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Perspectives on Adopting the Guideline for Multi-regional Clinical Trials in Korea: A Multi-stakeholder Survey

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ABSTRACT

Backgrounds: With the globalization of drug development, multi-regional clinical trials (MRCTs) have emerged to facilitate rapid availability of medicines to patients worldwide. The present study aimed to explore attitudes and perceptions towards adopting the Korean MRCT guideline. **Methods:** An online survey, consisting of 16 questions, classified into two subjects, was administered to stakeholders in Korea. Most quantitative components were measured using the Likert scales. A content analysis of the qualitative components was carried out to identify the keywords in open-ended responses. **Results:** A total of 94 survey responses were analyzed: 51 participants from pharmaceutical companies, 11 from clinical research organizations, and 21 from clinical trial centers. The content of the guideline was rated as appropriate for clarity, acceptability, and applicability (96.8, 96.8, and 93.6%, respectively). The local environmental impact of the systemic/political, academic/technical, and industrial/economic aspects of the guideline was rated as appropriate at 95.7, 97.9, and 91.5%, respectively. The suggested adoption period was 1~2 years (40, 42.6%). The concept and individuals' domestic circumstances were the key problems affecting the clarity, applicability, and local environmental impact of the guideline. **Conclusion:** The Korean MRCT guideline was well-developed. Their overall impact on the local environmental impact of MRCTs in Korea was expected to be beneficial, but methods are needed to minimize the negative impacts. The findings of this study can inform the priorities for the future adoption of the guideline in Korea.

KEYWORDS: Multi-regional clinical trial, global drug development, regulatory science, international conference on harmonisation, guideline

The MRCT is a means of global drug-development strategy that generates data, which are accepted by all regulatory authorities at once.¹⁾ MRCTs aim to facilitate simultaneous global drug development by reducing the number of clinical trials. Each region can be pooled, based on common intrinsic

and extrinsic factors, thus avoiding the ethical issue of unnecessary duplication of studies.²⁾ Given the growing trend of globalization and the need to make new or extended-use medicines rapidly available to patients worldwide, sponsors prefer MRCTs.³⁾

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Data from MRCTs are collected and submitted to multiple regulatory agencies, which currently find it difficult to evaluate such data for drug approval. Diverse challenges related to clinical assessments, clinical standards, patient populations, efficacy variables, safety assessments, and investigator sites emerge and must be resolved to ensure successful MRCTs.⁴⁾ For example, interpreting the different patient groups and medical-practice patterns in trial results and ensuring that findings can be applied to broad trial populations can generate significant debate during the regulatory decision-making process. In addition, operational problems that arise during clinical trials require attention. It is important to note that practice-site differences can create publication bias in various countries.⁵⁾ The same component of a medicine can result in different safety considerations when the drug is manufactured in other countries.⁶⁾ An audit is required to ensure that clinical trials to approve drugs are carried out to a high standard. However, foreign clinical trials are reviewed after the drug manufacturers have already applied for approval; as a result, federal regulators cannot be sure that patients were protected during the trials, while the research was being conducted.⁷⁾

To overcome such difficulties, various countries have worked to develop the guidelines.⁸⁾ Japan's regulatory agency, the Pharmaceuticals and Medical Devices Agency (PMDA), announced its *Basic Principles of Global Clinical Trials* in 2007, amending it with several reference cases in 2012.^{9,10)} In 2014, the PMDA published its requirements for pharmacokinetic data for Japanese MRCTs, mentioned in *Basic Principles for Conducting Phase I Trials in the Japanese Population Prior to Global Clinical Trials*.¹¹⁾ China's Food and Drug Administration (CFDA) released draft *Guidelines on International multi-center clinical trials* in 2015.¹²⁾ In 2016, the International Council for Harmonisation (ICH) Expert Working Group developed a set of draft guideline for MRCTs (E17): *General Principles for Planning/Designing Multi-Regional Clinical Trials*.¹⁾ The ICH E17 guideline presents general recommendations in planning and designing the MRCTs with basic principles.¹³⁾ The guideline targeted the readers who plan MRCTs for drug approval in multiple regulatory authorities and plan studies to satisfy post-marketing requirements.

