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REVIEW ARTICLE

CLINICAL TRIAL DESIGN OF MEDICAL DEVICES APPROVED BY THE PHARMACEUTICALS AND MEDICAL DEVICES AGENCY OF JAPAN

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ABSTRACT

In medical device development, a lifecycle approach is indispensable because devices are modified frequently. In clinical trials, double-blind sham-controlled procedures are difficult because they may cause adverse events. The verification of superiority in medical treatment is essential because of the invasive nature of medical devices, which may raise ethical issues with regard to control groups. Accordingly, typical prospective randomized double-blind studies are less common; the majority of studies are single-arm trials. To assess the clinical trial design of medical devices, 53 items approved in 2016 by the Pharmaceuticals and Medical Devices Agency of Japan (PMDA) were reviewed. The results indicate that more than half involved single-arm trials, whereas only 23% were prospective randomized trials. There was only one sham-controlled prospective randomized trial. With respect to single-arm trials, performance goals were established from raw data on a previous generation of the device in 33% of studies and from multiple publications in 33%. These results suggest that continuous data accumulation, such as a registry, could provide a control group based on patient-level data. The PMDA recognizes that the appropriate method to collect reliable and robust data based on a registry has the potential to facilitate a pre-market and post-market balance because medical device development is a lifecycle. The PMDA intends to move toward a fast-track approval scheme and controlled release of certain new medical devices to the market after conditional approval if benefits and risks can be reasonably proven from the available clinical data and an appropriate risk management plan is prepared.

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INTRODUCTION

Increasing numbers of medical products have been approved in recent years by the Ministry of Health, Labour, and Welfare (MHLW) in collaboration with the Pharmaceuticals and Medical Devices Agency of Japan (PMDA). As a regulatory agency, the PMDA maintains the fundamental principle that the effectiveness and safety of pharmaceuticals, medical devices, biologics and other products must be reasonably assured before they are provided to the market. However, it is also important to balance patient access to products with detailed pre-market evaluation. In this respect, it is crucial to make early decisions that are scientifically sound and reliable. In Japan, the legislative document governing medical products was amended as the Pharmaceuticals and Medical Devices Act in 2014 (http://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/dl/150407-01.pdf). The goal of the document is to reinforce safety operations for medical products as well as their early approval.

In addition, several policies by the MHLW facilitate the development of medical products, such as the Sakigake designation scheme (Kondo, 2017), and the promotion of international clinical trials. These efforts have successfully reduced the duration between application and approval dates.In the development of pharmaceuticals, prospective randomized double-blind clinical trials utilizing either placebo or standard drug therapy as a control are performed in most cases. Although the PMDA adheres to the principle of requesting prospective randomized clinical trials for the approval of new treatment modalities utilizing new medical devices, these clinical trials are not realistic in many cases of medical device development. There are several reasons why these clinical trials are difficult. First, blinding by placebo in pharmaceutical development is essential to minimize bias, and the use of medical devices is often obvious to both the operator who performs treatment or diagnostic testing and patients themselves. To conduct clinical trials of medical devices in a blinded fashion, a sham procedure is sometimes selected as a control, which unfortunately carries the risk of adverse events. Therefore, there is a potential ethical issue in the use of sham

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procedures. Second, the control group for clinical trials of medical device development can involve currently available standard therapy, such as pharmacological treatment with a limited therapeutic effect on patients. Because the use of medical devices is generally invasive to the patient, superiority verification against standard medical treatment is indispensable, which may raise additional ethical issues for the establishment of a control group. At the same time, if the control group involves a widely accepted standard therapy, the clinical design of a medical device may involve non-inferiority verification. In this situation, concomitant therapy may be sufficiently different so that it is sometimes difficult to identify the main treatment effect of a medical device. In addition, the learning curve for the procedure to manipulate the device must be considered. Immature technical operation could compromise the best treatment result of the procedure. Finally, because devices are frequently modified in the short term of their life cycle, device models may change even throughout a clinical trial. Therefore, interpretation of the study results may be ambiguous even if a prospective randomized trial is conducted. Generally, the functional mechanism of a medical device is well evaluated by bench testing or animal studies before it is used in clinical trials. Therefore, adverse events from the device can be reasonably understood before human clinical trials are initiated. Accordingly, standard prospective randomized double-blind trials for medical device development are less common. Single-arm trials are often preferred.

