

Provisional Translation (as of October 2020)

Administrative Notice
November 17, 2017

To: Pharmaceutical Administration Section, Health Departments (Bureaus),
Prefectural Governments

Medical Device Evaluation Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare

Release of Clinical Trial Guidance to Facilitate the Speedy and Accurate Approval and
Development of Medical Devices

Because medical devices are frequently upgraded or improved in various respects, those who intend to develop medical devices must assess the necessity of conducting clinical trial(s) based on evaluation of the features of the device candidate and also examine the design of the potential clinical trial, including the target population size.

In the “Research on Desirable Guidance to Facilitate the Speedy and Accurate Approval and Development of Medical Devices” (Research Representative: Shohei Nakano, Executive Director of the Japan Association for the Advancement of Medical Equipment. FY 2016 Grant by the Japan Agency for Medical Research and Development (AMED) for Research on Regulatory Science for Pharmaceuticals and Medical Devices), we sorted and analyzed concepts on necessity of clinical trials, appropriate clinical trial design, and the conduct based on the previous approved cases from the viewpoint of facilitating efficient development of medical devices. Here, we have organized “Clinical Trial Guidance to Facilitate the Speedy and Accurate Approval and Development of Medical Devices” as provided in the appendix.

The Ministry of Health, Labour and Welfare (MHLW) requests your cooperation in notifying all relevant business entities under your jurisdiction that this guidance and the attached reference materials should be consulted in conjunction with the development of medical devices.

Please note that copies of this Administrative Notice will be sent to the Japan Federation of Medical Devices Associations, the Medical Devices and Diagnostics Subcommittee of the American Medical Devices and Diagnostics Manufacturers’ Association in Japan, the Medical Devices and IVDs Committee of the European Business Council in Japan, the Chief Executive of the Pharmaceuticals and Medical Devices Agency (PMDA), and the Japan Certification Council for Drugs and Medical Devices.

* This English version of the Japanese Administrative Notice is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

Clinical Trial Guidance to Facilitate the Speedy and
Accurate Approval and Development of Medical Devices

March 2017

Preface

Movements to promote the commercialization of innovative, pioneering medical devices are becoming increasingly active. The international development will take on more importance to deliver innovative medical devices with global need to patients as swiftly as possible.

The key to promote the commercialization of world-leading innovative medical devices in Japan and establish global position of Japan-originated medical devices is how to proceed with international development and multinational clinical trials. It is therefore important to understand the characteristics of clinical trials for medical device development at a global level.

In addition, assessment of benefit risk balance for the clinical efficacy and safety is important in medical device review. Furthermore, consideration for timely access of patients to better clinical practices using medical devices has become a new social request.

For medical devices, accumulation of the clinical experience often reveals points to be upgraded for improvement of the clinical efficacy and safety. Accordingly, the important actions considered from the viewpoint of lifecycle management of medical devices are to proceed with the initial approval and marketing as soon as possible and thereby to accelerate subsequent accumulation of clinical results, which can lead to upgrading for improvement of clinical efficacy and safety or to development of the next generation medical devices.

From this viewpoint, early marketing of medical devices, especially ones designed to satisfy the unmet medical needs related to serious diseases, should be promoted even with limited pre-marketing clinical data, while the benefit risk balance of the medical devices is being kept by ensuring consistent pre- and post-marketing actions under the risk management plan, which intends to implement post-marketing risk management thoroughly and to instruct careful use until adequate clinical results accumulate.

Furthermore, the importance of post-marketing registry data has been increasing for appropriate lifecycle management of medical devices through efficient post-marketing safety measures. We expect that medical devices satisfying the needs in clinical practices can be developed, if real-world evidence obtained from Japan-original post-marketing use-results surveys and academia-initiated registry data is promptly presented to clinical practices, and consistent pre- and post-marketing actions ensure the clinical safety and efficacy.

Because necessity of clinical trials is one of key factors that determine development speed of a medical device, well-defined development of medical devices according to their individual characteristics and their evaluation will promote multinational clinical trials, which facilitate efficient development, and first-in-human (FIH) studies, which facilitate development of innovative medical devices. Furthermore, such development ensures effective allocation of development budget.

From the above standpoint, we have discussed concepts on necessity of clinical trials based on features of a medical device and desirable pre- and post-marketing clinical data with experts from industry, academia, and government and compiled our opinions into this clinical trial guidance to define the above concepts as a practical means that embodies desirable development and evaluation of medical devices in the future.

Shohei Nakano

Research Representative, Japan Association for the Advancement of Medical Equipment

Table of Contents

1.	Introduction.....	1
1.1.	Background and Objectives	1
1.2.	Positioning of this guidance.....	2
1.3.	Glossary	2
2.	Determination of necessity of clinical trials of medical devices.....	3
2.1.	Basic concept.....	3
2.2.	Prior investigation.....	4
2.2.1.	Development concept	4
2.2.2.	Clinical positioning.....	4
2.2.3.	Differences from approved similar medical devices.....	5
2.2.4.	Conceptual requirements	6
2.3.	Details of investigation	6
2.3.1.	Coverage of the data	6
2.3.2.	Example cases where no clinical trials are necessary (trial-unnecessary cases).....	6
2.3.3.	Handling of results from clinical trials in foreign countries	6
3.	Basic concepts on clinical trial design and sample size.....	7
3.1.	Concept on clinical trial design.....	7
3.2.	Concept on sample size.....	8
3.3.	Other points to consider.....	8
4.	Pre- and post-marketing actions.....	9
[1]	Conditional Early Approval System for Innovative Medical Devices (note: situation as of July 2017)	10
[2]	Handling of clinical trials for evaluation of compatibility with medical environment in Japan	10
[3]	Handling of clinical trials of improved medical devices in which clinical additional value is quite small and thus unlikely to raise a serious risk	11
[4]	Evaluation of diagnostic devices that measures physiological parameters to obtain potential reference information for diagnosis	12
5.	Conduct of good clinical trials and quality control of clinical trial data.....	13
6.	Conclusion	13

Major relevant notifications	15
Exhibit Document 1: Cases where no clinical trials are necessary (trial-unnecessary cases)	17
Exhibit Document 2: Sample size of clinical trials (related to Section 3.2).....	23
<<Medical devices in cardiovascular field>>	24
<<Medical devices in orthopedic field>>	28
<<Other medical devices>>	29
Study Group Members Contributing to the Clinical Trial Guidance	31

1. Introduction

1.1. Background and Objectives

In line with the “Strategy for Rebirth of Japan” decided by the Cabinet on July 31, 2012, “Act on Research and Development of Medical Devices as well as Promotion of their Use for Improvement of Quality of Medical Treatment Provided to Japanese Citizen” (abbreviated to “Medical Device Promotion Law”) was promulgated in June 2014, and “Master Plan based on Medical Device Promotion Law” was decided by the Cabinet in May 2016. This plan is the government’s first master plan that is specialized in medical device policies and comprehensively covers ministerial measures corresponding to each stage. Movement toward promotion of world’s leading commercialization of Japan-originated innovative medical devices has been increasingly activated. Measures to promote development of medical devices utilizing a clinical research core hospital in the National Strategic Special Zone have been taken to push forward medical innovation in this zone.

