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Present clinical trial regulatory system and strategies for improvement in Thailand

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ABSTRACT

The study aimed to identify gaps and to develop strategies for improving the clinical trial regulatory system in Thailand. Two-step cross-sectional survey was conducted. The first questionnaire addressed the present situation and the expected system sent by mail. The participants were from the lists of ethics committee (EC) members available online and others obtained from Food and Drug Administration (FDA). The second questionnaire determined the strategies and methods to improve the regulatory system. The participants were the attendees at the Thailand Toward Excellence in Clinical Trials meeting. The first questionnaire with response rate of 26.9% showed that the present situation was appropriate. However, to provide a better system, FDA and the EC should improve on several aspects. The second questionnaire with response rate of 32.5% showed that the present priority for the EC was the standard and accreditation, and that required for the FDA was the implementation of the quality system, especially the approval criteria. In addition, the capacity building was also important for all stakeholders. The study concluded that to improve the clinical trial regulatory system, the EC and FDA should implement the quality and accreditation systems toward the international standard, and capacity building should aim at good clinical practice training.

Keywords: Response, Clinical trial, Regulatory system, Strategies

INTRODUCTION

A clinical trial is pivotal for research and development of drug. This will ensure that safety and efficacy of medication have been established. A clinical trial involves human both healthy people and patients. Therefore, regulatory and ethical oversight is necessary to ensure not only individuals participating in a clinical trial are protected, but also data from the study are valid and integral.[1] During clinical trial process, risk of a drug must have been closely monitored. Several measures are incorporated in the process starting from a well-designed clinical trial, scientific reviewed process, and good clinical practice (GCP) compliance.[2]

Food and Drug Administration (FDA) is responsible for approval process and monitoring all drugs, including investigational drugs available in Thailand. Before 1989 (B.E.2532), there was no specific procedure for manufacturing and importing investigational drugs for clinical trials. However, there has been a Ministerial Notification related to drug importation for clinical trial since 1989 (B.E.2532).[3] This responds to patients' need for new drugs or new treatments that were still in the clinical trial phase or had not been approved in the country. The development and progress on procedures of importing and manufacturing investigational drugs have been made over the years. In the past, there were only a few clinical trials conducted in Thailand with a majority on Phase III or Phase IV. The number of clinical trials has notably been increased in recent years. The statistics showed that the number of investigational new drug importation was increased from 99 applications in 2004 (B.E. 2547) to 334 in 2009 (B.E.2552) and 1162 in 2016 (B.E. 2559). It was approximately 3.5 times increase within 5 years and ten folds within 12 years in the investigational drug applications with more studies on early phase (Phase II or Phase II/III).[4] The increased number of clinical trials in Thailand was influenced by many factors. For example, hospitals appeared to have good management and equipped with new and/or high-technology equipment to provide diagnosis as well as treatment. Health-care personnel were highly qualified and well trained. More ethics committees (EC) had been established. At present, a total of 19 EC are recognized by FDA. Seven of them are the EC of medical faculties. Two of them are from private hospitals and

the remaining are from other faculties and health institutions under Ministry of Public Health.[5] More institutions become interested and involved in conducting Phase I clinical trials in healthy individuals. Another influential factor was the Thai government policy on promoting Thailand to be a medical hub for medical services and education during 2017-2026 (B.E. 2560-2569).[6] The increasing number of early phase studies has exposed participants to risks related to the uncertainty of the safety and efficacy of new drugs. It was shown that there were cases related to ethical issues in the clinical trial conducted in developing countries.[7] At present, Thailand has no specific law or regulation to adequately protect subjects participating in clinical research. Although, the Human Research Act is during the process of proposing a law, it takes time before the enactment.[8] While no human protection law is implemented, the guideline recommended by the World Health Organization (WHO) could be applied. The WHO has developed and used data collection tool for the review of drug regulatory system.[9] The purposes are to assess the efficiency of the national medicine regulatory mechanism and regulatory capacity in all areas and to ensure the availability of good quality medicines, including the oversight of clinical trial. The key measures include clinical trials registration system and monitoring program on the GCP's compliance.

