Hamada et al., J Clin Trials 2014, 4:1
DOI: 10.4172/2167-0870.1000153

Journal of Clinical Trials
ISSN: 2167-0870

Research Article Open Access

Current Environment for Clinical Research with Medical Devices in Hospitals in Japan

Shota Hamada[1], Yukie Yamauchi[1], Osamu Miyake[1], Motoko Nakayama[1], Haruko Yamamoto[2] and Koji Kawakami[1]*

[1]*Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan*
[2]*Department of Advanced Medical Technology Development, National Cerebral and Cardiovascular Center, Osaka, Japan*

Abstract

Background: Medical devices are continuously being improved in routine clinical practice. As necessary, new or additional clinical data for an investigational medical device is collected through clinical research and/or registered clinical investigations. We conducted a questionnaire survey to determine the current environment for clinical research with medical devices, particularly focusing on infrastructure and human resources in hospitals.

Methods: The questionnaire for this study included 6 main topics: experience of clinical research, in-hospital manuals, issues on clinical research, related regulations, and effectiveness of a guidance published by the Medical Engineering Technology Industrial Strategy Consortium. The questionnaire was mailed to all 10 core clinical research centers and 30 major clinical trial institutions at the time of survey in Japan.

Results: Eighteen hospitals (45%) provided responses. Relatively few clinical research activities with medical devices had been conducted in each hospital, and two-thirds of respondents thought low number of clinical research activities was problematic. A shortage of experts in medical devices was also raised as an important challenge. Most of the hospitals had established in-hospital manuals for clinical research with medical devices; however, specific features required for the evaluation of medical devices might not be included in the manuals. Many hospitals had too few clinical research coordinators (CRCs) for support of clinical research with medical devices, but half of the hospitals could not afford to increase the number of CRCs.

Conclusion: Our study revealed that the current environment for clinical research with medical devices in hospitals has been partly organized, but it was suggested that a shortage of experts, the complexity of the regulatory system, and a need for financial support are remaining issues.

Keywords: Medical device; Clinical research; Clinical trial; Questionnaire survey; Clinical research coordinator

Introduction

Medical devices play key roles in diagnosis and treatment of diseases in modern healthcare. Unlike drugs, medical devices are continuously improved in routine clinical practice during the development and post-marketing phases to meet the needs of medical staff and patients. However, not all of advanced medical devices used in other countries are available in Japan [1]. Correction of this problem requires establishment of regulations related to development of medical devices and development or improvement of human resources, infrastructure and funding for clinical research and registered clinical investigations with medical devices. In this paper, clinical research is defined in a limited sense as research activities not including registered clinical investigations with Good Clinical Practice (GCP) for a marketing approval application.

During the development process, investigational medical devices are firstly evaluated based on clinical evidence including clinical data such as literature data and/or clinical experience. In response to the needs of new or additional clinical data, clinical research and/or registered clinical investigations are conducted. In particular, an innovative and/or invasive medical device for which clinical data are required for a marketing approval application under the Pharmaceutical Affairs Law (PAL) is evaluated in registered clinical investigations in accordance with the Ministry of Health, Labour and Welfare (MHLW)'s Ministerial Ordinance on GCP for Medical Device. Such clinical investigations are mostly sponsored by medical device companies. Once the safety and effectiveness of a medical device have been evaluated and ensured by the Pharmaceuticals and Medical Devices Agency, the regulatory authority in Japan, and subsequently approved by the MHLW, the medical device becomes accessible to medical staff and patients across the country. In contrast, clinical research with medical devices are predominantly initiated by clinicians in hospitals and generally conducted under permission of each hospital, in accordance with the Ethical Guideline for Clinical Research [2]. Clinical research assures timely evaluations of prototypes of medical devices with novel or altered technologies and with improved usability and/or performance.

In Japan, clinical research and registered clinical investigations are regulated separately and the system is complicated. Clinical investigations are regulated more clearly than clinical research and must be conducted in accordance with the PAL and GCP. Unapproved medical devices are regulated by the PAL, and therefore there was a concern that the supply of unapproved medical devices for clinical research conducted in hospitals constitutes a breach of the PAL. This background caused problems when companies make decisions on supplying medical devices to be tested in clinical research.

