

Present Status and Perspectives on Future Roles of Japanese Clinical Research Coordinators

Hiroaki Yanagawa^{a, e}, Hiroshi Nokihara^a, Hideto Yokoi^b, Hitoshi Houchi^b, Masahiro Nagai^c, Risako Yamashita^c, Narufumi Suganuma^d, Masamitsu Hyodo^d, the Shikoku Collaborative Group for Promotion of Clinical Trials

Abstract

Background: The new Clinical Trials Act that recently came into effect in Japan emphasizes the reliability of investigator-initiated clinical trials. Although Japanese clinical research coordinators have been mainly engaged in operational roles in industry-initiated clinical trials for drug approval (registration trials), broadening their contribution to cover more types of clinical research may lead to quality improvement of clinical research. To ultimately establish a clinical research infrastructure that meets the needs of the new era of Clinical Trials Act, here we gathered basic information on how clinical research coordinators might make such contributions.

Methods: We conducted a survey using self-reporting questionnaires in clinical research-related personnel to examine present status and the perspectives toward broader contribution of clinical research coordinators. The study participants were attendee of group discussion of a clinical research-related meeting in Shikoku area of Japan held in August 2017.

Results: Among 88 participants, 69 responded (response rate: 78.4%) and 68 respondents (98.6%) were engaged in support and management of clinical research. The main area of involvement was industry-initiated registration trials (48, 69.7%), and main roles of involvement were cooperators who plays roles under the guidance of investigators (41, 59.5%). When divided by occupation into clinical research coordinators (n = 41) and other clinical research-related personnel (n = 28), approximately half of the respondents in each group replied positively to wanting broader involvement of clinical research coordinators as a clinical research professional.

Conclusion: The present study revealed that about half of the clinical research coordinators and other clinical research-related personnel view a broadening of involvement of clinical research coordinators in research activities positively. Accordingly, a structured practical program aimed at encouraging such involvement may help to expand and strengthen their contribution into the future. Whether greater involvement of clinical research coordinators in clinical research will help to ensure the reliability of investigator-initiated clinical research warrants further study.

Keywords: Clinical research coordinators; Clinical research; Role; Quality assurance; Perspective; Clinical Trials Act; Japan

Introduction

A clinical research team composed of various professionals with various occupations and various roles is known to promote clinical research [1-4]. On these teams, clinical research coordinators (CRCs) play an essential role [5]. CRCs are important to respond to study complexity [6-8] by assuring study quality and protect study participants considering issues in research ethics [9] by various actions such as screening and recruiting study participants, ensuring informed consent, collecting and recording data and supporting follow-up. The involvement of CRCs is known to be associated with efficient, higher quality trials [10, 11].

In Japan, the clinical research infrastructure including CRCs was initially created to promote clinical trials for drug approval (registration trials) in response to the introduction of Good Clinical Practice as a global standard in 1997 [12]. Through the Japanese government's vitalization plans for clinical trial, medical specialists such as nurses and pharmacists have been trained to work as CRCs in medical institutions in Japan [13-15]. In addition, CRC certification is available from the Japanese Society of Clinical Pharmacology and Therapeutics (JSCPT) [16]. The Japan Agency for Medical Research and Development (AMED) is responsible for conducting the government's advanced training courses for CRCs with practical experiences and recommendation of hospital director [17, 18].

In a Japanese ministerial ordinance on the implementation of registration trials [19], a CRC is defined as a cooperator in registration trials who plays roles under the guidance of investi-

Manuscript submitted September 4, 2018, accepted October 10, 2018

^aClinical Trial Center for Developmental Therapeutics, Tokushima University Hospital, Tokushima, Japan

^bClinical Research Support Center, Kagawa University Hospital, Kagawa, Japan

^cClinical Therapeutic Trial Center, Ehime University Hospital, Ehime, Japan

^dIntegrated Center for Advanced Medical Technologies, Kochi Medical School Hospital, Kochi, Japan