The clinical trial registration system is a clinical registry, in which registration is mostly conducted online. The WHO has established a voluntary platform known as International Clinical Trials Registry Platform to ensure a single point of access of information providing to patients, families, patient groups, and other stakeholders. The objectives of the system are to strengthen the transparency of clinical trial, to enhance the accountability of clinical data obtained, and to facilitate access to a new drug or new treatment for patients.[10] The Thai Clinical Trials Registry (TCTR) was established in 2009 (B.E.2552). It is a voluntary registration. TCTR became the primary registry in the WHO Registry Network on August 7, 2013 (B.E.2556).[11]

To strengthen the clinical trial regulatory system and to achieve the medical hub policy, the present situation and the strategies for improvement should be studied.

This study aimed to investigate the present clinical trial regulatory system and strategies for improvement in Thailand.

MATERIALS AND METHODS

Study Design

This two-step cross-sectional survey study using self-administration questionnaires was conducted in 2012. The study was designed to answer two objectives. The first objective was to understand the present situation of clinical trial regulatory system and expected system. The second objective was to prioritize strategies and methods to improve the clinical trial regulatory system in Thailand. Two sets of questionnaires were developed, one for each objective. While the mail survey questionnaire was used to collect data for the first objective, the second questionnaires aiming to prioritize the improvement strategy were distributed and collected at the Thailand Toward Excellence in Clinical Trials (ThaiTECT) Annual Meeting.

Population and Samples

For the first objective, the questionnaires were sent to 45 pharmaceutical manufacturers or importers, 460 investigators who were actively involved in the clinical trial protocol submitted to the FDA at the time of the survey, 760 members of Forum for Ethical Review Committees in Thailand (FERCIT), and the FDA personnel who were responsible for clinical trial authorization. All individuals under organizations/networks involved in clinical trial studies and processes were included as the study population totaling 1270 individuals. For the second objective, the questionnaire was designed based on the strategies and measures required to improve the clinical trial regulatory system and distributed to all 166 participants who attended the 2012 ThaiTECT annual meeting.

Data Collection Tools

The first questionnaire was developed based on the international guidelines of GCP[2] and the WHO data collection tool for the review of the drug regulatory system on the oversight of the clinical trial.[11] The objective of the first questionnaire was to identify the respondents' opinions on the present situation of the clinical trial regulatory system and the expected system. The questionnaires contained 17 questions on all the necessary areas, covering composition, role and responsibility, guideline, standard operating procedure (SOP), timeline, and training for all stakeholders. The respondents were asked to rate the present situation and the expected key issues in the clinical trial regulatory system on a 5-point Likert scale ranging from 1 to 5 with one representing inappropriate or unclear, two for somewhat appropriate, three for appropriate, four for much appropriate, and five for the most appropriate or most clear. Additional information on clinical trial registry and responsible agencies was also asked in the survey.

The gap analysis resulted from the first questionnaire and expert opinions were used as inputs to develop the second questionnaire which focused on the strategies to improve the clinical trial regulatory framework in Thailand. Expert opinions were obtained through semi-structured interview on strategies to improve the clinical trial regulatory system with representatives from sponsors of clinical studies, investigators, Contract Research Organization (CRO), and FDA. The interviews were conducted primarily by telephone and personal interview. All strategies recommended for system improvement were compiled and developed into the second questionnaires. The respondents were asked to rate each item on three aspects, agree with the strategy, importance, and feasibility. The binary scale of agree or not agree was used for the agreement opinion. Three-point Likert scale was used for importance and feasibility, where a score of three representing the most important/most feasible and score of one representing less important/less feasible. The content validity of both questionnaires was assessed by the three experts including senior Thai FDA expert, regulatory authority, and academia.

Statistical Analysis

Descriptive statistical analysis was used to describe the demographic of the respondents of both questionnaires. The central tendencies were analyzed for all items. Subgroup

analysis was also illustrated for comparison. Priority of each strategy was identified based on the level of importance and feasibility. The prioritization score was calculated by multiplying the important score by the feasibility score. The strategies with the high score represented the high priority and recommended to be implemented immediately.