If the medical device under development is obviously different from the existing medical devices in terms of the performance and structure (new medical device), attachment of clinical trial results will be required in principle. Many of the medical devices under development, however, are not completely new in clinical settings, and in fact the clinical efficacy and safety of these medical devices can be evaluated in non-clinical studies.

The scope where clinical trials of a medical device are necessary (hereinafter referred to as “necessity of clinical trials”) has been provided in “Scope of Cases where Medical Device Clinical Study Data is Necessary” (PFSB/ELD/OMDE Notification No. 0804001, by the Director of the Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare (MHLW), dated August 4, 2008) (hereinafter, the “Fundamental Notification on Clinical Studies”). Necessity of clinical trials of medical devices shall be comprehensively determined based on their individual properties, comparability to the existing medical devices, and non-clinical study results. It means that clinical trials should be conducted if evaluation on clinical efficacy and safety of the medical device is not possible with results from performance tests and non-clinical studies such as animal studies or the existing literature. Because medical devices vary widely, the concepts on necessity of clinical trials and clinical trial plan (design and sample size corresponding to the objective) are not necessarily uniform. Especially, quantities of medical devices produced and distributed are relatively smaller than those of drugs, and thus utmost clarification of the criteria for necessity of clinical trials even in consideration of feasibility may promote their development.

For medical devices which are highly needed in medical practices but of which development is not progressed in Japan, measures have been taken to increase opportunities of their product introduction. The existing systems to promote development of medical devices include: The designation system of medical devices for rare diseases that is intended to promote development of medical devices of which development is not adequately progressed in Japan due to the limited number of patients; the selection system that was proposed by “Study Meeting for Accelerated Introduction of Medical Devices Highly Needed in Medical Practices” which investigates medical devices highly needed in medical practices in Japan and thus qualified for accelerated introduction in consideration of requests from academic societies; and SAKIGAKE Designation Scheme that was established as a part of the June 2014 “Strategy of SAKIGAKE as a Package” by the Ministry of Health, Labour and Welfare and is intended to grant approval as soon as possible by providing various supports to medical devices which are developed in universities and research institutes in Japan before any other countries in the world and expected to have remarkable clinical efficacy. Furthermore, the Ministry of Health, Labour and Welfare issued the “Meeting for Promotion of Start-up Companies Assuming Medical Innovation” report in July 2017. This report proposed to establish a system that accelerates commercialization of medical devices with difficulties in clinical development (“Accelerated Approval System for Innovative Medical Devices”) by minimizing burden related to conduct of pre-marketing clinical studies but reinforcing post-marketing risk management from the viewpoint for prompt supply of innovative medical devices. In this way, scrupulous actions have been taken.

In addition, the reviewing authority in charge of medical devices, which aims to be an organization with

world-leading abilities in an era of globalization, has been pursuing promotion of multinational development in cooperation with the regulatory authority in the US. FDA to establish an environment in which corporations involved in medical devices in Japan can proceed with international development. For this aim, the reviewing authority also has been strengthening partnerships with the reviewing divisions and post-marketing safety management divisions.

As described above, movement toward promotion of commercialization of innovative medical devices and establishment of a development-encouraging environment has been activated. We discussed the clinical trial guidance that would define handling such as necessity of clinical trials of medical devices in the “Research on Desirable Guidance for Clinical Trials Required for Speedy and Accurate Approval and Development of Medical Devices” (Grant of Japan Agency for Medical Research and Development in FY 2016 for Research on Regulatory Science of Pharmaceuticals and Medical Devices) and have organized the guidance as provided below.

The objective of this guidance is to promote development of medical devices in Japan by sharing the concept on necessity of clinical trials in approval medical device review and common matters across various fields among the government, academia, and industry for more efficient commercialization of medical devices.

This guidance is expected to optimize time and resources invested in development and medical device review and to expedite marketing of desirable medical devices through shared understanding among the government, academia, and industry.

1.2. Positioning of this guidance

This guidance has been prepared based on notifications related to clinical trials including the Fundamental Notification on Clinical Studies to assist their concepts. That is, this guidance does not comprehensively cover theoretical matters or points to consider, but provides practical instructions about currently acceptable concepts on necessity of clinical trials in approval medical device review and common matters across various fields. In addition, this guidance also includes discussions and direction of the investigation for desirable clinical trials in the study group.

Accordingly, this guidance may be revised in response to future technical innovation or based on accumulation of knowledge, and thus it is not binding. Clinical evaluation of medical devices requires adequate understanding of characteristics of the individual medical devices and has to be conducted flexibly based on scientific rationality.

It is recommended to proceed with development of a medical device by utilizing various consultation services offered by the Pharmaceuticals and Medical Devices Agency (PMDA) even at the early stage where it is necessary to solve problems related to development and the application for approval.

In this guideline, a “clinical trial” is a clinical study conducted in accordance with GCP in Japan and/or foreign countries to acquire the marketing approval and do not include clinical evaluation reports based on literature. For the clinical evaluation reports, refer to “Handbook for Preparation of Clinical Evaluation Reports and Documents for Clinical Evaluation Consultation”, which is provided as a major notification.

1.3. Glossary

The terms used in this guidance shall be defined as follows.

- Clinical results: All the clinical experiences with the medical device
- Clinical data: All the data on the clinical safety and efficacy in clinical use of the medical device
- Clinical evaluation: Comprehensive evaluation and analysis of the clinical data
- Clinical trial: Clinical study that is conducted in accordance with GCP under the Pharmaceutical Products and Medical Devices Act and is aimed at collecting data related to results

from a clinical study, which are included in the data submitted in application for marketing approval.

- Pivotal clinical trial: Clinical trial positioned as the most predominant study to assess clinical efficacy and safety of medical devices in clinical evaluation
- Clinical research: Medical research in humans that is not a clinical trial

2. Determination of necessity of clinical trials of medical devices

2.1. Basic concept

Medical devices are used for diagnosis, treatment or prevention of diseases and thus have to be evaluated for clinical efficacy and safety. On the other hand, many of the medical devices are not completely new because they have been developed through progressive improving or improved. This means that some medical devices can be evaluated for clinical efficacy and safety based on clinical evidence accumulated for similar medical devices or non-clinical study results without collection of new clinical study results.

Accordingly, determination for is greatly influenced by assessment for novelty of the medical device and contents required for evaluation of the clinical efficacy and safety (conceptual requirements). More specifically, it is critically important to clarify a history of development and concept of the medical device to be developed and to investigate differences from similar medical devices, and thus a person who intends to develop the medical device (applicant) should organize such information even at the early stage of the development.