In accordance with Korea's role as the sixth signatory to the ICH Technical Requirements for Pharmaceuticals for Human Use, the current survey was carried out while the MRCT guideline was undergoing an external consultation process to gather stakeholder opinions. With MFDS funding, we had

developed a Korean translation draft of the ICH E17 guideline which has been published recently by National Institute of Food and Drug Safety Evaluation after verification.¹⁴⁾ Despite the potential benefits of the MRCT guideline, little is known about the stakeholders' perspectives on their use in Korea. The goal of this study was therefore to assess the developed guideline and the perspectives of various Korean stakeholders.

Methods

Survey design

Data for the study were collected using an online survey, which was developed and administered, following the recommendations of Dillman *et al.*, 2009.¹⁵⁾ The survey was reviewed and critiqued by the project director and staff of the Ministry of Food and Drug Safety (MFDS). Based on their feedback, changes were made to the question types, wording, and layout. The final version of the survey was created and approved for exemption by the Ethics Board of Seoul National University (IRB No. E1609/003-004).

The survey was entitled *Investigation of perspectives on adopting the guideline for multi-regional clinical trials*; it began with a disclosure statement that described the essential aspects of the research, including its goals, objectives, risks, benefits, protection of personal information, and informed-consent procedure. Perspectives on adopting the guidelines were evaluated in accordance with three themes: prior recognition, local environmental impact, and adoption period.

The survey consisted of 16 questions: 3 of which evaluated the content of the guideline; 3, various perspectives on adopting the guideline; 4, the reasons for each response; and 6, demographic information (age, sex, education level, worksite, department, and length of career). Participants were asked to answer Yes or No when asked whether they had prior recognition of the ICH guidelines for MRCTs. The questions used either a multiple-choice format, or a 5-point Likert scale, with the scales ranging from 1 (very unnecessary) to 5 (very necessary) for adopting the guideline; from 1 (very incomprehensible) to 5 (very comprehensible) for the content of the guideline; and from 1 (very inappropriate) to 5 (very appropriate) for the level of the guideline and their impact on systemic/political, academic/technical, and industrial/economic aspects. Open-ended questions asked participants to explain their reasons for each response. The survey was provided with the draft of ICH MRCT guideline to understand the original

meaning and the draft of Korean MRCT guideline which was slightly modified by consultation meeting.

Survey dissemination

The respondents were recruited from three key stakeholder groups: pharmaceutical companies (PCs), clinical research organizations (CROs), and clinical trial centers (CTCs). To be eligible for this study, all candidates were required to have work experience related to clinical trials (e.g., management, operations, trial design, clinical research, or drug development). Because the study aimed to evaluate the perspectives of various stakeholders, no exclusion criteria were set. The sample size of 100 ensured a margin of error at 10%, a 95% confidence interval, and a sufficient level of confidence to meet the standards of the IRB.¹⁶⁾

Participants were recruited with the support of the Korea Pharmaceutical Manufacturers Association (KPMA) and the Korean Research-based Pharma Industry Association (KRPIA), which notified their members by posting an announcement on the pharmaceutical association homepages. The researchers also sent emails to professionals and telephoned institutions. Data were collected between September and October 2016.

Data analysis

Questions related to the content of the guideline were evaluated using guideline-assessment tools, modified to match the themes of clarity, acceptability, and applicability.^{17,18)} “Clarity” relates to the structure, format, and clear wording of the guidelines. “Acceptability” is defined as the extent to which users are likely to adopt a recommendation. “Applicability”

indicates confidence that the recommendations are both internally and externally valid, as well as feasible in practice. All questions associated with the themes are listed in Table 1.