RESULTS

Of 1270 mailed questionnaires, 141 samples were not reachable. The response rate was 26.9% or 304 responses. Among all respondents, 58.2% of the respondents were physicians and 79.5% received GCP training [Table 1]. The study showed that all aspects of the present clinical trial regulation were perceived as appropriate to much appropriate with the lowest score at 3.3 and the highest score at 4.0 on the 5-point Likert scale. The composition of the EC and the level of GCP implementation had the highest score at 4.0 ± 0.6 and 4.0 ± 0.8, respectively. The lowest score was from the aspect of FDA consultation and timeline for approval at the score of 3.3 ± 0.8, the aspects of EC consultation and timeline for approval also illustrated the low scores of 3.6 ± 0.8 and 3.6 ± 0.9, respectively. Due to the most items/aspects were scored ranging from inappropriate (lowest Likert scale of one) to most appropriate (highest Likert scale of five), this illustrated that there was variation of experiences. Gaps for improvement on these aspects should be detected.

Table 1: Demographic characteristics of the first and the second questionnaire respondents

Demographic data	First questionnaire (%) (n = 304)	Second questionnaire (%) (n = 54)
Stakeholder		
Sponsor	6.4	35.2
Investigator	43.6	13.0
EC/IRB	16.8	20.4
Investigator and EC/IRB	15	
FDA	1.8	3.7
Other	16.4	7.3
CRO	-	20.4
Professional occupations		
Physician	58.2	13.0
Pharmacist	12.4	44.4
Nurse	11.4	22.2
Medical technologist	4.3	3.7
Lawyer	0.3	-
Other	13.4	16.7
Training participation		
GCP	79.5	-
Ethical related	69.8	-
Other	13.1	-
No training	1.7	-
Number of years involved in clinical trial (years)		
≤5	-	33.3
5–10	-	31.5
10–15	-	18.5
15–20	-	13.0
20–25	-	3.7

The sponsor group provided the opinions with the lower score than other groups. Out of 17 questions, 12 were rated lower than average scores. The much lower than average were on the EC related aspects, including EC consultation (3.1 ± 0.8), SOP for EC (3.1 ± 0.8), EC timeline for approval (3.2 ± 1.0), and procedure for EC approval (3.3 ± 0.5), and FDA related procedures, including FDA consultation (3.0 ± 0.8), FDA timeline for approval (3.1 ± 0.9), SUSAR report to FDA (3.4 ± 0.6), and progress report timeline to FDA (3.4 ± 0.5). In contrast, the comparable scores obtained from the EC and investigator groups were more positive. While EC scored lower than average in four aspects, EC composition, role, and responsibility not clearly identified, knowledge on GCP and implementation of GCP at the scores of 3.9 ± 0.6, 3.6 ± 0.8, 3.6 ± 0.9, and 3.8 ± 0.8, respectively, investigator group had only EC consultation with score lower than the average, at 3.5 ± 0.8 [Table 2]. The findings showed that 61.3% of responses did not register their clinical trials in any registry systems. While 31.5% of respondents registered through the United State of America Registry system at www.clinicaltrials.gov, only 4.2% of respondents registered through the TCTR at www.clinicaltrials.in.th, and 3.8% of respondents registered through the International Clinical Trial Registry Platform at http://www.who.int/ictrp/en. There were 5.9% of the clinical trials registered at the other platforms, including respondents' EC, research units, or universities.

The study demonstrated that all respondents agreed on the three objectives of the clinical trial regulations. First, the EC should have oversight to ensure the standard of ethical consideration. Second, the control of clinical trial by FDA should be effective. Finally, capacity building of all related agencies should be strengthened and implemented to promote clinical trial in Thailand.

The second survey on the strategies and methods to improve the clinical trial regulatory system based on the agreed three objectives was conducted. The response rate was 32.5%. Out of the total respondents, 13% were investigators, 20.4% were EC, and approximately 56% were sponsors and CRO [Table 1]. All parties agreed on all proposed measures offering the highest priority to the accreditation or recognition system for EC (priority score of 6.83), followed by the development of the standard, procedure, and criteria for evaluation by FDA (priority score of 6.61) and increasing the number of qualified investigators (priority score of 6.04). On the EC standard aspect, the findings indicated that the accreditation or recognition system was the highest priority at the score of 6.83 and 100% agreeable and priority was on setting up a specific agency for accreditation. For the FDA aspects, development of the standard, procedure, and criteria for evaluation the clinical trial protocol gained the highest priority at the score of 6.61 with a100% agreeable. Under this strategy, setting up a quality

Table 2: Summary of opinions about aspects of clinical trial regulatory system (n = 254)