Furthermore, because a clinical trial is an interventional study in humans and investigative, ethical principles must be observed. In addition, because conduct of a clinical trial may need extensive time, cost, and resources, it is vital to identify clinical data necessary for efficient development of the medical device. To this end, applicants shall comprehensively evaluate the medical device based on animal studies, non-clinical studies, existing clinical data, and literature and carefully investigate what means can be taken to ensure access of the medical device to patients as soon as possible.

This guideline provides fundamental matters applied to the investigation for determination of necessity of clinical trials based on characteristics of the medical device. Where necessary, applicants is recommended to use PMDA's service, consultation about necessity of clinical studies.

Investigation flow is provided in a chart below.

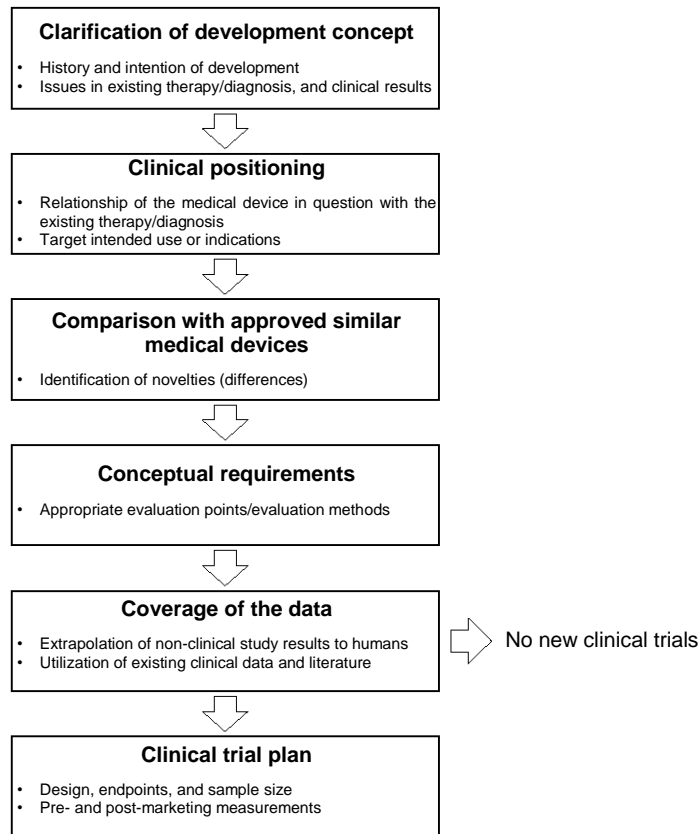


Figure. Flow of medical device development and clinical evaluation

2.2. Prior investigation

2.2.1. Development concept

Firstly, intention and design concept of development of the medical device shall be clarified based on background and history leading to decision of the development, natural history of the target disease (presence or absence of the existing therapy, and treatment course of the existing therapy), or actual situation in clinical settings (clinical results), severity of the disease, and current development status in and outside of Japan.

2.2.2. Clinical positioning

Clinical positioning means the aim to use the medical device or the effect provided by the medical device while characteristics of disease and patient or any other conventional therapies and diagnostics are considered. Also, the clinical positioning means the difference of performance, etc., the priority of the treatment to be undergone with the medical device (e.g. The therapy using the medical device to be developed is recognized as second line of therapy, if other conventional therapies not using the medical device in question are undergone as first line of therapy.), when the therapy using the medical device to be developed is compared with any other therapies. The character of the medical device is determined based on the clinical positioning. Therefore, the clinical positioning is directly related to the “Intended use or Indication” in the application for marketing approval. The clinical positioning shall be explained in such a manner that a third party can objectively and easily understand the expectations for the medical device to be developed. More specifically, the explanation shall cover expected relations of the medical device in question to the existing therapy or diagnosis (novelty of the medical device in question; clarification of improved points; role of the medical device in question in relation to the existing therapy or diagnosis, for instance, it is to be used as a replacement or used concurrently as an ancillary); clinical outcome expected to be improved; and expected indications in the case of a treatment device such as mortality decline, functional improvement, alleviation of symptoms, improvement of quality of life, and probability reduction of impairment; or expected indications in the case

of a diagnosis device such as detection of diseases, prediction of onset, diagnosis of diseases, and identification of patients potentially responsive to a particular therapy.

The clinical positioning of a medical device has a substantial impact on the post-approval marketing strategy because it will be a key determining factor for necessity of clinical trials as well as study design and primary endpoint in planning of clinical trials and also is related to the “Intended use or Indications”.

Points to investigate clinical positioning of a medical device to be developed are listed below to help development companies in organizing the information.

<Points to investigate for clinical positioning>

- Type: The medical device is expected to be used for treatment or for diagnosis.
- Mechanism of action or principle: How the medical device works to achieve what (novelty if the technology is new)
- Target diseases: Characteristics of the diseases such as severity, onset timing (acute or chronic), and the other therapeutic or diagnostic options (presence or absence)
- Actual situation of the existing therapy or diagnosis in clinical settings (clinical results)
- Relations of the medical device to the existing therapy or diagnosis: Role of the medical device in relation to the existing therapy or diagnosis. For instance, it is expected to be used as a replacement of the existing therapy or diagnosis, or used concurrently with the existing therapy or diagnosis to improve the therapeutic or diagnostic effect; it is expected to delay the time to invasive treatment or diagnosis; it is expected to assist the existing therapy or diagnosis; or it is expected to provide new therapeutic or diagnosis means to the disease for which no effective therapy or diagnosis is available.
- Effect obtained from the action (clinical significance):
 - ✓ Treatment: Mortality decline, functional improvement, alleviation of symptoms, improvement of quality of life, probability reduction of impairment, or symptomatic treatment or radical treatment
 - ✓ Diagnosis: Detection of diseases, prediction of onset, diagnosis of diseases, assistance of diagnosis, or identification of patients potentially responsive to a particular therapy
- Improvement of clinical efficacy or safety in comparison with the existing therapy
- Duration of the effect in comparison with the existing therapy: Predicted duration of benefit
- Differences in clinical positioning in Japan (in the case of the medical device developed in foreign countries): Differences in clinical positioning due to differences in medical environment in foreign countries (for instance, differences in concurrent therapies, priority order of therapies, differences of the user (doctor or technician)).

2.2.3. Differences from approved similar medical devices

If there are medical devices similar to one to be developed in terms of the structure, specifications, or use method, applicants shall clarify presence or absence of differences between the medical device to be developed and the similar medical devices (what are new in comparison with the similar medical device) and relationship to the development concept.

For this clarification, the information shall be organized using the comparison table below to determine whether details such as intended use, structure, principle, and energy output of the medical device to be developed are the same as or different from those of the similar medical devices. Whether the differences identified by the above activity can be evaluated only in non-clinical studies or not will be a key point in determination of necessity of clinical trials on the following page.