A content analysis was carried out on four open-ended questions that asked participants to explain their responses.¹⁹⁾ All qualitative responses were read to recognize content and context. An organizational process of grouping, categorizing, and abstracting each keyword condensed the qualitative information.²⁰⁾ To minimize subjectivity, two researchers independently reviewed the themes, keywords, and content, comparing them to the original qualitative responses. After discussion and reflection, minor amendments were made, with consensus among the researchers (Table 2).

Prior recognition was compared between worksites and departments and described using N and %. Scales of the impact of the guideline on systemic/political, academic/technical, and industrial/economic aspects of the general local environment were analyzed in relation to worksites, work departments, and themes to assess their local environmental impact. In particular, ranged choices for the period of adoption were analyzed using mean values per response choice; 5-point Likert-scale responses were taken at face value.

The quantitative data were analyzed using IBM SPSS Statistics for Windows, Version 23.0 Armonk, NY: IBM Corp. Nominal scales were analyzed as percentages. For the 5-point Likert scales, scores were compared using means and standard deviation (SD) and categorized as appropriate (3 points or more) or good (4 points or more), using percentages. According to the normality and variance, the differences in scores between the subgroups were analyzed with non-

Table 1. Themes of the survey components

Theme*	Associated questions
Appropriateness of the guideline contents	
Clarity	Do you clearly understand the contents of ICH guideline? If you answered incomprehensible (or very incomprehensible) in the above question, what is the reason?
Acceptability	Do you think it is essential to adopt the guideline of multi-regional clinical trial in Korea
Applicability	Considering the environment of domestic drug development, do you think the level of the ICH guideline is appropriate? If you answered inappropriate (or very inappropriate) in the above question, what is the reason?
Perspectives on adopting the guideline	
Prior recognition	Have you heard about ICH developing a guideline about multi-regional clinical trials?
Local environmental impact	How do you think adopting the guideline affects the local environment of three aspects in Korea? If you answered inappropriate (or very inappropriate) in the above question, what is the reason?
Period for adoption	When do you think it is appropriate to introduce the multi-regional clinical trial guideline? What is the reason for answering the above question?

Table 2. Summary of open-ended comments on four themes: clarity, applicability, local environmental impact, and adoption time

Theme*	Keywords	Contents
Appropriateness of the guideline contents		
Clarity	Concept	Overall concept, terminology (region, multiregional clinical trial and multinational clinical trial)
	Readability	Low readability
	Specificity	Specific examples, design, outcomes, region subpopulation size, each country's requirement
Applicability	Specificity	General contents, specific policy, recommend further discussion with authorities
	Domestic circumstance	Not fits to domestic situation, different insurance system, the capacity problem of domestic companies
	Definition	Need race classification
Perspectives on adopting the guideline		
Local environmental impact	Specificity	How to unify the countries request
	Domestic circumstance	Hard to obey global criteria
	Exclusion	Low demand, lessen work, lessen manpower
	Burden	Need fund, industrial cost, low commercialize rate
	Preparation time	Executive process, promotion, feedback, application, buffering, guideline publication, pilot-test, regulation acceptance, for grace, gradual adoption, regulation acceptance, education, standardization, review
Period for adoption	Sufficient discussion	Opinion convergence, modification, for quality of clinical trial, for regulatory acceptance, standardization, about risks, about various aspects
	International trend	International competitiveness, for Korea leadership as developed country of clinical trials, fast deals with outside situation, following other countries direction for less confusion, obeying global standardization
	Needs or necessities	Increasing number of MRCTs, domestic drug development, more clinical trials, global competition, already implementing, for clinical trial industry growth, clinical trial unify, for domestic drug development
	Domestic environment	Need protection for Korea industry, need to assess the objective level of Korea, assess the appropriateness, considering domestic drug development system

Keywords were identified from the open-ended questions using content analysis

parametric Kruskal Wallis test and *post hoc* comparisons by Mann-Whitney *U*-test with Bonferroni correction. Adjusted *p*-values less than 0.05 were considered significant. The internal consistency was good, with a Cronbach's alpha of 0.76.²¹⁾

Results

Participants

A total of 106 participants were enrolled to the survey. Of these, 94 responded to the survey and 12 were excluded for giving their consent but not answering any of the other questions. Among these, 11 respondents did not complete the demographic-information section part of the survey and were therefore excluded from further subgroup data analysis. Demographic information about the respondents is presented in Table 3. The group of the most participants were female (55, 58.5%); aged 30-39 (32, 34.0%); worked in the approval

and registration department (45, 47.9%); and had worked for 10-20 years (27, 28.7%).