^eCorresponding Author: Hiroaki Yanagawa, Clinical Trial Center for Developmental Therapeutics, Tokushima University Hospital, 2 Kuramoto-cho, Tokushima 770-8503, Japan. Email: niseko@tokushima-u.ac.jp

doi: <https://doi.org/10.14740/jocmr3602w>

gators (designated conventional activity in the present study). In other words, emphasis is placed on the supporting role that CRCs play throughout the various steps in a registration trial. CRCs are usually involved in registration trials conducted by industry, because money is available to fund their contributions and most registration trials are industry sponsored. CRCs are not often involved in registration trials conducted by investigators. These investigator-initiated registration trials are usually conducted using public funds, and those that are conducted for purposes other than obtaining government approval have been essentially conducted in accordance with national ethical guidelines. Therefore, the contribution of CRCs to investigator-initiated registration trials and other types of non-industry-sponsored clinical research has been limited, mainly for financial reasons [20].

However, in 2013, a scandal involving several clinical trials of the antihypertensive drug valsartan made headlines in Japan and around the world [21]. After valsartan was launched in the Japanese market, several academia-initiated clinical trials were conducted to compare its secondary benefits to those of other drugs. Although positive findings were reported, they were subsequently shown to be fraudulent and were retracted. At that time, and until only recently, no applicable law governing investigator-initiated clinical research existed in Japan. Investigators have had to perform trials independently, without the support of CRCs, mainly because of a lack of infrastructure. The 2013 scandal prompted a change in the Japanese regulations. Ethical guidelines put forth by the government have been strengthened and a new regulation on investigator-initiated clinical trials came into effect on April 1, 2018 [22]. This new Clinical Trials Act emphasizes the importance of reliability in clinical trials. As such, CRCs can be supposed to contribute more broadly to quality improvement in various types of clinical research. Nevertheless, there is still a knowledge gap in the perception of CRCs to partake a vital role in clinical trials and to expand their roles.

In this study, we conducted a survey of clinical research-related personnel to determine the present status of their role and their perspectives on possible future roles, with the aim of establishing a solid clinical research infrastructure in the new era.

Materials and Methods

Participants

The Shikoku Collaborative Group for Promotion of Clinical Trials was started in 2008 to promote clinical trials via person-to-person communication and discussions among clinical trial-related personnel by relevant departmental personnel in four university hospitals in Shikoku area of Japan [23]. The annual meeting and opportunities for training have been rotated among these four universities since 2009. The Eighth Annual Meeting was the final step of the second full rotation, and held in Takamatsu, Japan on August 19, 2017. In addition to CRCs, clinical trial-related personnel without medical qualifications, such as administrative officers, also attended the meeting. Study participants were 88 participants of group discussions on clinical

research-related issues at the Eighth Annual Meeting, and included CRCs and other clinical trial-related personnel.

Ethics approval was not sought for this study because the Ethical Guidelines for Medical and Health Research Involving Human Subjects of the Japanese Government [24] do not apply to this study: that is, the study does not involve human subjects with the purpose of obtaining knowledge to maintain and promote health or recovery from injury or disease or to improve patients' quality of life, through understanding the cause of diseases and their pathology or through improving measures to prevent injury and disease, improving measures for diagnosis and treatment, or through confirming the validity of such measures.

Design and questionnaire

Using a cross-sectional study design, we examined the perspectives of clinical research-related personnel on the present and future roles of CRCs, using an original questionnaire designed for use in this study (Supplementary Material 1). Six CRCs from Tokushima University Hospital preliminarily evaluated the questionnaire and provided suggestion. Among these six CRCs, four were certified CRCs by the JSCPT. The 15-item self-reporting questionnaire written in Japanese was anonymous and contained three parts: four items on gender, age, affiliation and basic qualification, eight items on present roles in clinical research, and three items on possible future roles and related questions. Some of the questions required a binary response of yes/no, and in some questions, a five-point scale was used (strongly agree, agree, neutral, disagree and strongly disagree).

The principal investigator (the first author) explained the outline of the study, such as purpose and methods, for the audience at the beginning of the meeting for about 15 min, and questionnaires were distributed to the meeting attendees. We also explained that participation was voluntary and that declining to participate would cause them no disadvantage. The questionnaires were collected at the end of the meeting. No follow-up was done for non-responders.