Table Comparison table with similar medical devices

Item	Proposed medical device	Similar medical device 1	Similar medical device 2	Information about the differences
Generic name				
Brand name				
Marketing authorization holder				
Approval number				

Date of approval				
Intended use or indications				
Shape, structure				
Principle				
Raw materials				
Performance and safety specifications				
Use Method				
Storage method and shelf life				
Manufacturing method				
Remarks				

Note) Select the appropriate items for comparison according to characteristics of the proposed medical device so that the differences from the similar medical devices can be clarified.

2.2.4. Conceptual requirements

Conceptual requirements are necessary evaluation points of the efficacy and safety of the medical device developed. In addition, appropriate evaluation methods based on features of the medical device shall be investigated. The differences from the approved medical devices shall be individually subjected to risk analysis followed by appropriate evaluation. Especially, if the medical device to be developed is completely new, comprehensive evaluation shall be made to ensure clinical efficacy and safety, using the existing evaluation methods too. Whether non-clinical studies adequately cover the conceptual requirements or not will be a key point in determination of necessity of clinical trials.

2.3. Investigation details

2.3.1. Data coverage

The applicant shall make a comprehensive clinical evaluation based on non-clinical study results from performance test and animal studies or existing clinical data and literature in consideration of the development concept, clinical positioning, differences from the approved similar medical devices, conceptual requirements. If there is an endpoint that has not been evaluated but is evaluated only in a clinical trial, a new clinical trial has to be conducted. For some of the medical devices of which application for approval requires submission of clinical study data, clinical evaluation only based on the clinical evaluation reports is acceptable.

2.3.2. Example cases where no clinical trials are necessary

Example cases where no clinical trials are necessary are provided in Exhibit Document 1. Because these example cases are just representative ones, actual trial-unnecessary cases are not necessarily limited to these. In addition, because they are ones considered applicable at present, the other cases may be also considered to be trial-unnecessary later, if future technological progress, advancement of non-clinical study method, or accumulation of clinical data demonstrates clinical usefulness at a substantial probability, indicating that non-clinical study results can ensure clinical efficacy and safety.

On the other hand, it should be noted that a case considered applicable to the above trial-unnecessary example cases is found trial-necessary due to novelty of the medical device.

From the viewpoint of further shared understanding, the government, academia, and industry should continue the investigation of such cases in collaboration, and make revision or addition as appropriate.

2.3.3. Handling of results from clinical trials in foreign countries

Under “Handling of Results from Clinical Studies of Medical Devices Conducted in Foreign Countries” (PFSB/ELD/OMDE Notification No. 0331006, by the Director of the Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated March 31, 2006),

data related to results from clinical studies conducted in accordance with the clinical practice standards in foreign countries are accepted if the standards in question are at least comparable to the medical device GCP. If results from clinical studies in foreign countries are available, necessity of clinical trials in Japan should be investigated in consideration of compatibility with the medical environment.

For realization of expedited access of the medical device to patients in Japan, it is particularly important to consider conducting a multinational clinical trial including Japanese, especially if the proposed medical device is completely new, and the clinical development has just started. For this purpose, differences between foreign countries and Japan should be taken into account even at the development stage.

Basic concept on conduct of a multinational clinical trial has been already provided in a counterpart guideline for drugs. For medical devices, ethnic factors (intrinsic and extrinsic factors) should be taken into account as with drugs. Ethnic factors that should be taken into account for medical devices are as follows:

- 1) Intrinsic factors: Ethnic differences (for instance, differences in body size, morphological differences such as bone thickness, disease type, differences in metabolic system for medical devices containing drugs)
- 2) Extrinsic factors: Novelty of procedures, differences in concurrently used drugs and devices, differences in standard therapy, differences in medical affairs (situation of transplantation therapy, extent of the prevalence of similar procedures, differences in qualification of healthcare professionals, and differences in aspects to therapy and intervention), differences in social background, lifestyle, and differences in cultural background

If the clinical efficacy and safety in Japan are evaluated based on results from clinical studies in foreign countries, and non-susceptibility of the clinical study results to differences between foreign countries and Japan is not adequately justified, the necessity of clinical trials in Japan shall be investigated in accordance with “2.3.1 Coverage of the data.”

3. Basic concepts on clinical trial design and sample size

3.1. Concept on clinical trial design

A clinical trial shall be planned as follows: Endpoints and objective of the clinical trial shall be defined in consideration of the intended use to be approved and clinical positioning; and then effective clinical trial design (single-arm, parallel-group, or crossover study) should be invented according to its position in the development plan overall (exploratory or confirmatory clinical trial), also in consideration of collection of pre-marketing and post-marketing clinical data.

Although an exploratory clinical trial is not always required for application for approval of a medical device, conduct of the exploratory clinical trial may efficiently facilitate development because such trial potentially enables stabilization of the procedure, identification of applicable patients, and establishment of an appropriate primary endpoint in the development process of a medical device, in which progressive upgrading of the design as well as investigation of target subjects and examination of related procedures take place in parallel in some cases.

A confirmatory clinical trial is desirably conducted in a randomized controlled trial (RCT) design because this evaluation method relatively reduces bias and thus is considered to provide quality results. By contrast, evaluation in a single-arm study may be acceptable if accumulated clinical evidence allows an applicant to establish the target result to be achieved appropriately; factors that affect the clinical study results are identified to some extent; and consensus has been reached for endpoints and results to be evaluated in the clinical study. If historical data or registry data are used as control results, the use in question should be justified based on applicable patients, intended use, and clinical positioning.

The primary endpoint shall be established to be as objective in clinical settings as possible in consideration

of the intended use of the medical device and clinical significance. If a surrogate endpoint is used as an endpoint, use of the surrogate endpoint in evaluation shall be justified, including a relationship to the true endpoint.

For a controlled study design, considerations should be given to ensuring clinically appropriate setting of the control group (active-device control, placebo, conservative treatment, surgical treatment, etc.) and use of an appropriate bias-minimizing method (randomized, blinded, etc.) according to the objective of the clinical trial.

3.2. Concept on sample size

Sample size appropriate for evaluation of the clinical efficacy and safety should be established based on statistical rationale in consideration of the objective of the clinical trial and primary endpoint. If the sample size is established in additional consideration of feasibility of the clinical trial, the clinical significance should be explained. For an exploratory clinical trial, the sample size may be established in consideration of what can be evaluated at an assurance level, but not necessarily based on statistical rationale.

If the proposed medical device is involved in a particular circumstance, for instance, it is a medical device for rare diseases which patients are extremely limited (that is, ultra-orphan device), the target sample size may be determined through in-depth discussion with experts in the field in question and consultation with MHLW and PMDA. In the above discussion and consultation, what sample size makes the clinical trial feasible and is enough size for evaluation of the clinical safety and efficacy of the medical device.