From January through December 2016, 53 new or modified medical devices whose application included clinical evaluation were reviewed by the Office of Medical Device at the PMDA. The method for evaluating the clinical effectiveness and safety is shown in Figure 1a. Only 23% of the clinical trials were prospective randomized trials compliant with good clinical practice (GCP). Fifty-six percent of the items had an attachment of a single-arm trial compliant with GCP. With regard to the design of prospective randomized trials, there was only one sham procedure controlled trial (Figure 1b). This exceptional example was a trial of thermal ablation for idiopathic essential tremor that is refractory to medication. In this case, the major endpoint of the effectiveness for tremor was a numerical rating scale that has variability based on the observer. Therefore, blinded control data were essential for sound scientific evaluation. Figure 1c presents how to establish the control group or performance goal in single-arm trials. Device companies adopted the GCP-compliant raw data of previous clinical trials to which they belonged in their own database in 33% of cases, and the performance goal was established by a survey of multiple publications in 33% of cases. Seventeen percent had clinical trials that compared post-treatment results with pre-treatment values and essentially had no control group.

This survey showed how clinical trials in medical device development differ from standard methods. For a single-arm clinical trial, performance goals must be established with a statistical basis. This can be developed from the results of multiple peer-reviewed publications, although patients' background is not matched with those in the single-arm trial. It is more reliable and robust to establish a control group if patient-level data on a previous generation of the device are available. The accumulation of patient-level data can contribute to a high-quality control group and significantly facilitate medical device development. It is reasonable to

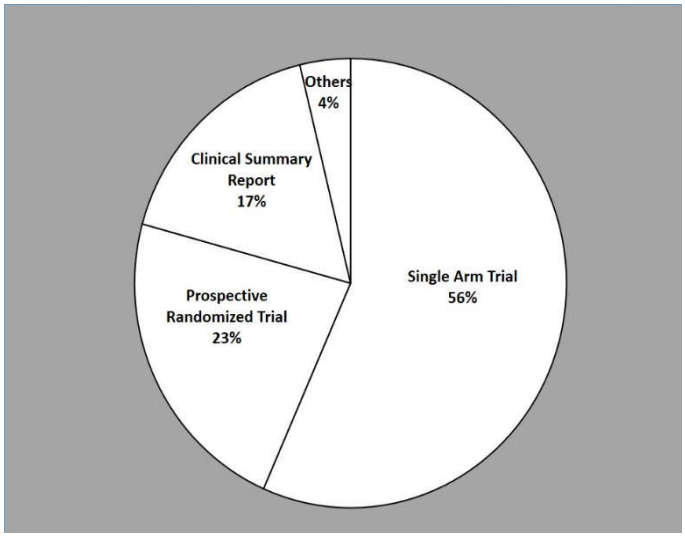

Figure 1a. Upper image: Clinical trial design of 53 brand new or modified medical devices approved from January through December 2016 by the Pharmaceuticals and Medical Devices Agency (PMDA)