Statistical analysis

Responses were compared based on the job categories of the participants and the differences analyzed using Fisher's exact test. P values < 0.05 were considered significant, and all were based on two-sided tests. All statistical analyses were carried out using JMP, ver. 13 (SAS Institute Inc.).

Results

Respondent characteristics

In total, 69 of 88 participants (78.4%) responded. As shown in Table 1, more than 80% of the respondents were women. Nurse (37.7%) and medical technologist (20.3%) were major basic qualifications, and around 20% were without medical

Table 1. Respondent Characteristics

	Number (%) Respondents (n = 69)
Gender	
Male	11 (15.9)
Female	58 (84.1)
Age	
20 - 29	8 (11.6)
30 - 39	24 (34.8)
40 - 49	20 (29.0)
> 50	17 (24.6)
Basic qualifications	
Medical doctor	4 (5.8)
Pharmacist	7 (10.1)
Nurse	26 (37.7)
Medical technologist	14 (20.3)
Clinical nutritionist	4 (5.8)
No medical qualifications	14 (20.3)
Affiliations	
Medical institution	50 (72.5)
Contract research organization	1 (1.4)
Site management organization	18 (26.1)
Pharmaceutical company	0
Others	0

qualifications. More than 70% of the respondents were affiliated with medical institutions.

Experience of roles in clinical research and perspectives on the present roles

Field and total length of main engagement are shown in Table 2. All respondents were engaged in support and management of clinical research except one whose role was an investigator of registration trials. More than 80% of the respondents had experiences of their engagement of one or more years.

When asked about a feeling of isolation in their present role, 25 (36.2%) agreed (strongly agreed or agreed), 13 (18.8%) were neutral and 29 (42.0%) disagreed (disagreed or strongly disagreed). There were missing responses in two questionnaires. Almost all respondents (65, 94.2%) agreed (strongly agreed or agreed) that the annual meeting was a useful event for communicating with participants who had similar roles.

Present areas and main activities in involvement in clinical research and status in CRC certification

As shown in Table 3, most respondents were involved in in-

Table 2. Field and Total Length of Main Engagement

	Number (%) Respondents (n = 69)
Field of main engagement	
Support and management	68 (98.6)
Investigator of registration trials	1 (1.4)
Investigator of clinical research	0
Not involved	0
Others	0
Total length of main engagement	
< 6 months	8 (11.6)
6 - 12 months	2 (2.9)
1 - 5 years	31 (44.9)
≥ 5 years	28 (40.6)

dustry-initiated registration trials (48, 69.7%), followed by 10 in investigator-initiated clinical research (14.5%). As for the respondents' main roles, the major answer was conventional activities of a CRC in registration trials (41, 59.5%).

Of the 69 respondents, 21 (30.4%) had CRC certification from JSCPT. There were 48 respondents without CRC certification. In these respondents without CRC certification, 13 (27.1%) showed willingness to become certified. Eight respondents had attended government CRC training courses conducted by AMED.

Perspectives on the future roles of CRCs and related questions

Table 4 shows the respondents' perspectives on the involvement of CRCs as professionals in clinical research beyond their conventional activity in industry-initiated registration trials under the guidance of investigators. For this analysis, we divided respondents into two categories. "CRCs" and "Others" are designated as those who answered conventional activities of a CRC in registration trials as their main roles (41, 59.4%), and as those who provided other answers (28, 40.6%) in question Part 2, No. 5, respectively. Approximately half of the respondents in each group agreed (strongly agreed or agreed) that the contributions of CRCs should be broadened. Of the 20 CRCs who responded positively, four were pharmacists (57.1% of all participating pharmacists), 10 were nurses (38.5% of all participating nurses) and six were medical technologists (42.9% of all participating medical technologists). No clinical nutritionists responded positively to this question. No significant differences were observed in positive response rates between job categories (pharmacists versus nurses, $P = 0.422$; pharmacists versus medical technologists, $P = 0.659$; nurses versus medical technologists, $P = 1.000$). As for levels of experience among the 20 CRCs who responded positively, 10 had less than 5 years and 10 had 5 or more years of experience.