In a clinical trial including the limited number of subjects, impacts of differences and variations in subject condition and doctors' skill cannot be appropriately removed, and thus data from each subject may have a substantial impact on the overall evaluation result of the medical device in question. If an event of which actual frequency is low occurs in a clinical trial including the limited number of subjects, the frequency may appear to be high due to the small population parameter. When planning a clinical trial including a limited number of subjects, applicants should examine adequately if the sample size is appropriate, paying attention to such a possibility.

(Reference)

Analysis on new medical devices (48 products) approved between FY 2010 and FY 2014 showed the mean registered sample size for pivotal clinical trials was 216.6 subjects for controlled studies (median, 120) and 92.8 (median, 50) for single-arm studies. The sample size, however, largely differed depending on clinical positioning and novelty of the medical device and study design.

In addition, Exhibit 2 provides reference cases including the registered sample size for clinical trials (mainly pivotal studies) of approved medical devices (for details, refer to review reports and package inserts of the medical devices in question). It should be noted that the above exhibit provides only particular cases and thus cannot be used as anything other than a reference material because the number of collected cases is limited, a clinical trial design largely differs depending on features and novelty of the medical device, a history of the development, non-clinical study results, characteristics of the therapy, presence or absence of similar medical devices, and presence or absence of data on similar therapy.

3.3. Other points to consider

- 1) If long-term results are presumed to become available around the evaluation time point for the primary endpoint, applicants may prepare a final study report after evaluation of the primary endpoint and submit the application form for approval during the clinical trial. The above application strategy may be applicable to medical devices requiring long-term follow-up period such as initial coronary drug-eluting stents, of which the primary follow-up period was 1 year, but the long-term follow-up period was 5 years. In such a case, applicants shall submit updated data during the review process between the application for approval and the approval as appropriate. It should be noted that the primary follow-up period and long-term follow-up period are individually determined according to a history of the development of the medical device in question and development status of similar medical devices.

- 2) Unlike drugs, medical devices are subject to model change during the development. If a design of the medical device used in a clinical trial is different from that in the application for approval, applicants shall clarify improved points and then justify extrapolation of the clinical evaluation on the medical device used in the clinical trial to that on the proposed medical device based on non-clinical study results. It should be noted that another clinical trial may have to be conducted if it is not properly justified.
- 3) Clinical trials results not only facilitate clinical positioning of the medical device and specification of the intended use or effect but also indicate value of the medical technology. When considering the medical device development plan or study design of a clinical trial, applicants should keep in mind that clinical trial data may be used in evaluation related to health insurance coverage.
- 4) In development of a medical device of which size variation is critical such as artificial heart valve, conduct of a multinational clinical trial including Japan may be appropriate from the viewpoint of sales strategy with expectations of its sales in countries where people have a similar body constitution to that of Japanese.

4. Pre- and post-marketing actions

A medical device is reviewed on the precondition that non-clinical and clinical study data are sufficient for evaluation of the clinical efficacy and safety as well as assessment of benefit risk balance, but in fact, it is difficult to explain completely malfunctions and adverse events experienced by actual patients in post-marketing various clinical environment only based on evaluation in the strictly controlled clinical trial conducted in particular subjects at specified medical institutions. Recently, post-marketing risk management and collection of safety information have become increasingly important. In addition, in consideration of total product lifecycle of medical devices, their actual use may reveal clinical usefulness other than initially expected. Expedited clinical use realized by early marketing potentially deepens clinical values, expanding the development strategy.

Meanwhile, medical devices meeting unmet medical needs related to serious diseases, especially, development itself is suspended in some cases because such devices have the limited patient population, are not profitable for companies, and impose substantial burden on the development due to prolonged clinical trials, etc. For medical devices that are highly needed in medical practices but have difficulties in development as mentioned above, their early commercialization should be promoted to accelerate the speed toward access to patients by supporting the development with benefit risk balance being maintained. For this purpose, consistent pre- and post-marketing actions should be ensured under the following risk management plan in view of total product lifecycle of the medical device so that pre-marketing regulatory requirements for approval can be met. The plan intends to implement post-marketing risk management thoroughly even if pre-marketing clinical data are limited and to instruct careful use until adequate clinical results accumulate; and then the above plan should be simultaneously checked in the review.

To minimize the pre-marketing development burden, while meeting regulatory requirements for marketing approval, applicants should give consideration to promotion of proper use and collection of post-marketing clinical data. The clinical safety and efficacy of medical devices can vary depending on appropriate selection of patients including anatomical requirements, actual procedure and use method, and actions on complications. Where necessary, consideration should be given to preparation of standards for proper use (requirements for doctors and facilities that use the medical device) in cooperation with related academic societies and measures for promotion of proper use such as training sessions for doctors under a proctor system. In addition, post-marketing clinical data collected through use-results survey and post-marketing clinical study results should be reflected in safety measures appropriately.

Consistent pre- and post-marketing actions can contribute to fulfillment of unmet medical needs and realization of timely access, but the actions should be taken on a case-by-case basis. It is therefore vital for the government, academia, and industry to proceed with development and investigation through substantial communication.

The following measures are considered effective in promoting the development, while ensuring consistent pre- and post-marketing actions, appropriately managing the total product life cycle of the medical device, and maintaining benefit risk balance of the medical device.

[1] Conditional Early Approval System for Innovative Medical Devices (note: as of July 2017)

To promote early commercialization of medical devices which can be recognized as new medical devices for serious diseases with no effective therapies available and have certain clinical data for evaluation but of which conduct of an additional clinical trial is considered difficult, “Conditional Early Approval System for Innovative Medical Devices” was introduced (PSEHB Notification No. 0731-1, by the Director-General of the Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated July 31, 2017). Under this system, the clinical safety and efficacy of the applicable medical devices are assessed in the review on the following precondition: The applicant shall implement post-marketing risk management appropriately under the condition of approval, which requires “Post-marketing Risk Management Plan for Medical Devices” that includes the standards for proper use prepared in cooperation with related academic societies and plan for collection and evaluation of post-marketing data.

If utilizing the “Conditional Early Approval System for Innovative Medical Devices”, applicants should clarify their specific development plan at the stage of design development, which covers pre-marketing evaluation to be implemented, method to collect post-marketing clinical data, and measures to promote proper use. Then, applicants shall prepare for the application by seeking partnerships with related academic societies and discussing with the reviewing agency through PMDA’s “pre-development consultation” and “consultation about necessity of clinical studies” offerings.

After approval, applicants shall collect clinical data through use-results survey in compliance with the standards for proper use including requirements for doctors and facilities that use the medical device.

Such accumulation of clinical data may allow applicants to consider adding facilities, and collection of real-world long-term clinical results may reveal further clinical significant and more appropriate target patients.