Contents of the multi-regional clinical trial guideline

The majority of the participants considered the content of the guideline appropriate, in relation to clarity, acceptability, and applicability (96.8, 96.8, and 93.6%, respectively); more than half considered it good (64.9, 84.0, and 54.3%, respectively; see Table 4). The scores for clarity, acceptability, and applicability were 3.67 ± 0.63 , 4.09 ± 0.46 , and 3.52 ± 0.68 . CTC stakeholders considered the guideline comprehensible and responded more positively than CRO or PC stakeholders in assessing their clarity, acceptability, and applicability. When departments were compared, the department of approval and registration needed the most and the department of research and development the least to assess the guideline acceptability (4.17 ± 0.79 and 3.75 ± 0.79 , Table 4). In response to an open-

Table 3. Demographic characteristics of respondents

	All respondents (n=94)* N (%)	Pharmaceutical Companies (n=51) N (%)	Clinical research organizations (n=11) N (%)	Clinical trial centers (n=21) N (%)**
Gender				
Male	28 (29.8)	12 (23.5)	4 (36.4)	12 (57.1)
Female	55 (58.5)	39 (76.5)	7 (63.6)	9 (42.9)
Age				
20-29	13 (13.8)	9 (17.6)	2 (18.2)	2 (9.5)
30-39	32 (34.0)	25 (49.0)	4 (36.4)	3 (14.3)
40-49	29 (30.9)	16 (31.4)	3 (27.3)	10 (47.6)
50-59	9 (9.6)	1 (2.0)	2 (18.2)	6 (28.6)
Education level				
B.S.	35 (37.2)	20 (39.2)	8 (72.8)	7 (33.3)
M.S.	31 (33.0)	28 (54.9)	3 (27.3)	0 (0.0)
Ph.D	17 (18.1)	3 (5.9)	0 (0.0)	14 (66.7)
Work department				
Clinical trial management	18 (19.1)	11 (21.6)	10 (90.9)	14 (66.7)
Approval and registration	45 (47.9)	21 (41.2)	1 (9.1)	0 (0.0)
Research and development	20 (21.3)	19 (37.3)	0 (0.0)	7 (33.3)
Number of years in the career				
Less than 1 year	5 (5.3)	3 (5.9)	0 (0.0)	2 (9.5)
1-3 years	11 (11.7)	8 (15.7)	1 (9.1)	2 (9.5)
3-5 years	11 (11.7)	7 (13.7)	2 (18.2)	2 (9.5)
5-10 years	22 (23.4)	17 (33.3)	3 (27.3)	2 (9.5)
10-20 years	27 (28.7)	14 (27.5)	5 (45.4)	8 (38.1)
More than 20 years	7 (7.4)	2 (3.9)	0 (0.0)	5 (23.8)

*The demographic table of each work site contains the information about 83 respondents because 11 people skipped answering the personal information. Therefore, 11.7% of the respondents are categorized to unknown state which is not displayed on the table.

