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A comparative method of evaluating quality of international clinical studies in China: Analysis of site visit reports of the Clinical Research Operations and Monitoring Center

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ABSTRACT

Due to the extremely competitive market, the pharmaceutical industry has been conducting clinical drug studies in emerging markets such as Russia, India and China, and submits data for new drug approval. But whether or not they follow the International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines remains a critical concern to FDA. Site visit reports of the Comprehensive International Program of Research on AIDS (CIPRA), an international research program on HIV/AIDS sponsored by the US National Institutes of Health, were pulled out to compare the studies of the China CIPRA program and the US studies for GCP adherence. To compare adherence, GCP data were abstracted from the reports and transcribed into an assessment tool, which recorded GCP activities. The frequency distribution for the responses to each individual item was examined. The generalized linear model was used to assess the adherence differences between the China CIPRA studies and US studies. In addition, a multinomial generalized linear regression model with GEE analysis was conducted on the assessment of the overall GCP performance using the variables — group (China vs. US) and three level of GCP adherence. The GCP adherence data of the two groups were similar in distribution pattern. The difference of the protocol adherence area was statistically significant between the two groups ($p=0.0425$). Specifically, the China group had less "failure to perform study procedures or to obtain authorization to deviate" than the US group (13(81.25%) vs. 8(47.06%, $p=0.0488$)). There was no significant difference ($p=1.0000$) on the overall GCP performance between the two groups (China vs. US), for three level of GCP adherence. As a preliminary study, our results showed that the China CIPRA program was at least equivalent to the US studies in overall from ICH/GCP perspective.

1. Introduction

Due to the extremely competitive market, the pharmaceutical industry has been conducting clinical drug studies in emerging markets such as Russia, India and China, and submits data for new drug approval. Accordingly, the US Food and Drug Administration (FDA) has been accepting data from international studies since 1975 provided that certain provisions were met regarding the data collected [1]. Rapid recruitment and cost savings are considered two most important benefits of conducting clinical drug studies in these emerging markets, but whether or not they follow the International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines remains a critical concern to FDA — the purposes of the ICH/GCP guidelines are to protect the rights of human subjects who participate in clinical studies and to ensure the scientific validity and credibility of the data collected. Since AstraZeneca established the company's Clinical Research Unit-East Asia in Shanghai in 2002, today most multinational drug companies have set up clinical research centers in China as part of their global clinical trials network, but there is lack of study evaluating

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the quality and human subject protection of clinical studies conducted in China.

Comprehensive International Program of Research on AIDS (CIPRA) is an international research program on HIV/AIDS sponsored by the US National Institutes of Health (NIH). The CIPRA program supports comprehensive research and development efforts in eligible nations to develop practical, affordable and acceptable methods to both prevent and treat HIV/AIDS in adults and children. To date, 33 CIPRA awards have been made to institutions in 24 different countries including South Africa, Thailand, Senegal, Peru and China. NIH also established the Clinical Research Operations and Monitoring Center (CROMC) to help establish, implement, and oversee the CIPRA programs and relevant domestic HIV/AIDS studies. The China CIPRA program consists of five research studies: (1) Epidemiology of HIV transmission and disease, (2) Behavioral interventions for preventing transmission of HIV, (3) Immunology and virology of HIV infection, (4) Safety and efficacy of drugs for treatment of HIV, and (5) Development of vaccines for prevention of HIV/AIDS in China. To ensure successful implementation, expert consultants from the United States collaborate with Chinese investigators on the design and implementation of these studies.

One objective of this article is to evaluate if the China CIPRA program was at least equivalent to the studies conducted in the United States from ICH/GCP perspective. Another objective is to analyze and discuss the major operational challenges for conducting globally accepted clinical studies in China. Although this article did not evaluate the overall quality of Chinese clinical research practice, it explored the feasibility of doing clinical research at globally accepted standard in China and other developing countries. One developing country may differ from another, but they are very similar for less experienced and trained research staff, limited financial resource and less strict regulations.

2. Methods

Reports of site interim visits (SIV) were pulled out to compare the studies of the China CIPRA program and the US studies for GCP adherence. All the visits were conducted by the same clinical monitor under the Clinical Research Operation and Monitoring Center (CROMC) scheme. The NIH contractor for CROMC is one of the foremost full-service contract research organizations (CRO) in the United States. As the Clinical Research Operations and Monitoring Center (CROMC), the CRO provides (1) technical support to facilitate protocol development, (2) monitoring clinical studies and quality assurance, (3) training and guidance on policy, procedures and Good Clinical Practice, and (4) administrative plus logistical support for non-network clinical projects funded by NIH. The responsibility of the CROMC under the work statement of monitoring clinical studies includes evaluation and monitoring of the individual clinical sites preparedness and adequacy to initiate and conduct studies in accordance with US and international guidelines (such as adherence to Good Clinical Practices and other relevant regulatory and ethical guidance to safeguard volunteers). Whenever needed, the CROMC recruits and trains site monitors, and develops contractor's standard operating procedures (SOP) for initial and ongoing training of monitors.

For the China CIPRA program, the CRO assigned an experienced monitor who was well trained on ICH/GCP and clinical research methodology in the United States. A registered nurse with extensive clinical practice experience in both China and US, the monitor was familiar with the Chinese and American healthcare systems. The monitor was also assessing US studies when assigned to the China CIPRA program, so was in a very good position evaluating both sites for quality and other operational performance. The monitor conducted 17 SIVs for the China CIPRA studies between January 2004 and May 2007 and 16 SIVs for the US studies between December 2003 and August 2005. To compare adherence, GCP data were abstracted from the site visit reports and transcribed into an assessment tool (see Appendix), which recorded GCP activities using 66 essential elements as derived from the ICH/GCP guidelines. Each SIV report had an assessment record.

2.1. Assessment of GCP adherence and data collection

We modified and utilized the assessment tool developed from the GCP regulations (see Appendix) by the Veterans Affairs Cooperative Studies Program's Site Monitoring and Review Team (SMART) [1]. The questions of the assessment tool were taken directly from the GCP regulations to be valid. Questions were not rated per se; each assessment question had one of the three possible responses: yes, no, or not applicable (NA). The summary results did put equal weight on all questions within a category as shown below (Table 1). But the overall summary of GCP adherence scale (Table 2) was a compilation of the assessment of those selected critical GCP items (see Appendix).

For each assessment record, GCP adherence was assessed within eight areas: (1) patient consent issues; (2) protocol adherence; (3) safety monitoring; (4) institutional review board; (5) essential documents (investigator file)/regulatory documents; (6) essential documents (investigator file)/patient records; (7) drug or device accountability and handling; and (8) site operation/investigator involvement, and divided into three categories [1]:

1. High GCP adherence, defined as no or few recommendations for improvements;
2. Average to good GCP adherence, defined as several recommendations for improvements, which are easily addressed. Procedures and practices in this category typically do not raise serious questions about study conduct; and
3. Below average GCP adherence, defined as critical GCP non-adherence, requiring immediate follow-up and resolution. Procedures and practices in this category are those that may raise questions of data integrity or adequacy of patient protections.

The categorized GCP adherence data then were compared between the China CIPRA studies and the US studies (Table 3).

2.2. Data analysis

The frequency distribution for the responses to each individual item was examined. The generalized linear model was used to assess the adherence differences between the China CIPRA studies and US studies.