[2] Handling of clinical trials for evaluation of compatibility with medical environment in Japan

If the clinical efficacy and safety of a medical device have been verified in a pivotal clinical study in foreign countries, the clinical efficacy and safety in Japan will be evaluated in consideration of ethnic factors, and then necessity of clinical trials in Japan will be investigated (see Section 2.3.3). In addition to medical devices that have been developed in foreign countries and require completely new procedures, development in Japan would give rise to issues, mainly related to extrinsic factors such as prevalence of the procedures in question in Japan (including actions on complications). Therefore, whether the medical efficiency and safety are observed in the medical environment in Japan as done in pivotal clinical trial in foreign countries is evaluated in pre-marketing. And the appropriate post-market safety measurements are taken with reference to the medical evaluation in pre-marketing. Some of these medical devices, however, may be used in a safe and appropriate manner without evaluation in pre-marketing clinical trials if the medical device in question is used carefully in the specified facilities after marketing, and data collection and safety measures are appropriately in place.

More specifically, applicants may consult adequately with PMDA even at the early stage of the development in Japan about the following strategy to ensure the clinical safety and efficacy of the medical device in question, for instance: A clinical trial including the limited number of subjects is conducted additionally; instead of such a small trial, measures for ensuring the proper use and collection of post-marketing data are implemented in consideration of points in risk and benefit potentially affected by differences in medical environment between foreign countries and Japan. Important actions in such a case are to prepare the standard for proper use in cooperation with related academic societies of which members are supposed to use the medical device in question actually and to draw a training implementation plan for doctors. In addition to the above, the following actions will be assigned as conditions of approval: Initial data

collection plan in the specified facilities under post-marketing use-results evaluation system; setting of criteria for allowing additional facilities to use the medical device in question; and subsequent expanded data collection plan. If these measures are taken, the clinical efficacy and safety observed in studies in foreign countries may be ensured without necessarily conducting a national pre-marketing clinical trial. The above actions should be considered wherever applicable because they possibly contribute to reduction of the period to introduce medical devices approved in foreign countries in Japan as well as early access of such devices to patients in Japan. If the extrinsic factors identified as issues in such development mainly raise safety concerns due to not only complete novelty in the procedures but also concurrently used drugs or medical devices and differences in social background, or completely unknown, benefit risk balance should be evaluated before marketing, and additional clinical trials in Japan should be considered.

[3] Handling of clinical trials of improved medical devices in which clinical additional value is quite small and thus unlikely to raise a serious risk

Improved medical devices do not have novelty compared with new medical devices (medical devices of which structure, principle, usage method, indications, performance, etc. is clearly different from those of the existing medical devices), but are not practically equivalent to the existing ones in terms of structure, usage method, or indications. Of improved medical devices, ones that belong to the “Improved Devices requiring Clinical Trials” category, such as implants with modified surface coating and stent graft using thinner materials require clinical evaluation to verify the safety and efficacy related to upgrading.

For one part of these devices, improving-related differences from the existing ones are presumed to be unlikely to raise a serious risk, and non-clinical study results or accumulated clinical evidence can explain comparability of the clinical efficacy and safety to the existing ones. For some of them, however, clinical trials including the limited number of subjects are conducted as evidence of the above presumption, and based on results from actual use in humans, the safety and efficacy are confirmed.

For many medical devices, impacts of the structure and materials on human bodies are relatively definitive, and thus the safety and efficacy can be readily presumed in non-clinical studies, but for some of them, it is difficult to extrapolate the non-clinical study results directly to humans. Therefore, the safety and efficacy of improved medical devices are confirmed by conducting clinical trials described above, although applicability of the above clinical trials may depend on content or extent of the differences from the existing ones. That is, for an improved medical device, the following confirmation is required: It has been used in humans actually, and use in the limited number of subjects has not raised particular problems.

For medical devices that were improved from a currently marketed medical device with substantial clinical use results, of which the safety and efficacy are evaluated by comparison from the existing ones, and of which differences from the existing one are presumed to be fairly unlikely to raise a serious risk, however, if it is approved without use in humans before marketing, safety problems compromising benefit risk balance are fairly unlikely to occur after marketing. For a medical device in which various problems are likely to occur at the initial stage of introduction, and of which use in humans are completely lacking, on the other hand, benefit risk balance must be optimized. It is critical to identify issues specific to the medical device as soon as possible, and to take measures against them immediately.

Therefore, for the medical device in question, the following actions are considered to allow applicants to confirm consistent pre- and post-marketing safety and efficacy, and thereby to ensure the safety and efficacy irrespective of presence or absence of pre-marketing clinical trials: The medical device is used in a certain sample size at the initial stage of the introduction; and company’s medical representatives in charge of medical devices frequently visit each facility to collect detailed information about the safety and efficacy in clinical settings irrespective of presence or absence of malfunctions as to whether the safety or efficacy is the same as inferred from the non-clinical study results, or whether the risk reduction actions are effective. More specifically, the following actions may be considered.

For the medical device in question, pre-development consultation may be conducted to confirm the following matters and then identify potential issues in the review attributable to the fact that data from its use experience in humans are lacking. The consultation is supposed to confirm that the clinical safety and efficacy

are mostly evaluated based on the non-clinical study results or accumulated clinical evidence because differences from the existing ones are quite small; the medical device can be explained at high probability based on the principle, technique, and experience with similar medical devices; potential adverse events can be inferred from experience with similar medical devices; and the medical device is unlikely to raise a serious risk compared with the existing medical devices.

Then, based on results from the pre-development consultation, where necessary, applicants shall conduct additional non-clinical studies and organize additional information and literature about the similar medical devices. Again, they shall perform risk analysis by estimating potential risk (adverse events) in clinical settings based on the intended use of the medical device. Subsequently, they shall evaluate residual risk and overall acceptance of the risk and investigate the method for consistent pre- and post-marketing confirmation of the safety and efficacy using post-marketing risk control (post-marketing early safety information collection plan). It should be noted that the post-marketing early safety information collection plan is mainly intended to collect relatively short-term data on an improved medical device in which clinical additional value is quite small and thus unlikely to raise a serious risk and thereby confirm the safety and efficacy at the early post-marketing stage; and it is different from the use-results evaluation which mainly collects mid-to-long-term use results on a new medical device.

Then, they shall have PMDA's consultation about the necessity of clinical studies to proceed with discussions about appropriateness of post-marketing early safety information collection plan, which is to be used as a method for consistent pre- and post-marketing confirmation of the safety and efficacy.

Based on the results, they shall explain the "post-marketing early safety information collection plan" in the Risk Management section in the data to be submitted with the application form for marketing approval and then proceed with preparation for the application. Because the plan is to serve as post-marketing surveillance for use in actual clinical settings, this section shall include events to which special attention should be paid; period of and medical institutions subject to intensive information collection; method of information collection; planned time of reporting to PMDA, and method to reflect the collected information in the medical device.

