Questionnaire Survey Regarding Troubles and Concerns Related to Clinical Research Based on the Clinical Trial Act for Clinicians and Academics

TOKUNORI IKEDA, SONOKO ISHIHARA, SAORI MITSUMASU, YOSHINORI YAMANOUCHI, HISASHI KANEMARU, KOURIN SAKAKIDA, JUN MORINAGA AND EIICHI ARAKI

Department of Clinical Investigation, Kumamoto University Hospital, Kumamoto 860-8556, Japan

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Summary: The Clinical Trial Act came into force in 2018 in Japan. A questionnaire survey was conducted with personnel at Kumamoto University Hospital engaged in research and development, to explore their perceptions of troubles and concerns about clinical research related to the Clinical Trial Act. We collected 127 comments about troubles and 149 about concerns. Text mining (co-occurrence network and hierarchical cluster analysis) was used to extract the characteristics or tendencies in these comments. The analysis extracted 18 key terms for troubles and 21 for concerns. Most troubles and concerns had to do with concrete examples of clinical research or protocols and biostatistics information. Our results emphasized the importance of clinical research support organizations, and suggested that appropriate workshops and information covering specific situations are necessary to perform clinical research under the new regime.

Keywords clinical trial act, questionnaire survey, clinical research, text mining

INTRODUCTION

Circumstances surrounding clinical research in Japan have changed rapidly. For example, since 2015, principal investigators have been required to perform monitoring in invasive intervention studies from an ethical guidelines perspective for medical and health research involving human subjects [1]. Moreover, the new Clinical Trial Act came into force on April 1, 2018, and research corresponding to this act is called “specified clinical trials” [2]. This Act placed importance on reliability in clinical research, and required investigators to present a detailed conflicts of interest declaration when they make a submission to a “certified review board”, which refers to special research ethics committees that function in accord with the

Clinical Trial Act. These revisions increased the quality of clinical research and decreased the risk of research misconduct, but they may also have increased the burden on investigators (e.g., cost, increased paperwork, including protocols).

We therefore conducted a questionnaire survey to investigate the troubles associated with clinical research experienced by personnel engaged in research and development, and any concerns created by their interest in clinical research.

MATERIALS AND METHODS

This retrospective study was conducted at Kumamoto University Hospital, Japan. Questionnaire forms were distributed to participants in lectures about clini-
cal research, and collected at the end of the lecture. Participants were undergraduates, graduates, and staff from Kumamoto University Hospital and the Graduate School of Life Sciences of Kumamoto University. In total, there were seven 60-minute lectures given in 2018, all in Japanese. Lecture topics were planning for clinical research, the Clinical Trial Act, clinical trials, clinical research design, translational research, and conflict of interest management. The questionnaire form included two questions: 1) “If you have experienced troubles in investigator-initiated clinical research, please describe them”; and 2) “Please describe any concerns about clinical research that you wanted to mention”. This questionnaire form was distributed to participants in print form before the start of the lecture and collected immediately after the lecture ended. The characteristics of each lecture are shown in Table 1. The analysis used R version 3.5.3 (The R Foundation for Statistical Computing, Vienna, Austria).

This study was approved by the Institutional Review Board of Kumamoto University (Permit Number 1810). Informed consent was obtained from participants on an opt-out basis, and all procedures were performed in accordance with the Declaration of Helsinki.

The text mining used KH Coder (version 3), which is free software for quantitative content analysis or text mining (http://khcoder.net/en/). In KH Coder, we performed morphological analysis using ChaSen, a Japanese morphological analysis system. In morphological analysis, useless comments (e.g., “none”, “none in particular”), verbs, adjectives and single-kanji were removed after checking the meaning. Forced extraction was used to extract technical or compound terms considering their meaning. These judgments were determined by discussion between researchers. In total, 398 terms for question 1 and 300 for question 2 were extracted.

Next, we used a co-occurrence network to investigate the interactions between extracted terms mentioned more than six times. We used the Jaccard coefficient to capture the degree of similarity between terms, and described the sixty top interactions between two terms from this. In some cases, we used the category variables (question 1 and 2) for external variables in the co-occurrence network. We also used Ward’s hierarchical cluster analysis to investigate the interactions between key terms. Terms mentioned more than six times were identified and a dendrogram was produced using the Jaccard coefficient. The analysis used Japanese terms, and the final results were translated into English following discussion between at least two researchers.