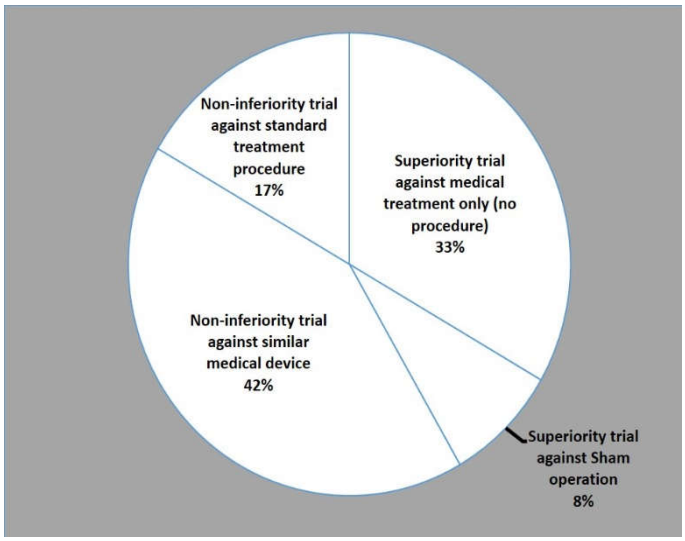

Figure 1b. Bottom left image: Clinical trial design of 12 prospective randomized trials of medical devices approved from January through December 2016 by PMDA

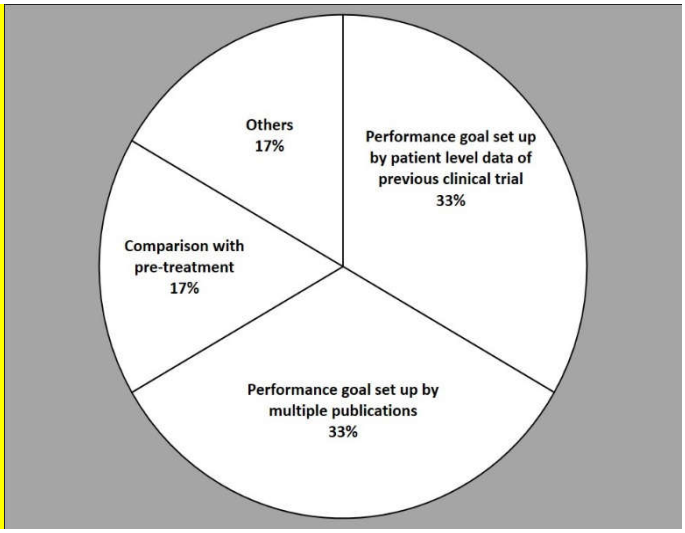

Figure 1c. Bottom right: Control group of single-arm trial of brand new or modified medical devices approved from January through December 2016 by PMDA

assess the difference between a product that applies for approval and one of the previous generation. Device identification in any medical device (the specification of the device generation in any modification) is essential even if the number of a specific device model provided to the market is small. Several existing registries in Japan provide a strong tool for identifying the exact generation of devices as well as real-world clinical data in the market. The availability of reliable and robust data is particularly useful for permanently implantable medical devices. The PMDA has already utilized registry data for post-marketing safety operations, such as case surveillance of left ventricular assist devices and bio-prosthesis of trans-catheter aortic valve replacement, as a control group in a clinical trial of certain medical devices.A recent publication from the US Food and Drug Administration disputed the effective utilization of real-world data, including registries, claims data and other electronic health information (Rachel, 2016). In Japan, the MHLW and PMDA in collaboration with academic societies lead the initiatives of the "Clinical Innovation Network (CIN)," which promotes the development of registries that are useful for regulatory decision making. At present, discussion is ongoing in CIN regarding good registry practice. The PMDA has participated in the International Medical Device Regulators Forum, which involved discussion of the assessment of data quality and the framework of registry utilization (http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-160930-principles-system-registries.pdf and http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-170316-methodological-principles.pdf). The PMDA recognizes that the appropriate method to collect reliable and robust data based on the registry has the potential to facilitate the pre-market and post-market balance because medical device development is a lifecycle.

The MHLW and PMDA intend to move toward a fast-track approval scheme and controlled release of certain new medical devices to the market after conditional approval if benefits and risks can be reasonably proven from the available clinical data and an appropriate risk management plan is prepared.

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