**The results are given as N (%).

Table 4. Appropriateness of clarity, acceptability, and applicability for guideline contents

	All respondents (n=94) ^a	Work sites			Work departments		
		Clinical trial centers (n=21)	Pharmaceutical Companies (n=51)	Clinical research organizations (n=11)	Clinical trial management (n=18)	Approval and registration (n=45)	Research and Development (n=20)
Clarity ^b	3.67±0.63	4.00±0.45 ^f	3.61±0.70	3.64±0.51	3.94±0.64	3.64±0.53	3.65±0.81
Appropriate ^c	91 (96.8%)	21 (100%)	48 (94.1%)	11 (100%)	18 (100%)	44 (97.8%)	18 (90.0%)
Good ^d	61 (64.9%)	19 (90.5%)	31 (60.8%)	7 (63.6%)	14 (77.8%)	30 (66.7%)	13 (65.0%)
Acceptability ^b	4.09±0.46 ^e	4.19±0.75	4.06±0.65	4.00±1.00	4.17±0.79	4.20±0.63	3.75±0.79
Appropriate	91 (96.8%)	20 (95.2%)	50 (98.0%)	10 (90.9%)	17 (94.4%)	45 (100%)	18 (90.0%)
Good	79 (84.0%)	19 (90.5%)	44 (86.3%)	8 (72.7%)	16 (88.9%)	40 (88.9%)	15 (65.0%)
Applicability ^b	3.52±0.68	3.86±0.57 ^f	3.49±0.67	3.36±0.81	3.61±0.70	3.58±0.72	3.50±0.61
Appropriate	88 (93.6%)	20 (95.2%)	49 (96.1%)	9 (81.8%)	17 (94.4%)	41 (91.1%)	20 (100%)
Good	51 (54.3%)	18 (85.7%)	24 (47.1%)	6 (54.5%)	11 (61.1%)	28 (62.2%)	9 (45.0%)

^aThe demographic table contains the information about 83 respondents because 11 people skipped answering the personal information

^bThe results are given as mean±SD

^cThe criteria appropriate is defined with the score of 3-point or more and given as N (%).

^dThe criteria good is defined with the score of 4-point or more and given as N (%).

^eThe total acceptability score was different from other scores by a Kruskal Wallis test ($p<0.05$).

^fThe scores of Clinical Trial Centers were significantly different from those of Pharmaceutical Companies by a *post hoc* Bonferroni corrected Mann-Whitney U-test ($p<0.05$).

A. Clarity of the guideline contents **B. Applicability of the guideline contents** **C. Concerns on ecological impact** **D. Concerns on adoption time** **Fig. 1.** Keywords of the open-ended questions

ended question about clarity, only nine participants explained the reasons for their assessments. Of these, the key problems of clarity were related to the concept (41.7%), readability (8.3%), and specificity (25.0%) (Fig. 1A). The stakeholders emphasized the importance of clearly defining the overall concept of region and difference between multinational and multi-regional clinical trials. Also, they pointed out that the guideline is too general, which requires further explanations or examples. Eleven participants gave opinions on the open-ended applicability question. The key applicability problems involved scope (8.3%), specificity (33.3%), and domestic circumstances (58.3%) (Fig. 1B). The stakeholders suggested that the guideline might not be suitable for drug development in Korea, due to differences in clinical-trial environments, insurance systems, and the capacity of domestic companies. Similar opinions were given here; that the specific directions were less and the guideline suggested to consult to each regulatory authority.

Perspectives on adopting the guideline to Korea

The participants' perspectives on adopting the guideline are shown in Fig. 2A. Of the whole pool of respondents, 66 (70.2%) had prior recognition of the ICH E17 guideline; of these, 15 (71.4%) were at the CTC site, 35 (68.6%) at the PC site, and 7 (63.6%) at the CRO site. Categorizing the participants by work department showed that 13 (65.0%) of those who worked in management, 30 (66.7%) of those who worked in approval & registration, and 14 (77.8%) of those who worked in research & development departments had previous exposure to the MRCT.