Table 3. Main Area and Roles of Involvement

	Number (%)
	Respondents (n = 69)
Main area of involvement	
Industry-initiated registration trials	48 (69.7)
Investigator-initiated registration trials	1 (1.4)
Industry-initiated clinical research	5 (7.2)
Investigator-initiated clinical research	10 (14.5)
Others	0
No response	5 (7.2)
Main roles of involvement	
Conventional activities of a CRC in registration trials	41 (59.5)
Ethics committee support	17 (24.7)
Study planning and/or biostatistics	1 (1.4)
Project management	1 (1.4)
Data management	2 (2.9)
Monitoring and auditing	2 (2.9)
Others	0
No response	5 (7.2)

Of 41 CRCs, 11 (26.8%) were already working as professionals in clinical research beyond the guidance of investigators. Of the 30 CRCs not yet involved, seven (23.3%) agreed (strongly agreed or agreed) with expanding CRCs’ future involvement in clinical research.

Discussion

In this study, 21 respondents (30.4%) had JSCPT CRC certification and 25 respondents (36.2%) reported feeling isolated. In our previous survey examining the status of clinical trial-related personnel in a rural area of Japan, which we conducted with participants at the first meeting of the Shikoku Collaborative Group for Promotion of Clinical Trials in 2009, 10.3% of the respondents had already acquired JSCPT CRC certification

and the most common response selected for participation was “willingness to contact staff from other medical institutions or organizations” as support staff (CRCs and administrative officers) [23]. Feelings of isolation and tension throughout the duration of clinical trials have been reported by clinical research nurses, even after gaining skills and confidence in their roles [25]. These results suggest that CRCs may still feel insecure despite having acquired more skills.

Recently, more attention has been focused in Japan on the roles of CRCs in investigator-initiated clinical trials that go beyond their conventional activities as contributors in industry-initiated registration trials under the guidance of investigators, as designated by the Japanese ministerial ordinance on the implementation of clinical trials. In an international comparison of the roles of CRCs, Brinkman-Denney [26] reported that CRCs of some countries including Japan had less contribu-

Table 4. Perspectives of the Two Groups of Respondents - CRCs and Others - on CRC Involvement as Professionals in Clinical Research Beyond Their Conventional Activity in Industry-Initiated Registration Trials

	Number (%)		
	CRCs* (n = 41)	Others* (n = 28)	Total (n = 69)
Strongly agree	9 (22.0)	8 (28.6)	17 (24.6)
Agree	11 (26.8)	5 (17.9)	16 (23.2)
Neutral	7 (17.1)	9 (32.0)	16 (23.2)
Disagree	11 (26.8)	4 (14.3)	15 (21.7)
Strongly disagree	3 (7.3)	1 (3.6)	4 (5.8)
No response	0	1 (3.6)	1 (1.4)

“CRCs” and “Others” are designated as those who answered conventional activities of a CRC in registration trials as their main roles, and as those who provided other answers in question Part 2, No. 5, respectively.

tion to protocol assessment than those of India, the USA and the UK. In Italy, CRCs' duties include attending investigator's meetings, receiving monitoring visits, managing administrative tasks and completion of the case report forms [27], and the situation is similar in Japan. Another Japanese reality is that nurse CRCs often play roles of clinical research nurses simultaneously [14]. Although the scope of CRCs may be different in various countries, ensuring practical involvement of CRCs in the various steps of clinical research could contribute to expanding and strengthening the role of CRCs as professionals in clinical research.

As a Japanese proposal, Kohara [28] highlighted the involvement of CRCs in various processes during clinical research, such as planning of study protocols and ethical reviews. In the new era of Clinical Trials Act, these activities should be promoted, since quality improvement in various types of clinical research cannot be achieved without establishment of infrastructure with broader contribution of CRCs on clinical trials in addition to the role to ensure reliability of each clinical trial.

In Japan, nurses and pharmacists at key hospitals often take on the CRC role. In our previous survey of 597 nurses, 26% of the respondents expressed their willingness to work as CRCs [29]. In another survey of pharmacy students, we found that more than 90% were aware of the CRC role and 29% and 41% were willing to carry out and coordinate research, respectively [30]. Exposure on and education of the broader role of CRCs to nurses, pharmacists and their students may lead to establish a suitable clinical research team in the future.