Recently, the MHLW released two notices regarding clinical

***Corresponding author:** Koji Kawakami, Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Yoshidakonoecho, Sakyo-ku, Kyoto, Japan, Tel: +81-75-753-4459; Fax: +81-75-753-4469; E-mail: kawakami.koji.4e@kyoto-u.ac.jp

Received December 02, 2013; **Accepted** January 07, 2014; **Published** January 09, 2014

Citation: Hamada S, Yamauchi Y, Miyake O, Nakayama M, Yamamoto H, et al. (2014) Current Environment for Clinical Research with Medical Devices in Hospitals in Japan. J Clin Trials 4: 153. doi:10.4172/2167-0870.1000153

Copyright: © 2014 Hamada S, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

research with unapproved medical devices [3,4]. These notices indicated that supply of unapproved medical devices for clinical research is exempted from the PAL. To clarify these notices, the Medical Engineering Technology Industrial Strategy Consortium (METIS) published a document entitled "Guidance on clinical research with unapproved medical devices" [5] to streamline the process of clinical research with medical devices. This guidance includes information on the overall picture of clinical research, overviews of related regulations, classification of medical devices, practical considerations at each stage of clinical research, checklists for protocol and informed consent form, and relevant templates for documents such as a collaborative research agreement.

This guidance further defined the regulatory requirements for clinical research with medical devices that are not regulated by the PAL or GCP; however, the current environment for conducting such clinical research in hospitals remains unclear. In Japan, individual hospitals are relatively small and are scattered nationwide, and this situation presents a barrier to efficient development of medical devices and drugs. Therefore, we conducted a questionnaire survey to determine the current environment for clinical research with medical devices, particularly focusing on infrastructure and human resources in hospitals, and to identify issues related to the conduct of clinical research from a hospital perspective.

Materials and Methods

A questionnaire for this study was developed to examine the current environment for clinical research with medical devices in hospitals. The questionnaire included 6 main topics: experience of clinical research, in-hospital manuals, issues on clinical research, roles and sufficiency of support staff, related regulations, and effectiveness of the METIS guidance. The support staff refers to as Clinical Research Coordinators (CRCs) who support clinical research and/or registered clinical investigations. Most of the questions were multiple-choice for the purpose of reducing the time and effort of the respondents, but free descriptions were also obtained as necessary (Table 1).

The survey was conducted between 23 March and 25 April 2012. The questionnaire was mailed to directors of support offices for clinical investigations at all 10 core Clinical Research Centers (CCRCs) and 30 Major Clinical Trial Institutions (MCTIs) at the time of survey in Japan. The MHLW has designated these hospitals for financial support for human resources and infrastructure for smooth and efficient conduct of clinical research and registered clinical investigations [6]. It is particularly important to understand the current status of clinical research with medical devices in these hospitals since they have key roles in development of medical devices and drugs. Data were compiled using Microsoft Office Excel 2010.

Results

Eighteen hospitals (45%) responded to our questionnaire, but some respondents did not answer all of the questions. The reported experience of clinical research with approved or unapproved medical devices in each hospital are shown in Table 2. Relatively few clinical research activities with medical devices had been conducted in the last 2 years. The median number of clinical research activities with medical devices was 5 per hospital when calculated with experience in 12 hospitals where had reported experience of at least one clinical research activity with medical devices, with considerable variation among the hospitals (range, 1-22 per hospital).

The results from the questions on preparation of in-hospital manuals for clinical research and registered clinical investigations with medical devices are shown in Table 3. Thirteen hospitals had established manuals for clinical research with medical devices, and 3 of these hospitals had manuals for clinical research in compliance with GCP. Manuals for clinical research with medical devices were the same as those used for drugs in 15 hospitals, and only 6 of these hospitals have manuals that cover clinical research with both approved and unapproved medical devices. Similarly, manuals for registered clinical investigations with medical devices were the same as those used for drugs in most hospitals.

There were several general issues on conduct of clinical research with medical devices (Figure 1). In particular, two-thirds of respondents thought that the much lower number of clinical research activities with medical devices compared to those with drugs was problematic. In this context, 4 respondents suggested that there was a shortage of experts in this field and/or indicated a lack of applicability of experience in clinical research with drugs due to methodological differences. There was an opinion that the low number of clinical research activities is one of the reasons why they could not hire staff specialized in medical device. Five respondents felt that separate management of investigational medical devices for clinical research and medical devices for routine practice was complicated. One of respondents' requests for medical device companies is more proactive technical support, for example, assistance on how to manage investigational medical devices.