RESULTS

For question 1, regarding troubles experienced in investigator-initiated clinical research, we extracted 18 key terms mentioned more than six times. The frequencies of the terms “clinical research” and “cost” were high (Table 2). Fig. 1A shows the co-occurrence network for the key terms. We found five clusters, which merged into four using hierarchical cluster analysis (Fig. 1B).

| TABLE 1. Characteristics of the seven lectures |
|------------------------------------------------|
| **Content of lecture** | Planning for clinical research | Clinical Trial Act | Clinical trial | Clinical research design | Clinical trial | Translational research | Conflict of interest management |
|------------------------|---------------------------------|--------------------|----------------|--------------------------|----------------|------------------------|-------------------------------|
| Participants           | 144                             | 224                | 222            | 91                       | 94             | 60                     | 79                            |
| Status (undergraduate / graduate / staff) | 0 / 22 / 122 | 2 / 22 / 200 | 0 / 10 / 212 | 4 / 11 / 76 | 0 / 10 / 84 | 0 / 4 / 56 | 0 / 9 / 70 |
| sex (female / male)    | 39 / 105                        | 69 / 155           | 62 / 160       | 43 / 48                  | 26 / 68        | 16 / 44                | 25 / 54                       |
| Comments for question 1| (18.8%)                         | (11.6%)            | (17.6%)        | (12.1%)                  | (10.6%)        | (8.3%)                 | (11.4%)                       |
| Comments for question 2| (22.2%)                         | (11.6%)            | (16.2%)        | (19.8%)                  | (13.8%)        | (13.3%)                | (20.3%)                       |

Numbers of links for each variable are shown. Question 1 was about troubles experienced in investigator-initiated clinical research. Question 2 covered concerns about clinical research that investigators want to pick up. Comments for questions 1 and 2 show the number of meaningful comments provided by participants.
Fig. 1. The results of text mining for comments about troubles encountered in investigator-initiated clinical research. A: The co-occurrence network generated by key terms mentioned more than six times, out of 398 terms from question 1. The size and color of balloon show the frequency of appearance and cluster (subgraph). The density of line shows the tie strength between each term (coefficient); B: The dendrogram for 18 key terms based on hierarchical cluster analysis. The color shows the cluster.

Fig. 2. The result of text mining for comments about concerns relating to clinical research among personnel engaged in research and development. A: The co-occurrence network generated by key terms mentioned more than six times out of 300 terms for question 2. The size and color of balloon show the frequency of appearance and cluster (subgraph). The density of line shows the tie strength between each term (coefficient); B: The dendrogram for 21 key terms based on hierarchical cluster analysis. The color shows the cluster.
For question 2 (concerns about research that investigators wanted to mention), there were 21 key terms mentioned more than six times. The terms “clinical research”, “research”, “biostatistics”, “case”, and “concrete” had high frequencies (Table 2 and Fig. 2A). The co-occurrence network and hierarchical cluster analyses (Fig. 2B) both clustered four groups.

Finally, to investigate the relationship between items in the two questions, the responses for the two questions were combined into a single text, and we created a co-occurrence network using the category “question 1 or 2” for external variables. There were differences in the strength of the correlation, but almost all terms were common to both questions (Fig. 3).

**DISCUSSION**

We identified four main troubles (question 1) experienced by personnel engaged in research and development (including investigators) in performing clinical research. These were: 1) cumbersome process for submitting documents (including protocols) to research ethics committees; 2) burden corresponding to clinical research, including clinical trials; 3) analysis plan (biostatistics) at the time of research planning; and 4) costs, including monitoring and lack of support.

There were also four main concerns (question 2): 1) clinical trials, including doctor-initiated clinical trials; 2) how to document (including protocols) materials for submission to research ethics committees; 3) concrete examples of invasive intervention studies or specified clinical trials; and 4) general biostatistics.

![Fig. 3. The result of text mining for comments about both concerns and troubles. The responses to questions 1 and 2 were combined into a single text. The targets were terms extracted in Fig. 1A and 2A, and co-occurrence network was performed with the category variables (Q1: question 1 and Q2: question 2) for external variables. The size and color of balloon show the frequency of appearance and degree. The density of line shows the tie strength between each question (coefficient).](image-url)
The extracted terms were relatively similar for both troubles and concerns. This may show that participants’ perceived troubles were related to their concerns. A causal inference based on these results suggested that participants needed information about concrete examples or biostatistics because they had experienced these as problem areas when performing clinical research.

It was possible that participants had hoped the lectures would offer concrete examples for planning clinical research and creating protocols. In addition, because the Clinical Trial Act had recently come into force, participants had an interest in the details of this legislation. Biostatistics was identified as a major concern. Recently, it has been recommended that data analysis and reporting of results be performed in accordance with guidelines (e.g., STROBE (the Strengthening the Reporting of Observational Studies in Epidemiology) statement [3] for observational studies; CONSORT (Consolidated Standards of Reporting Trials) statement [4] for randomized controlled trials). There have been increased opportunities for biostatisticians to review research when investigators submit their papers to journals. However, personnel engaged in research and development may have little knowledge of biostatistics [5,6]. This might be partly why our survey suggested a demand for biostatistics help among personnel engaged in research and development. This suggests that workshops on biostatistics and cooperation between researchers and biostatisticians have become increasingly important.

CONCLUSION

Our survey highlighted troubles and concerns among personnel engaged in research and development in Japan. Because a lot of time and effort is invested in performing clinical research in addition to daily work, researchers may experience burnout when their physical and mental burdens are increased [7]. Therefore, the existence and role of clinical research support organizations are important [8], and provision of appropriate workshops and information covering specific situations is recommended. It would also be helpful to have more institutional support for the promotion and development of clinical research.

CONFLICTS OF INTEREST: The authors have declared that no competing interests exist in this research.

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