Most participants considered that the content of the guideline was appropriate at the systemic/political, academic/technical, and industrial/economic level (95.7, 97.9, and 91.5%, respectively). More than half felt that the content was good (72.3, 68.1, and 54.3%, respectively) (Table 5). The total scores for participants' perspectives on the local environmental impact of each aspect were 3.77 ± 0.66 , 3.76 ± 0.70 , and 3.50 ± 0.76 ,

A. Prior recognition of ICH MRCT guideline **B. Expected adoption time**

Fig. 2. The perspectives of the stakeholders on adopting the guideline. The numbers in the chart A. show the percentages of answering 'YES' within each group. The numbers in the chart B. show the percentages of the answers within each group. Abbreviations: CRO, clinical research organizations; CTC, clinical trial centers; ICH, international conference on harmonisation; MRCT, multi-regional clinical trial; PC, pharmaceutical companies; R&D, research and development

respectively. The scores for industrial/economic aspects (3.37 ± 0.77) at the PC site were lower than those at the CTC site (3.86 ± 0.66). They were also lower than the scores for systemic/political (3.73 ± 0.67) and academic/technical aspects (3.73 ± 0.72) within the PC site. The department of research and development was most concerned about industrial/economic aspects (3.10 ± 0.79) with few regarding them as good (35.0%). Eleven participants answered the open-ended question about local environmental impact; key ecological-impact problems involved specificity (9.1%), domestic circumstances (36.4%), exclusion (27.3%), and burden (27.3%) (Fig. 1C). The stakeholders were mostly concerned about the negative effects that domestic industries would not be chosen for

clinical trial sites when the region was merged. Furthermore, domestic industries with little budget would find it hard to develop a new medicine. For the adoption time, most stakeholders expected the guideline to be adopted within 2 years ($N=61$, 64.9%) (Fig. 2B). The majority of stakeholders who expected the guideline to be adopted in 1-2 years were from CTC (52.4%), while the majority who expected the guideline to be adopted within 1 year were from CRO (27.3%). Eighty-six participants answered the open-ended question about adoption time; the key issues that concerned them involved preparation time (41.9%), the guideline requirements (22.1%), the need to ensure sufficient discussion (12.8%), whether Korea should follow international trends

Table 5. Appropriateness of the local environmental impact for adopting the guideline

	All respondents (n=94) ^a	Work sites			Work departments		
		Clinical trial centers (n=21)	Pharmaceutical companies (n=51)	Clinical research organizations (n=11)	Clinical trial management (n=18)	Approval and registration (n=45)	Research and development (n=20)
Systemic/Political impact ^b	3.77±0.66	3.90±0.77	3.73±0.67	3.91±0.30	3.78±0.88	3.80±0.51	3.80±0.77
Appropriate ^c	90 (95.7%)	20 (95.2%)	49 (96.1%)	11 (100%)	17 (94.4%)	44 (97.8%)	19 (95.0%)
Good ^d	68 (72.3%)	16 (76.2%)	35 (68.6%)	10 (90.9%)	11 (61.1%)	36 (80.0%)	14 (70.0%)
Academic/Technical impact ^b	3.76±0.70	3.95±0.50	3.73±0.72	3.64±0.92	3.78±0.73	3.78±0.70	3.75±0.72
Appropriate	92 (97.9%)	21 (100%)	50 (98.0%)	10 (90.9%)	18 (100%)	44 (97.8%)	19 (95.0%)
Good	64 (68.1%)	18 (85.7%)	31 (60.8%)	9 (81.8%)	11 (61.1%)	33 (73.3%)	14 (70.0%)
Industrial/Economic impact ^b	3.50±0.76	3.86±0.66	3.37±0.77	3.55±0.93	3.61±0.85	3.67±0.71	3.10±0.79 ^e
Appropriate	86 (91.5%)	21 (100%)	44 (86.3%)	10 (90.9%)	17 (94.4%)	43 (95.6%)	15 (75.0%)
Good	51 (54.3%)	15 (71.4%)	24 (47.1%)	8 (72.7%)	9 (50.0%)	31 (68.9%)	7 (35.0%)

^aThe demographic table contains the information about 83 respondents because 11 people skipped answering the personal information

^bThe results are given as mean±SD

^cThe criteria appropriate is defined with the score of 3-point or more and given as N (%).