The strength of the present work lies in the fact that it reflects real perspectives of those who attended a group discussion in a clinical research-related meeting. These attendees have high motivation in clinical research-related roles and provide basic information to build up an effective infrastructure of clinical research, considering their perspectives as stakeholders. At the same time, this study has several limitations. Mainly, it was conducted in just one area in Japan. Meetings such as those of the Shikoku Collaborative Group for Promotion of Clinical Trials are conducted on a regional basis in Japan, so this survey may not fully reflect the situation of CRCs across Japan. The clinical research infrastructure varies by country, so the generalizability of our results to international settings should be examined in future studies.

The results of this study revealed the Japanese situation that about half of the CRCs and other clinical research-related personnel view a broadening of CRCs' involvement in research activities positively. Accordingly, a structured practical program aimed at encouraging such involvement may help to expand and strengthen their contribution into the future. Whether greater involvement of CRCs in clinical research will help to ensure the reliability of investigator-initiated clinical research warrants further study.

Acknowledgments

The authors would like to thank Kenshi Takechi and Masayuki Chuma, Clinical Trial Center for Developmental Therapeutics,

Tokushima University Hospital for their encouragement and support.

Conflict of Interest

The authors have no conflict of interest to disclose with respect to the present study.

Financial Support

This research received no external funding.

References

1. Baer AR, Zon R, Devine S, Lyss AP. The clinical research team. *J Oncol Pract*. 2011;7(3):188-192.
2. von Niederhausern B, Fabbro T, Pauli-Magnus C. The role of Clinical Trial Units in investigator- and industry-initiated research projects. *Swiss Med Wkly*. 2015;145:w14161.
3. Tang C, Hess KR, Sanders D, Davis SE, Buzdar AU, Kurzrock R, Lee JJ, et al. Modifying the clinical research infrastructure at a dedicated clinical trials unit: assessment of trial development, activation, and participant accrual. *Clin Cancer Res*. 2017;23(6):1407-1413.
4. Marchesi E, Cagnazzo C, Quattrini I, Leopardi MP, Villa C, Grignani G, D'Ambrosio L, et al. How a Clinical Trial Unit can improve independent clinical research in rare tumors: the Italian Sarcoma Group experience. *Clin Sarcoma Res*. 2017;7:4.
5. Norris D. *Clinical Research Coordinator Handbook*, 2nd Ed. Medford (NJ): Plexus Publishing, Inc.; 2001.
6. Getz KA, Campo RA, Kaitin KI. Variability in protocol design complexity by phase and therapeutic area. *Drug Inf J*. 2011;45(4):413-420.
7. Vose JM, Levit LA, Hurley P, Lee C, Thompson MA, Stewart T, Hofacker J, et al. Addressing administrative and regulatory burden in cancer clinical trials: summary of a stakeholder survey and workshop hosted by the American Society of Clinical Oncology and the Association of American Cancer Institutes. *J Clin Oncol*. 2016;34(31):3796-3802.
8. Getz KA, Campo RA. Trial watch: Trends in clinical trial design complexity. *Nat Rev Drug Discov*. 2017;16(5):307.
9. Davis AM, Hull SC, Grady C, Wilfond BS, Henderson GE. The invisible hand in clinical research: the study coordinator's critical role in human subjects protection. *J Law Med Ethics*. 2002;30(3):411-419.
10. Rico-Villademoros F, Hernando T, Sanz JL, Lopez-Alonso A, Salamanca O, Camps C, Rosell R. The role of the clinical research coordinator - data manager - in oncology clinical trials. *BMC Med Res Methodol*. 2004;4:6.
11. Street A, Strong J, Karp S. Improving patient recruitment to multicentre clinical trials: the case for employing a data manager in a district general hospital-based oncology