After marketing, applicants shall actively collect information about the events to which special attention should be paid in accordance with the early safety information collection plan. For this purpose, they shall ask each medical institution to provide such information for a specified period at the time of launch. Then, applicants shall prepare a list of malfunction reports including events subject to intensive collection during the specified period, investigate necessity of actions to ensure the safety according to the reported malfunctions (revision of the package insert, necessity of additional precaution), prepare the report, and submit it to PMDA promptly.

[4] Evaluation of diagnostic devices that measures physiological parameters to obtain potential reference information for diagnosis

If the medical device to be developed is a device that measures physiological parameters which are considered to be potential reference information for diagnosis but of which relationships to clinical symptoms, pathological conditions, or physiological conditions have not been widely recognized, and thus the clinical significance or medical criteria have not been firmly established, an evidence-based explanation about clinical significance of the medical device in question is required for the development. These devices may contribute to advancement of medical practices and medical science through their extensive use. In the future, therefore, the following development strategy may be effective for these devices. Under consultation with PMDA, they may be approved for the limited intended use or indications which have been demonstrated by the previous clinical results and test results on mechanical performance (measuring performance), even if their final target clinical significance has not been established. When clinical evidence is established based on use experience in clinical settings after marketing, application for approval of partial changes is filed where necessary.

More specifically, for medical devices that meet the following characteristics, discussion with the reviewing agency through PMDA's pre-development consultation may be useful: [1] Non-invasive medical

device actively monitoring physiological indicators related to biological signals (biophysical phenomenon examination device, bioelectrical phenomenon examination device, biological phenomenon monitoring device, etc.); [2] medical device positioned as a device that provides one of several criteria as reference information for diagnosis; and [3] medical device that provides the information in question of which impact on the original diagnosis result is unlikely to raise safety concerns.

The above handling, however, may not be necessarily appropriate for medical devices of which examination or diagnosis technology has a substantial impact on medical judgment such as cancer therapy regimen, or which are involved in a developing field with new information increasingly becoming available day by day, such as genetic examinations because more detailed information is expected in clinical settings.

5. Conduct of good clinical trials and quality control of clinical trial data

- 1) To conduct a good clinical trial, all the individuals involved in the clinical trial (principal investigator, investigators) must adequately understand the concept of the clinical trial, including objective, design, and activities. To this end, the sponsor must sufficiently explain the concept of the medical device under development and clinical trial plan to each medical institution and physicians to obtain common understanding.
- 2) The sponsor shall conclude an agreement with medical institutions for details about recording and retention methods of source documents in advance because omission from records in source documents (records necessary for reconstruction and evaluation of the clinical trial) at medical institutions or inconsistency within source documents are not acceptable from the viewpoint of quality control of clinical trial data and efficient conduct of the clinical trial. The sponsor shall specify location of responsibility for retention of records and documents, record the fact in an accurate and objective manner, keep the information always current, and ensure the consistency. In addition, they shall control original copies of records and documents, and ensure that any correction in records can be identified by a person who has corrected it, the content, and date.
- 3) Medical institutions shall be fully aware that the clinical trial is scientific evaluation and then include subjects in compliance with the inclusion and exclusion criteria. For randomization, an appropriate method shall be used to ensure objectivity of the randomization (methods hardly ensuring objectivity such as an envelope method is not recommended).
- 4) Registration of cases non-conforming to the inclusion and exclusion criteria may compromise quality of the clinical trial and result. Actions such as use of a third-party evaluation in case assessment shall be taken where necessary.
- 5) If a long-term or large-scale clinical trial plan is considered, the sponsor shall take appropriate actions to achieve quality clinical trials, being aware that appropriate control of the clinical trial is critical in ensuring quality of the data. For instance, the sponsor may confirm the clinical trial protocol with each medical institution before the conduct, and then implement inspections at a certain interval during the trial to see if the clinical trial is conducted appropriately.

6. Conclusion

For continuous creation of innovative medical devices, company-initiated development strategies will be increasing important. That is, the expected strategy is that efficient development focused on the total product lifecycle of medical devices facilitates the next development. In addition, the development strategy should cover sales strategy and insurance reimbursement in advance.

Especially, positioning of international development and post-marketing measurements will be further increasingly important. Companies are required to develop more effective and safe medical devices basically

by conducting high-quality clinical trials but also utilizing measures to ensure post-marketing compliance with standards for proper use and post-marketing evidence in clinical settings (Real World evidence), which are collected through use-results evaluation and post-marketing clinical studies. For post-marketing proper use and collection of clinical data, further cooperation and partnerships among academic societies, medical institutions, and companies are necessary. These cooperative activities become increasingly important from the viewpoint of advancement of medical practices.

Recently, in addition to company-initiated use-results evaluation, construction of post-marketing registry under cooperation among industry, academia, and government has been gaining a key position. Well-designed quality post-marketing registries may contribute to prompt implementation of safety measures, optimization of treatment for patients, understanding of true performance of a medical device, and development of the next generation medical devices. Post-marketing registries under cooperation among industry, academia, and government (J-MACS, J-TVT registry, etc.) have been already operated in Japan. In the future, usefulness of the evidence obtained from the registries will be investigated with expectations for more efficient operations of high-quality registries.

In addition, establishment of clinical trial environment in Japan has increasingly gained in importance to promote global clinical trials further aiming at the international development. For instance, the following actions are expected: Further international regulatory harmonization and compliance inspection; reduction of clinical trial-related cost; strengthening of cooperative system between PMDA and the US FDA toward use of single protocol; establishment of development infrastructure for a database in which disease registry or genome information is matched with related clinical information; and incentives to conduct of global clinical trials.

More than 10 years have passed since establishment of PMDA, and during this period, reinforcement of the review system for medical devices and accumulation of review cases have been implemented. The current review period taken PMDA has become comparable to that of the US FDA. This is one of the achievements of medical institutions, industry, Ministry of Health, Labour, and Welfare, PMDA which have been striving to make progress in medical practices. That is, the reviewing regulatory authority in charge of medical devices in Japan has been becoming an organization with world-leading abilities through experience with approval reviews of various innovative medical devices. This guidance was also prepared to reflect PMDA's reviewing experience and completed through multiple discussion sessions among the government, academia, and industry. Superior medical devices are necessary not only for healthcare professionals at present but also for future healthcare professionals and patients in the next generation. All the government, academia, and industry individuals concerned should be aware of such needs, and the strong awareness leads to advancement of medical practices.

We strongly expect that this guidance is reviewed at a certain interval, and an environment that allows continuous creation of innovative medical devices is further encouraged.