Item	Range of response (Likert scale)	Overall (Mean±SD) n=254	Sponsor (Mean±SD) n=19	Investigator (Mean±SD) n=133	Ethics committee (Mean±SD) n=51	Investigator and Ethics committee (Mean±SD) n=46	FDA (Mean±SD) n=5
1. Composition of EC as ICH GCP	3-5	4.0±0.6	3.9±0.6	4.0±0.6	3.9±0.6	4.3±0.6	4.0±0.0
2. Role and responsibility of involved persons are clearly identified	2-5	3.8±0.7	3.8±0.7	3.9±0.6	3.6±0.8	4.0±0.7	3.7±0.6
3. SOP for EC	1-5	3.8±0.7	3.1±0.8	3.8±0.7	4.0±0.6	4.1±0.6	3.5±0.6
4. Procedure for EC approval	2-5	3.7±0.7	3.3±0.5	3.7±0.7	3.9±0.6	4.0±0.6	3.5±0.6
5. GCP training	1-5	3.7±1.2	3.1±1.2	3.7±1.2	4.0±1.1	4.0±0.9	3.4±0.9
6. Level of knowledge and understand of GCP	1-5	3.8±0.8	4.1±0.6	3.8±0.7	3.6±0.9	4.2±0.6	4.4±0.5
7. GCP implementation/ compliance	1-5	4.0±0.8	4.2±0.9	4.1±0.8	3.8±0.8	4.3±0.5	4.6±0.5
8. SUSAR report to FDA	1-5	3.7±0.8	3.4±0.6	3.7±0.8	3.7±0.8	3.7±0.7	4.0±0.7
9. Progress report timeline to FDA	1-5	3.5±0.8	3.4±0.5	3.6±0.8	3.5±0.7	3.4±0.6	4.0±2.0
10. FDA consultation	1-5	3.3±0.8	3.0±0.8	3.4±0.9	3.5±0.7	3.3±0.6	3.7±0.6
11. Submission guideline for FDA approval	1-5	3.5±0.8	3.6±0.7	3.5±0.8	3.5±0.7	3.6±0.7	4.2±0.8
12. FDA timeline for approval	1-5	3.3±0.8	3.1±0.9	3.3±0.8	3.5±0.7	3.3±0.6	4.4±0.5
13. ADR report to EC	1-5	3.7±0.8	3.1±0.8	3.8±0.7	3.8±0.9	3.9±0.7	3.7±0.6
14. Progress report timeline to EC	1-5	3.7±0.7	3.8±0.4	3.7±0.7	3.8±0.9	3.8±0.8	4.3±0.5
15. EC consultation	1-5	3.6±0.8	3.1±0.8	3.5±0.8	3.8±0.7	3.8±0.7	4.0±0.0
16. Submission guideline for EC approval	2-5	3.8±0.6	3.5±0.8	3.9±0.6	3.8±0.7	4.1±0.6	4.0±0.0
17. EC timeline for approval	1-5	3.6±0.9	3.2±1.0	3.6±0.8	3.7±0.8	3.9±0.9	3.0±0.0

The results from the main related stakeholders are presented in the table, not included results from the other group

system to be implemented at FDA was seen as priority. The survey showed that the capacity building needed to increase the number of qualified investigators through GCP training at the priority score of 7.59 [Table 3].

DISCUSSION

The main key factors driving the appropriate conduct of clinical trial include investigational drug approval by the FDA, ethical approval by EC, qualified investigators, and clinical trial registry. The findings from the study reflected that all aspects of the clinical trial regulations in Thailand were appropriate with moderate scores rated by all stakeholders. However, the range of responses varied from 1 to 5 in most aspects. This suggested that there were some gaps needed to be improved on certain aspects. The designed strategies and methods were verified and prioritized as shown in Table 3. The clinical trial registry was not a mandatory by FDA and EC. Although the TCTR has been established since 2009 (B.E.2552) by Clinical Research Collaboration Network and later renamed Medical Research Network (MedResNet), not all clinical trial studies were registered. This is consistent with the situation occurred in other countries.[10-15] The study conducted in Argentina showed that only 38.5% of the clinical trial approved by the National Administration of Drugs Foods and Medical Devices (ANMAT) were registered with ICTRP between 1999 and 2006.[15] In India, the Clinical Trials Registry-India (CTRI) was established in 2007. The number of the clinical trials registered with CTRI was increased due to the mandatory registration of clinical trials requiring approval by the Indian drug regulatory authority.[12] Even the registry platform has been established, the success of implementation

