherence and clinical trial quality.

Keywords: *Good clinical practice; clinical trial; certification; pharmaceutical medicine*

Introduction

Good Clinical Practice (GCP) is an international quality standard for clinical trials involving human subjects. In its own definition, it addresses "the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials" with the objective of having "assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected" (1). GCP has been instrumental in formalizing roles and responsibilities of all parties involved in clinical trials.

GCP is not without downsides and at times considered a nuisance because of its demands on researchers' time, resources and money (2, 3). Moreover, GCP itself is a guideline based on consensus rather than scientific evidence, and it has not been updated since 1996 (3). However, with its vigorous ethical requirements and extensive quality control processes, it plays an important role in protecting study subjects and ensuring integrity of clinical trial data.

Researchers involved in clinical trials in the US are required to follow GCP and provide proof of being an "expert in the clinical investigation of drugs" before participating in a clinical study (4, 5). However, this can be done with a curriculum vitae showing previous clinical trial experience; formal training and certification in GCP is not required. As a result, clinical researchers sometimes have only superficial

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knowledge of GCP. In a recent survey among research staff in Australia, GCP processes like obtaining consent and document storage were often only partially understood; 74% of research staff stated they would like to have more education in GCP, but only 10% reported having undertaken formal GCP training (6).

Two US-based international associations offer such training and certification. The Academy of Pharmaceutical Physicians and Investigators offers physicians a program to become Certified Physician Investigators (CPI) (4, 7). For non-physicians, the Association of Clinical Research Professionals offers certification as Clinical Research Coordinator (CCRC), among others (8).

Certification for clinical research seems intuitively to be a good way to improve knowledge of and compliance with GCP, which again should contribute to better clinical research quality (9). However, as in other areas in pharmaceutical medicine, there is a lack of scientific evidence to support this assumption. The objective of this study was to assess the impact of formal training and certification in GCP on the quality of clinical trials.

Methods

This was a retrospective study based on data collected from four recent multicenter trials. All four trials were in the area of allergic diseases and conducted in the US in 2008. The trials are registered under ClinicalTrials.gov with the following identifiers: NCT00619801, NCT00621959, NCT00628108, NCT00653224 (10). Approval of an ethics committee was not required for this analysis.

Certification as physician investigator (CPI) or clinical research coordinator (CCRC) was used as proof of formal training in GCP. Protocol adherence was used as a proxy for the quality of clinical trials. It was quantified by the number of protocol deviations.

The certification of investigators and site coordinators was verified against the official online Certification Registry of ACRP (11). All sites were then stratified into four groups: Group A = no certification (neither investigator nor clinical research coordinator certified); Group B = CCRC-only certification (investigator not certified as CPI, but clinical research coordinator certified as CCRC); Group C = CPI-only certification (investigator certified as CPI, but clinical research coordinator not certified as CCRC); Group D = both CPI and CCRC certifications (both investigator and clinical research coordinator certified as CPI and CCRC, respectively).

For each of these four trials and according to internal standard operating procedures, all discrepancies identified as protocol deviations were pre-defined in a Specifications of Protocol Deviations document prior to the pre-analysis review of the data before database lock. Protocol deviations could either be minor or major. A major protocol deviation leads to partial or total exclusion of the subject from one of several analysis populations (intention-to-treat; per-protocol; PK; PD; safety); a minor protocol deviation does not lead to any exclusion. In this study, the numbers of protocol deviations were stratified into minor, major, and total deviations, and were standardized by the number of randomized subjects per site. The primary variable for analysis was the total number of protocol deviations per randomized subject and site.

Descriptive statistics were used to summarize the protocol deviations. As this was a pilot study, no outliers were excluded. Statistical analysis was carried out using InStat 3 for Macintosh (GraphPad Software, Inc., La Jolla, CA, USA). Confidence Intervals were calculated using the approximation of Woolf. The primary variable was analyzed using Fisher's Exact Test. Statistical tests were two-tailed at the 5% level of significance, and compared Groups B, C and D to Group A.

Results

A description of the four clinical trials providing the source data for this study is presented in Table 1. A total of 1,418 subjects were randomized across 123 sites, with 520 protocol deviations. Trials 1 and 2 were safety studies in children, trials 3 and 4 were efficacy studies in adults. Since the two pediatric studies were exclusive safety studies, major deviations were not applicable to them. The resulting profile of protocol deviations is quite different: high incidence per subject in the two pediatric safety trials 1 and 2 without major deviations; low incidence per subject with approximately equal distribution of minor and major deviations in the normal efficacy studies.

Investigators and clinical research coordinators could participate in more than one of these four

Table 1. Description of the four clinical trials providing the source data for analysis of site certifications and protocol deviations.

	Trial 1	Trial 2	Trial 3	Trial 4	Total
Population	Child	Child	Adult	Adult	-
Number of sites	30	39	25	29	123
Number of randomized subjects	69	173	596	580	1418
Number of minor deviations	114	137	50	59	360
Number of major deviations	N/A	N/A	66	94	160
Total number of deviations	114	137	116	153	520

N/A = Not Applicable.

Table 2. Number of protocol deviations per subject, separate for each certification type and group. The odds ratios compare Groups B, C and D with the respective type of deviation of Group A. P-values were only calculated for the primary variable and compare the Groups B, C and D vs. Group A.