The roles of CRCs were mainly to support registered clinical investigations in more than a half of the hospitals (Table 4). The median number of CRCs in each hospital was 7 (range, 2-18). Seven hospitals assigned a median of 2 CRCs (range, 1-5) as staff specialized in clinical research and registered clinical investigations with medical devices. Most respondents thought that more CRCs were needed in their hospitals, but half of the hospitals could not afford to increase the number of CRCs. These results suggest a common trend of an insufficient number of CRCs in the hospitals, particularly for support of clinical research with medical devices.

The notification on supply of unapproved medical devices issued by MHLW was highly recognized (16/18, 89%). Out of those who answered that they know the notification, 10 respondents agreed that clinical research will be more activated by the notification. To the question whether regulations should be eased so that unapproved medical devices can be provided to researchers at the request of companies, the respondents were almost equally divided between those who agreed and disagreed. In addition, out of 6 respondents disagreed that clinical research will be more activated by the notification, 4 respondents agreed to the aforementioned question whether regulations should be eased.

The METIS guidance was highly appreciated. The respondents thought the guidance was useful for physicians, dentists, CRCs and administrative officers associated with clinical research, including staff in charge of ethical review. The followings were listed as especially useful among the contents of the guidance: procedures for clinical research with medical devices, a template for a collaborative research agreement, classification of medical devices, and methods for management of investigational medical devices. In particular, the visual summaries shown as flowcharts and tables, including the overall picture of clinical research and the classification of medical devices, were highly praised. Some additions to the current guidance were proposed, including a template for a study protocol and methods for dealing with malfunctions of investigational medical devices.

Topic	Question [Question type]	Response options
Experience of clinical research	Which and how much experience does your hospital have related to clinical research with medical devices, excluding experience related to registered clinical investigation? [Filling in numbers of all applicable experience within the last 2 years]	• Experience with approved medical devices within the approved indications • Experience with approved medical devices under off-label use • Experience with unapproved medical devices • No experience
In-hospital manuals	Have manuals for clinical research been established? [Single answer]	• Yes / No
	If no, are manuals for clinical research in preparation? [Single answer]	• Yes / No
	Are the manuals for clinical research with medical devices the same as those used for drugs? [Single answer]	• Yes / No
	Are the manuals for registered clinical investigations with medical devices the same as those used for drugs? [Single answer]	• Yes / No
Issues on clinical research	Which issue do you face when conducting clinical research with medical devices? [Multiple answers allowed]	• Lack of applicability of experience in clinical research with drugs. • Shortage or none of experts in medical devices in the hospital. • More difficult to recruit participants compared to clinical research with drugs. • Separate management of investigational medical devices for clinical research and medical devices for routine practice is complicated. • Much lower number of clinical research activities with medical devices compared to those with drugs. • Insufficient support from medical device companies.
	If any comments on cooperation from medical device companies, please specify. [Open-ended]	
	If any other issues, please specify. [Open-ended]	
Roles and sufficiency of support staff	What are CRCs in your hospital involved in? [Single answer]	• Only registered clinical investigations • Mainly registered clinical investigations • Both at about the same level
	Do you think the number of CRCs in your hospital is sufficient? [Single answer]	• Yes / No
	Does your hospital plan to increase the number of CRCs? [Single answer]	• Yes / No
Related regulations	Do you agree that clinical research will be more active thanks to the notification “Application of Pharmaceutical Affairs Law to supply of unapproved medical devices used in clinical research” issued on March 2010? [Single answer]	• Agree / Disagree / Do not know the notification
	Do you agree that regulations should be eased so that unapproved medical devices can be provided to researchers at the request of companies? [Single answer]	• Agree / Disagree
Effectiveness of the METIS guidance	What kinds of professional are likely to find the METIS guidance useful? [Multiple answers allowed]	• Medical doctor / Dentist / Nurse / Pharmacist / Other paramedics / CRC / Officer of clinical research center / Member of ethical committee
	If other, please specify. [Open-ended]	
	Which part of the METIS guidance is considered to be useful? [Multiple answers allowed]	• Classification of medical devices • Differences in regulatory systems between non-registered clinical research and registered clinical investigations • Procedures for clinical research with unapproved medical devices • Preparation of protocol and informed consent form • Templates of contracts • Management of investigational medical devices • Protection of participants in clinical research • Interruption, cancellation, and termination of clinical research • Check-lists for protocol and informed consent form
	If other, please specify. [Open-ended]	

Table 1: Contents of Questionnaire.