^dThe criteria good is defined with the score of 4-point or more and given as N (%).

^eThe score of Research and Development were significantly different from that of Approval and Registration by a *post hoc* Bonferroni corrected Mann-Whitney U-test ($p < 0.05$).

(12.8%), and the domestic environment (10.5%) (Fig. 1D). In summary, the guideline was sure necessary to adapt, but it still needed further review and discussion.

Discussion

This study is the first to investigate the adoption of MRCT guideline by examining the perspectives of three key stakeholders, using an online survey. The results show that stakeholders consider the content of the guideline to be appropriate, in terms of clarity, acceptability, and applicability. They view Korea's adoption of the guideline in a positive light, giving positive responses to questions about the systemic/political, academic/technical, and industrial/economic aspects of the guideline. Previous research has investigated industry perspectives on MRCT, due to its growth prior to the publication of the guidelines; these studies have pointed to the risks associated with interpreting regional differences.²²⁾ Later, draft MRCT guideline, containing general principles, was developed. Our survey: *Investigation of perspectives on adopting the guideline for multi-regional clinical trials* has provided further insight into the local environmental impact of the guideline on national drug development, identifying problems left to solve.

The content of the guideline was assessed in relation to the themes of clarity, acceptability, and applicability. The standard is somewhat different from other clinical-practice guidelines

(CPGs), which make evidence-based recommendations. The principles underpinning the current guideline have been generated through discussions with professionals at the regulatory agencies.²³⁾ For this reason, different evaluation themes were deemed necessary and the criteria were modified. All guidelines must be assessed for clarity because clear communication is essential for appropriate implementation.^{24,25)} The present study has also focused on the meaning of these guidelines for Korea; they have received high enough acceptability and applicability ratings to be suitable for evaluation.

When regarding the guideline as appropriate, it should be understood that the median point does not normally mean something positive. But, the tools evaluating the guidelines do not have exact criteria and it is reported that the score could have varied among the different evaluators.²⁶⁾ Because of that, some of the studies considered the guidelines to be appropriate when the score was over the median.^{27,28)} All the content of the guideline was considered appropriate, receiving a score higher than 3.00. Therefore, we consider the Korean guideline well developed.

Worksite were significantly associated to clarity, assessed as comprehensiveness, which indicates that certain stakeholders may have found the guideline more familiar and easier to understand than others. As the "concept" was the factor most difficult to understand (41.7%), further explanations for the region and the MRCTs, such as the explanatory and case

materials, were demanded by the stakeholders. Applicability, at the level assessed for Korea, was endorsed by 54.3% of the participants. Most of the respondents were concerned about the application of the MRCT guideline. Even though it is cheaper to conduct MRCTs by integrating similar regions—and more time-efficient if approval times are speeded up—it still costs more than a single clinical trial.⁴⁾ Stakeholders commented that it would be difficult for small domestic companies to handle if a MRCT were to fail in phases 2 or 3. So far, the concept of an MRCT could be applied during the drug-development stage, in accordance with each company's capability.

The industrial/economic aspect of the local environment score was lower than that of the systemic/political or academic/technical aspects. The main difference between an MRCT and other international clinical trials is the possibility of integrating data related to similar ethnic factors, such as genetic factors, disease morbidity, and medical and regulatory practices.²⁹⁾ It has been suggested that the data from East Asian countries could be merged, because people are genetically similar and some extrinsic factors are negligible, as mentioned in the draft ICH E17 guideline.^{30,31)} The stakeholders were concerned that this proposition required more evidence for practical use. Moreover, for drug approval using such integrated data, the consensus among the regulatory authorities should be concluded ahead, and it was considered hard to bring to reality. Factors that influence the selection of clinical trial sites include the cost of running the clinical trial, the size of the market, the speed of ethics approval, and the study experience of site personnel.³²⁾ The cost of conducting a clinical trial varies, with India and China having 60% lower-than-average costs; their large markets result in a fast growth rate.³³⁾ The stakeholders also concerned that even though Korea is considered one among the top-ten countries implementing clinical trials with high-quality performance,³⁴⁾ the Korean clinical trials could be excluded when planning the global drug development if the data are merged. This was the reason for negative points relating to the industrial/economic aspect. The stakeholders demanded specific plans to attract developers who could guarantee the industry at each site. As strategies that enroll patients from other countries in U.S. and European trials have been launched to speed up patient enrollment, Korea could also consider promoting faster recruitment.³⁵⁾ Subsequently, the drug would have to be approved without the Korean data, which was the reason for negative points for the