	Type of Deviation	Mean	Median	Min	Max	OR [95% CI]	p-value
Group A	Minor deviations	0.31	0.19	0.00	4.00	1.00 [0.798; 1.253]	-
	Major deviations	0.11	0.00	0.00	0.50	1.00 [0.718; 1.392]	-
	Total deviations	0.42	0.44	0.00	4.00	1.00 [0.810; 1.235]	-
Group B	Minor deviations	0.34	0.24	0.00	5.33	1.13 [0.790; 1.629]	-
	Major deviations	0.13	0.00	0.00	0.83	1.18 [0.703; 1.967]	-
	Total deviations	0.47	0.42	0.00	5.33	1.20 [0.852; 1.688]	0.3344
Group C	Minor deviations	0.21	0.14	0.00	2.75	0.59 [0.415; 0.840]	-
	Major deviations	0.13	0.00	0.00	0.50	1.17 [0.746; 1.831]	-
	Total deviations	0.34	0.22	0.00	2.75	0.70 [0.513; 0.953]	0.0256
Group D	Minor deviations	0.12	0.06	0.00	3.25	0.30 [0.204; 0.435]	-
	Major deviations	0.10	0.00	0.00	0.41	0.84 [0.539; 1.308]	-
	Total deviations	0.21	0.21	0.00	3.25	0.37 [0.273; 0.507]	< 0.0001

OR = Odds Ratio; CI = Confidence Interval.

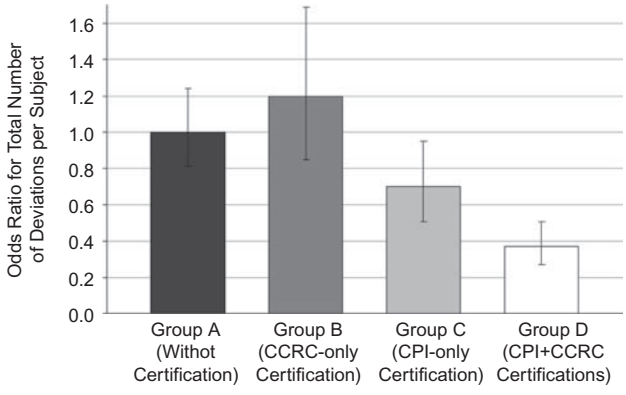

Figure 1. Odds ratios (OR) for the total number of deviations per randomized subject and site, compared to the reference Group A (OR = 1.0). The error bars indicate the 95% Confidence Intervals.

trials. The number of individual investigators in total was 101, of which 29 (29%) were certified as CPI. The number of individual clinical research coordinators was 109, of which 32 (29%) were certified as CCRC.

The analysis of the incidence of protocol deviations stratified by Group is presented in Table 2. As expected based on the differing profiles of the four source trials, the number of minor deviations is generally higher than the one for major deviations. The difference between the medians and the means and the range illustrate that the distribution is skewed. When looking at the total incidence of deviations, Group A (mean 0.42, median 0.44) is similar to Group B (mean 0.47, median 0.42); Group C (mean 0.34, median 0.22) and Group D (mean and median 0.21) seem to have lower incidences than Group A.

The results of inferential statistics are presented in Table 2 and Figure 1. When using Group A as reference group with OR = 1.0 (95% Confidence Interval [CI]: 0.810–1.235), the Odds Ratios (OR) for the total incidence of protocol deviations were for Group B OR = 1.20 (95% CI: 0.852–1.688; p NS compared to Group A), for Group C OR = 0.70 (95% CI: 0.513–0.953; p = 0.0256 compared to Group A), and for Group D OR = 0.37 (95% CI: 0.273–0.507; p < 0.0001 compared to Group A).

Discussion

The results of this study show that the total number of protocol deviations in four clinical trials in the US was significantly lower if the investigator was certified as CPI, particularly if in addition the clinical research coordinator was certified as CCRC, compared to sites where neither the investigator nor the clinical research coordinator were certified. When considering the type of deviation, then this trend seemed more pronounced for the minor deviations than for the major deviations (see Table 2).

The certification of the clinical research coordinator, without the investigator being certified as CPI, did not result in a difference in this study compared to the sites without certified staff. However, this does not support the conclusion that the CCRC certification is without benefit. On the one hand, adding the CCRC certification to the CPI certification resulted in a relevant reduction of the incidence of protocol deviations (the 95% Confidence Intervals of Groups C and D are not overlapping). On the other, the results of Group B may have been confounded by a few outliers with a very high number of protocol deviations per subject.

As such, the lack of pre-defined definition of outliers to be excluded from analysis can be regarded as a limitation of this study. Other limitations could be addressed with a prospective design and a larger sample size. More importantly, the use of the total

number of protocol deviations per subject may not be the best proxy for clinical trial quality. Giving different weights to minor and major protocol deviations in the total number could reflect better the fact that many minor protocol deviations do not have any impact on the clinical trial quality, ie the safety of subjects and the integrity of the data.

Going one step further, a combined score that takes into account not only protocol deviations but also other factors reflective of protocol and GCP adherence might be an even better representation of clinical trial quality. A combined score has recently been employed in a study by Chang et al., which compared the level of GCP adherence in China and the US (12). However, an assessment tool has not been validated yet, so more work needs to be done to establish objective ways to measure GCP adherence and clinical trial quality.

In conclusion, this was the first study showing that formal training and certification of investigators and clinical research coordinators in GCP has the potential to increase protocol adherence and improve clinical trial quality.

***Declaration of interest*:** The author reports no conflict of interest.

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