Table 3: Strategies for clinical trial framework (n=54)

Strategy and method	Agree (percent)	Important (Likert scale)	Feasibility (Likert scale)	Priority (important x Feasibility)
Aspect of the standard of the ethics committee				
Strategy 1: Accreditation or recognition system	100	2.79±0.34	2.45±0.68	6.83
Method 1.1 Define or set up a specific agency responsible for accreditation or recognition	98	2.73±0.45	2.32±0.68	6.33
Method 1.2 Monitor periodically (every 2 years)	91.7	2.48±0.41	2.26±0.70	5.60
Strategy 2: National Standard for Ethics Committee	96	2.76±0.40	2.16±0.63	5.96
Method 2.1 Each institution formally established an ethics committee or recognized other institution's ethics committee complied with ICH-GCP standard	100	2.73±0.43	2.45±0.71	6.69
Method 2.2 Food and Drug Administration issues the regulation on ethics committee recognition	98	2.76±0.52	2.33±0.63	6.43
Method 2.3 New Human Research Acts	96	2.76±0.40	2.16±0.70	5.96
Aspect of the efficiency regulatory of clinical trial by Food and Drug Administration				
Strategy 1: Develop standard, procedure, and criteria for evaluation	100	2.85±0.4	2.33±0.71	6.61
Method 1.1 Set up quality system	98	2.85±0.4	2.53±0.63	7.21
Method 1.2 Issue new regulation to identify different types of investigational drug; never registered in any countries, registered in Thailand and registered in other countries with new indication, new posology or new patient group	98.1	2.63±0.46	2.54±0.71	6.68
Method 1.3 Issue new regulation to specify role and responsibility of involved parties for approval, monitor, and revoke	98	2.62±0.55	2.51±0.82	6.58
Method 1.4 Improve timeline for approval	89	2.83±0.71	2.32±0.73	6.57
Method 1.5 Submit the report of finished or ending study within specific timeline	96	2.53±0.59	2.45±0.63	6.20
Method 1.6 Online submission for application	96	2.65±0.58	2.26±0.57	5.99
Method 1.7 Submit progress report within specific timeline	92	2.49±0.66	2.40±0.71	5.98
Method 1.8 Provide the registered number of TCTR in the application	85	2.32±0.60	2.29±0.68	5.31
Method 1.9 Set up the consultation process for developing the clinical trial study protocol	94	2.47±0.53	2.11±0.56	5.21
Method 1.10 Update the progress of clinical trial in TCTR	89	2.31±0.73	2.12±0.68	4.90
Strategy 2: Develop safety monitoring process	98	2.77±0.5	2.15±0.78	5.96
Method 2.1 Report of ADR within the specific timeline	91	2.66±0.58	2.42±0.65	6.44
Method 2.2 Online submission of ADR in clinical trial	98	2.62±0.64	2.25±0.72	5.90
Method 2.3 GCP inspection	94	2.56±0.58	2.10±0.73	5.38
Aspect of capacity building				
Strategy 1: Increase the number of qualified investigators	98	2.72±0.52	2.22±0.74	6.04
Method 1.1 GCP training	100	2.82±0.37	2.69±0.53	7.59
Method 1.2 Promote and support new investigator working with qualified investigator	96	2.48±0.61	2.34±0.73	5.80
Method 1.3 Include GCP in the curriculum of health professional education	84	2.42±0.52	2.30±0.63	5.57
Strategy 2: Increase the number of clinical sites with good quality	96	2.64±0.51	2.19±0.67	5.78
Method 2.1 Develop and support laboratory to have a Good Laboratory Practice (GLP)	96	2.75±0.70	2.21±0.72	6.08
Method 2.2 Support the conduct of clinical trial in clinical trial center	92	2.44±0.59	2.20±0.72	5.37
Method 2.3 Develop the clinical trial management network to have the same standard and reduce management cost	94	2.50±0.5	2.08±0.73	5.20

(contd...)