systemic/politic aspect. As there is an alternative regulatory process using the bridging study, defined as “*a supplemental study performed in the new region to provide pharmacodynamic or clinical data on efficacy, safety, dosage and dose regimen in the new region that will allow extrapolation of the foreign clinical data to the new region*” in ICH E5²⁹⁾, more deeper discussions are required to apply the MRCT. Overall, the current guideline has suggested the concept of pooled regions which could be gradually introduced.

In consonance with international movements, the guideline will be eventually adopted in most countries that have global drug-development goals. Specific plans for optimal adoption are therefore needed. After identifying and quantifying the obstacles through a context analysis, we were able to identify key focus areas to improve. Our results suggest three steps for successful adoption: acceptance, preparation, and application. At the acceptance stage, it is essential to discuss the modification, standardization, and convergence of the guideline. The guideline offers general principles but it is hard to carry out MRCTs without specific directions. Many previous studies have focused on solving technical problems involving design and analysis.³⁶⁻³⁸⁾ As an opinion argued, additional explanatory materials that include methodologies and examples would be valuable. At the adaptation stage, it is efficient to carry out a pilot test with feedback inspect cases from other countries, and modify the guidelines to ensure regulatory acceptance. According to our results, it is profitable to follow international trends and to carry out the two preparatory steps for approximately two years before execution. The final application stage involves the education and promotion of the MRCT guideline, followed by further improvements resulting from trial and error. Previous recognition of MRCTs was lowest in the CRO group and the department of approval and registration; for this reason, the guideline must be promoted, especially within that group. CROs are expected to handle regional bias, while the approval & registration department must plan the exact method of global drug registration. Overall, with active use, problems can be detected more easily; the MRCT guideline will be amended with further experience.

We used structured criteria created by formal tools to interpret questions that assessed the content of the guideline, however, the respondents may have responded from different points of view. They may also have interpreted the local environmental impact in individual ways. To overcome this problem, we attempted to analyze the open-ended questions

objectively, identifying specific opinions. Even though current survey reached the overall target sample size, it may not be safe to present the current results as the representative opinions of stakeholders of subgroups (e.g. work site). Almost half of the participants work either at PCs or in the approval and registration department. Some mean scores of those groups were different with other groups; however, the mean scores of the rest groups were comparable to the half. Therefore, we consider the effect of the participants' distribution to be small. Various participants were included, and in this sense, the current data does represent the opinions of various stakeholders.

Although we concluded the guideline to be appropriate, the guideline still needs some modifications. For a more specific evaluation of the content of the guideline and plans for adopting the guideline, further delphi surveys, deep-focus group interviews, and public discussions with professionals other than pharmaceutical experts are needed for each section, policy, or piece of legislation related to the guidelines.^{39,40)}

Conclusion

After adopting regulatory feedback including opinions from Korean agencies the final version of the ICH E17 was published in 2017. From the perspective of the stakeholders in Korea, the draft Korean MRCT guideline was well developed and has been published with modifications following the final ICH E17 guideline. Countries with similar political or industrial environments for new-drug development, such as other East Asian countries, may obtain profit and solutions from our research.

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Declaration of conflicting interests

The views expressed in this publication are those of the

authors and do not necessarily reflect the official policies of the National Institute of Food and Drug Safety Evaluation, commercial practices, or imply endorsement of organization by the Republic of Korean government.

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