- centre. *Clin Oncol (R Coll Radiol)*. 2001;13(1):38-43.
12. Miyake S. Introduction of new GCP (good clinical practice). *Gan To Kagaku Ryoho*. 1998;25(5):645-649. (In Japanese).
 13. Asaka K. Clinical trial development and the clinical research coordinator - From a working group report on the current situation of personnel conducting clinical trials. *J Anal Bio-Sci*. 2007;30(5):381-386. (In Japanese).
 14. Yanagawa H, Akaishi A, Miyamoto T, Takai S, Nakaniishi R, Irahara M. Role of clinical research coordinators in promoting clinical trials of drugs for surgical patients. *Int Arch Med*. 2008;1(1):26.
 15. Miyamoto T, Akaishi A, Takagai T, Kida K, Akaike M, Yanagawa H. Implementation of clinical research coordinator hospital certification course to spread understanding of clinical trials. *Jpn J Clin Pharmacol Ther*. 2018;49(1):7-11.
 16. Japanese Society of Clinical Pharmacology and Therapeutics. System of certified clinical research coordinator by the Japanese Society of Clinical Pharmacology and Therapeutics. Available online: <http://www.jscpt.jp/seido/crc/> (accessed on October 5, 2018). (In Japanese)
 17. Ohashi Y, Ohtsu H, Hashimoto Y, Matsuura C, Yajima T, Shinano H, Sato M. Report on 2015 workshop to train senior clinical research coordinators and other clinical trial-related persons hosted by the Japan Agency for Medical Research and Development (AMED). *Jpn Pharmacol Ther*. 2016;44(suppl-1):s49-s54. (In Japanese)
 18. Yoshida Y. AMED's supports for establishing of a base in order to ensure proper clinical trials and research. *Jpn Pharmacol Ther*. 2017;45(suppl-1):s24-s26. (In Japanese)
 19. Available online: <http://elaws.e-gov.go.jp/search/elaws-search/Elawssearch/lsg0500/detail?lawId=409M50000100028&openerCode=1> (accessed on October 5, 2018). In Japanese)
 20. Yanagawa H. Current regulatory systems for clinical trials in Japan: Still room for improvement. *Clin Res Regul Aff*. 2014;31(2-4):25-28.
 21. Normile D. Japan. Tampered data cast shadow on drug trial. *Science*. 2013;341(6143):223.
 22. Clinical Trials Act (Act No. 16 of April 14, 2017). Available online: <https://www.mhlw.go.jp/file/06-Seisakujouhou-10800000-Iseikyoku/0000213334.pdf> (accessed on October 5, 2018).
 23. Yanagawa H, Irahara M, Houchi H, Kakehi Y, Moritoyo T, Nomoto M, Miyamura M, et al. View and present status of personnel involved in clinical trials: a survey of participants from the First Symposium of the Shikoku Collaborative Group for Promotion of Clinical Trials. *J Med Invest*. 2011;58(1-2):81-85.
 24. Ethical guidelines for medical and health research involving human subjects. Available online: <https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000153339.pdf> (accessed on October 5, 2018). (In Japanese).
 25. Spilsbury K, Petherick E, Cullum N, Nelson A, Nixon J, Mason S. The role and potential contribution of clinical research nurses to clinical trials. *J Clin Nurs*. 2008;17(4):549-557.
 26. Brinkman-Denney S. An international comparison of the clinical trials nurse role. *Nurs Manag (Harrow)*. 2013;20(8):32-40.
 27. Cinefra M, Cagnazzo C, McMahon L, Arizio F, Campora S, Camisa R, Canzanella G, et al. The critical role of the clinical research coordinator for clinical trials: a survey in oncology. *Med Access @ Point Care*. 2017;1(1):e76-e81.
 28. Kohara I. Significance and practice of contribution of clinical research coordinators on protocol planning and ethics review. *Jpn Pharmacol Ther*. 2017;45(9):1429-1432. (In Japanese).
 29. Yanagawa H, Takai S, Yoshimaru M, Miyamoto T, Katashima R, Kida K. Nurse awareness of clinical research: a survey in a Japanese University Hospital. *BMC Med Res Methodol*. 2014;14:85.
 30. Ise N, Takechi K, Miyamoto T, Ishizawa K, Yanagawa H. Pharmacy students' knowledge and attitude toward registration trials and clinical research: a survey in a Japanese university hospital. *Pharmacy*. 2017;5(4):67.