Table 3: *(Continued)*

Strategy and method	Agree (percent)	Important (Likert scale)	Feasibility (Likert scale)	Priority (important x Feasibility)
Strategy 3: Develop database and network information related to clinical trial	98	2.73±0.60	2.04±0.70	5.57
Method 3.1 Set up the website containing information related to clinical trial	100	2.48±0.67	2.50±0.65	6.20
Method 3.2 Promote the utmost use of information in TCTR	92	2.47±0.58	2.37±0.70	5.85
Method 3.3 Promulgate and publish the list of non-clinical laboratory in Thailand	96	2.41±0.58	2.27±0.59	5.47
Method 3.4 Member of International Clinical Trials Registry Platform (ICTRP)	94	2.37±0.62	2.24±0.69	5.31
Method 3.5 Set the requirement of registration number of TCTR before published any information in Journal in Thailand	84	2.20±0.74	2.12±0.74	4.66
Strategy 4: Increase knowledge on research and development of drug or herbal drug	98	2.73±0.48	2.04±0.67	5.57
Method 4.1 Training on research and development process, data requirement for registration	98	2.62±0.54	2.45±0.64	6.42

depends on knowledge and understanding of the system and its benefit.[10-16]

Regarding the standard of the EC, currently, there is no law to regulate the EC at the national level. Only regulation or good practice in each institution or organization has been available and implemented. There have been many efforts to harmonize and standardize the EC. FERCIT was established in 2000 (B.E.2543) to promote and develop the standard and the protection of subjects and ethical control in clinical studies, but it was voluntary. National Research Council of Thailand (NRCT) established the office of human research standard to develop, promote, certify, and monitor ethical standards in the EC. National EC Accreditation System in Thailand (NECAST) was established to be an accreditation body for the EC.[15] Furthermore, there has been an attempt to enact a human research protection act since 2007 (B.E.2550). The present draft is a version of the year 2017 (B.E.2560) and is still in the process. Without the enactment of the law, the success of ethical control is limited. While the human research act is still in the process of issuing, the accreditation of EC was a pivotal step to ensure the quality of ethical approval for clinical trial study, leading to the protection of subjects participating in the clinical trial study. At present, the only available two agencies of EC accreditation include Thai FDA and NECAST. To improve the efficiency and standard of EC accreditation, there should be only one system available. NECAST is recommended to balance approval authorities between the study approval by NECAST and investigational drug control by the Thai FDA.

For the improvement of efficiency regulatory control of clinical trial, this study suggested that the priority area for Thai FDA improvement was related to the development of standards, procedures, and criteria for evaluation of investigational drugs. Thai FDA has implemented quality management system in place since 2007; however, no specific criteria are available for evaluation and approve clinical trial protocols and investigational drugs. The evaluation requires specific scientific knowledge and insights. With the rapid scientific and technological change and advancement and the limited resource and staff, it is difficult to keep the criteria for evaluation up to date. The Thai FDA could contribute more human resources to ensure proper implementation of this strategy.

Capacity Building

Medical Research Network of the Consortium of Thai medical school (MedResNet) was established in 2011(B.E.2554) to serve as the center for collaboration and networking of the medical and public health research parties. Several clinical trials in Thailand were mostly conducted in medical school hospitals. This networking could play an important role to connect all stakeholders to disseminate and distribute all information related to research and development.

There were some limitations in this study. The response rate of first survey was only 26.9%. However, with the number of respondents was more than 300, the result could represent the situation to some extent. The high proportion of respondents was from investigator and ethical committee, thus the result would be in line with the perception of these two groups. However, distribution of participants from the second survey was more balanced. Even though the survey was conducted in 2012, the findings still provide accurate results and the circumstances remain unchanged, for example, the new act has not been introduced.

CONCLUSION

This study illustrated that the clinical trial regulatory system in Thailand was positively evaluated. However, the continuous improvement of the clinical trial regulatory system was very crucial to ensure the right and well-being of subjects and value, validity, and merit of scientific data. Due to the intertwining among the roles and functions of all stakeholders, there should be cooperative efforts among all involved parties.

The policy recommendation to the government could be classified into two main areas: Regulatory and knowledge management aspects. To strengthen the regulatory system, the

quality and accreditation systems were the highest priority to be set up and implemented. The government and concerned agency bodies should commit to enact human research protection act into law. As of knowledge management, the coordination and the cooperative efforts to educate all stakeholders about GCP including the guidelines and clinical trial knowledge should be performed through all possible channels, especially academic institutions and professional councils.

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