Discussion

Medical devices are continuously being improved in routine clinical practice. As necessary, new or additional clinical data for an investigational medical device is collected through clinical research and/or registered clinical investigations. To our knowledge, this report is the first survey of the environment for clinical research with medical devices in hospitals in Japan.

In-hospital manuals for clinical research with medical devices were established or in preparation at the time of the study; however, two major issues with these manuals were identified that might affect the quality of clinical research. The first is that some hospitals prepared the manuals in compliance with GCP. Clinical research with medical devices is not necessarily conducted in compliance with GCP under the current regulatory system, and the conduct of clinical research with such high level of quality is an overreach and a waste of time,

	n (%)
With approved medical devices	12 (67%)
Within the approved indications	11 (61%)
Under off-label use	9 (50%)
No reply	5 (28%)
With unapproved medical devices	9 (50%)
None or unknown	5 (28%)
No reply	4 (22%)

Table 2: Experience with clinical research with medical devices in each hospital (N=18).

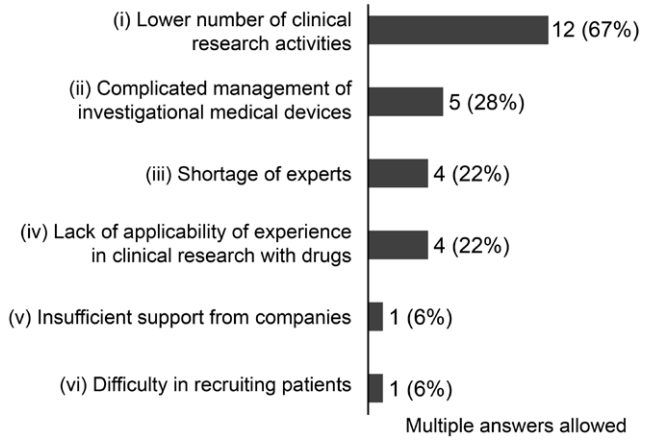

Figure 1: Issues on clinical research with medical devices.
(i) Much lower number of clinical research activities with medical devices compared to those with drugs.
(ii) Separate management of investigational medical devices for clinical research and medical devices for routine practice is complicated.
(iii) Shortage or none of experts in medical devices in the hospital.
(iv) Lack of applicability of experience in clinical research with drugs.
(v) Insufficient support from medical device companies.
(vi) More difficult to recruit participants compared to clinical research with drugs.

	Yes	No	No reply
	n (%)	n (%)	n (%)
Have manuals for clinical research been established?	13 (72%)	4 (22%) [a]	1 (6%)
Are the manuals for clinical research with medical devices the same as those used for drugs?	15 (83%)	1 (6%)	2 (11%)
Are the manuals for registered clinical investigations with medical devices the same as those used for drugs?	13 (72%)	4 (22%)	1 (6%)

a: All the 4 hospitals had not established manuals for clinical research, but had been preparing at the time of the survey

Table 3: Manuals for clinical research and registered clinical investigations with medical devices (N=18).

money and effort of researchers and companies. The complexity of regulatory systems might underlie this problem. Different regulatory systems are applied separately to clinical research and registered clinical investigations [7,8]. A possible solution may be to unify the two systems for one system like investigational device exemption in the United States.

The second issue is that the manuals for clinical research, as well as registered clinical investigations, with medical devices were the same as those used for drugs in most of the hospitals (Table 3). This implies that specific features required for the evaluation of medical devices are not included in the manuals. The respondents indicated substantial differences in procedures in clinical investigations and clinical research with drugs and medical devices, and experience in clinical research with drugs cannot always be applied to medical devices (Figure 1). This issue may arise from insufficient experience with clinical research and clinical investigations with medical devices; thus, specific procedural descriptions might not be included in the in-hospital manuals.

Relatively few clinical research activities with medical devices had been conducted in each hospital. Therefore, the experience and findings from clinical research with medical devices should be shared among hospitals and medical device companies to improve development of medical devices to the extent possible. The METIS guidance will be updated based on the needs of medical staff and medical device companies and on changes in the environment for medical device development. The updated guidance is expected to include some case studies and more specific procedural advice, which should partly complement the knowledge and experience in hospitals and companies.

A shortage of experts in medical devices was raised as an important challenge (Figure 1). In Japan, the delay of clinical research and clinical investigations with drugs and medical devices following basic research is often pointed out [9]. In particular, the characteristics of medical devices vary widely and multidisciplinary knowledge is needed in medical device development. A recent comparison of undergraduate and graduate education at universities in Japan and the United States for development of human resources for promotion of development and application of medical devices led to several proposals [10]. These included continuous funding for the centers of excellence in research and education as necessary, quality control of educational programs, accreditation for educational programs, and strengthening of regulatory science education. Such education can also enhance the effectiveness of on-the-job training and achieve flexible application of knowledge.

There are several limitations that affect the validity of the study. We sent the questionnaire to all CCRCs and MCTIs designated by the MHLW at the time of the survey, but the response rate was only 45% and some respondents did not answer all of the questions. An unbalanced distribution of non-respondents and respondents limits the internal validity of the study. Generalizability of the study may also be limited because CCRCs and MCTIs are highly organized compared to most hospitals in Japan. Further studies need to include smaller hospitals because innovation in medical devices can occur anywhere. In addition to the issues raised by the present study, other challenges may exist in medical device development in Japan, as discussed in the United States [11]. Issues and challenges will vary with changes in the regulatory system and accumulation of experience in medical device development

	n (%)
What are CRCs in your hospital involved in?	
- only registered clinical investigations	2 (11%)
- mainly registered clinical investigations, but also clinical research	11 (61%)
- both registered clinical investigations and clinical research at about the same level	4 (22%)
No reply	1 (6%)
Do you think the number of CRCs in your hospital is sufficient?	
- sufficient	2 (11%)
- insufficient, but plans to increase	8 (44%)
- insufficient, and no plan to increase	7 (39%)
No reply	1 (6%)

Table 4: Roles and sufficiency of clinical research coordinators (CRCs) (N=18).

in hospitals and companies, and these should be identified and resolved on an ongoing basis.

In conclusion, our study revealed that the current environment for clinical research with medical devices in hospitals has been partly organized, but it was suggested that a shortage of experts, the complexity of the regulatory system, and a need for financial support are remaining issues. Measures to meet these challenges should be taken to create a positive cycle of medical device development.

Conflict of Interest

All authors declare no conflict of interest with regard to this work.

References

1. Numata S, Oguchi S, Yamamoto Y, Imura H, Kawakami K (2010) Medical device development in crisis: A movement for technology innovation in health and medicine in Japan. Innovation 12: 330-336.
2. Imoto M (2010) [Review of the 2008 revision of the ethical guidelines for clinical studies]. Brain Nerve 62: 511-518.
3. Ministry of Health, Labour and Welfare (2010) Notice from the Director-General of Pharmaceuticals and Food Safety Bureau, MHLW (PFSB 0331 No.7). Application of Pharmaceutical Affairs Law to supply of unapproved medical devices used in clinical research.
4. Ministry of Health, Labour and Welfare (2011) Notice from the Director of Compliance and Narcotics Division, Pharmaceuticals and Food Safety Bureau, MHLW (PFSB-CND 0331 No.7) Q&A on “Application of Pharmaceutical Affairs Law to supply of unapproved medical devices used in clinical research”.
5. Medical Engineering Technology Industrial Strategy Consortium (2011) Guidance on clinical research with unapproved medical devices (1stedn).
6. Ministry of Education, Culture, Sports, Science and Technology, Ministry of Health, Labour and Welfare (2007) The New 5-Year Clinical Trial Activation Plan.
7. Kawakami K, Yamane H (2007) Clinical research in Japan: ways to alleviate unnecessary regulatory burdens. Rev Electron Comun Inf Inov Saude 1: 57-61.
8. Yanagi K, Fukuda E, Jotatsu Y, Shikano M, Miyake S (2012) Regulatory frameworks for cell therapy products in Japan. J Artif Organs 15: 325-330.
9. Sato Y, Koyama K (2010) Clinical research in Japan: past, present and future. Keio J Med 59: 104-109.
10. Omoe H (2012) Human resource development toward the development and practical application of medical devices in Japan. Discussion Paper No.81. National Institute of Science and Technology Policy.
11. Linehan JH, Chaney A (2010) Academic/Industry challenges for medical device development. Sci Transl Med 2: 63mr6.