Major relevant notifications

- “Application for Medical Device Marketing Approval” (PFSB Notification No. 1120-5, by the Director-General of the Pharmaceutical and Food Safety Bureau, MHLW, dated November 20, 2014)
- “Points to Consider for Preparation of Medical Device Marketing Approval Application” (PFSB/MDRMPE Notification No. 1120-1, by the Director of the Medical Device and Regenerative Medicine Product Evaluation Division, Pharmaceutical and Food Safety Bureau, MHLW, dated November 20, 2014)
- “Points to Consider for Preparation for Attached Data to Medical Device Marketing Approval Application” (PFSB/MDRMPE Notification No. 0120-9, by the Director of the Medical Device and Regenerative Medicine Product Evaluation Division, Pharmaceutical and Food Safety Bureau, MHLW, dated January 20, 2015)
- “Good Review Practices (GRP) for Medical Devices” (Joint Administrative Notice, by the Directors of the Office of Medical Devices I, Office of Medical Devices II, and Office of Medical Devices III, PMDA, dated June 3, 2016)
- “Scope of Cases where Medical Device Clinical Study Data is Necessary” (PFSB/ELD/OMDE Notification No. 0804001, by the Director of the Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated August 4, 2008)
- “Handling of Results from Clinical Studies of Medical Devices Conducted in Foreign Countries” (PFSB/ELD/OMDE Notification No. 0331006, by the Director of the Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated March 31, 2006)
- “Handbook for the Preparation of Clinical Evaluation Reports and Documents for Clinical Evaluation Consultations” (Clinical Evaluation Committee, the Japan Federation of Medical Devices Associations, dated February 1, 2016)
- “Handling of Clinical Trial Plan Submissions for Medical Devices and Equipment” (PFSB/ELD/OMDE Notification No. 0329-10, by the Director of the Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated March 29, 2013)
- “Points to Consider regarding the Handling of Results from Clinical Studies of Medical Devices Conducted in Foreign Countries” (Administrative Notice by the Director of the Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated March 31, 2006)
- “Questions and Answers regarding the Handling of Results from Clinical Studies of Medical Devices Conducted in Foreign Countries” (Administrative Notice by the Director of the Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated June 23, 2006)
- “Handling of Use-Results Surveys related to Marketing Approval of Medical Devices and *In Vitro* Diagnostics” (PFSB/MDRMPE Notification No. 1121-44, by the Director of the Medical Device and Regenerative Medicine Product Evaluation Division, Pharmaceutical and Food Safety Bureau, MHLW, dated November 21, 2014)

- “Partial Correction of ‘Handling of Use-Results Surveys for Marketing Approval of Medical Devices and *In Vitro* Diagnostics’” (Administrative Notice, by the Director of the Medical Device and Regenerative Medicine Product Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated December 28, 2015)
- “Basic Concept on Subjects to be Included in Use-Results Surveys for Marketing Approval of Medical Devices and *In Vitro* Diagnostics” (PFSB/MDRMPE Notification No. 1226-3, by the Director of the Medical Device and Regenerative Medicine Product Evaluation Division, Pharmaceutical and Food Safety Bureau, MHLW, dated December 26, 2014)
- “Procedures regarding the Necessity of Designation of Medical Device Use-Results Surveys, Surveillance Period, and Actual Operations” (PSEHB/MDRMPE Notification No. 1228-1, by the Director of the Medical Device and Regenerative Medicine Product Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated December 28, 2015)
- “Questions and Answers about Use-Results Surveys” (Administrative Notice, by the Director of the Medical Device and Regenerative Medicine Product Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated December 28, 2015)

Exhibit 1: Cases where no clinical trials are necessary

(corresponds to Section 2.3.2)

[Case 1] Addition or change on probe shape of active surgical instrument for surgical procedure (except for ones used for treatment such as cancer ablation) with the same intended use

[Generic names, etc.] Surgical electric devices and equipment such as microwave surgical knives, ultrasound surgical instruments, automatic electric surgical instruments, general-purpose cryosurgery units

Attachment of clinical trial results is not required if the proposed medical device is an active surgical instrument for surgical procedure (except for ones used for treatment such as cancer ablation) and has the same principle and intended use as those of the approved medical device, and non-clinical studies demonstrate that the performance, and safety and efficacy of its functions (incision, hemostasis, coagulation, vascular sealing, tissue resection) are comparable to those of the approved medical device. The above shall not apply to cases where the change causes clinically significant differences or leads to different clinical positioning.

[Case 2] Use of an orthopedic implant with the same surface processing used in a different orthopedic field

[Generic names, etc.] Orthopedic implant

In cases where the surface processing with use results is applied to an implant used in a different part from that for the approved medical device, as described in PFSB/ELD/OMDE Notification No. 1008001, by the Director of the Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated October 8, 2008; attachment of clinical study results is not required if non-clinical comparison with an approved implant used in the additional part in question demonstrates comparability in the safety and efficacy, and extrapolation of the clinical efficacy and safety data at the original part to those at the new part can be explained. In cases where the surface processing of the proposed medical device is different from that on the approved medical device (for instance, different pore rate or pore size); attachment of clinical trial results is not required as well if animal-origin intraosseous implant study, etc. demonstrates comparability in performance.

The above shall not apply to cases where performance of the surface processing on the proposed medical device has to be examined in humans.

[Case 3] Change of coil detachment principle or delivery system of a prosthetic material for intravascular embolization in the central circulatory system which can be evaluated in a cerebrovascular model

[Generic names, etc.] Vascular embolization coils (prosthetic material for intravascular embolization in the central circulatory system)

In cases where the proposed medical device is used for implantation of a vascular embolization coil, which is also included in the approved medical device with the intended use of vascular embolization for arterial aneurysm, arteriovenous malformation, and arteriovenous fistula located in the head, but their detachment mechanism is different; attachment of clinical trial results is not required if the following matters are met: The coil is implanted at a place as intended by the operator even under a stress condition potentially occurring at the application site; and local impact around the detachment site (risk of substances and energy released into the body) and risk of adjacent tissue and systemic impacts can be evaluated in non-clinical studies.

[Case 4] Additional indication of vascular embolization coil which has been approved for use in the cerebrovascular field, such as use for cerebral arterial aneurysm: Additional use in the peripheral arterial area

[Generic names, etc.] Vascular embolization coils (prosthetic material for intravascular embolization in the central circulatory system)

In cases where a vascular embolization coil which has been approved for use in the cerebrovascular field, such as use for cerebral arterial aneurysm, an additional indication of use in peripheral arteries is proposed; attachment of clinical trial results is not required if compatibility to the approved medical device can be evaluated in non-clinical studies and based on known information in terms of risk of coil migration due to different blood flow rate and risk of coil compaction in consideration of differences between peripheral arteries to be potentially used and cerebral blood vessels.

[Case 5] Change of delivery system for stent, etc. with intention to improve operability

[Generic names, etc.] Intravascular stents (coronary stent, stent for iliac artery), gastrointestinal stents, vascular embolization coils (prosthetic material for intravascular embolization in the central circulatory system), and transcatheter bovine heart valves

In cases where change of a delivery system is proposed to improve performance in delivering stent to an implantation site; attachment of clinical trial results is not required if comparability or superiority of the intended delivery performance to that of the approved medical device is evaluated in non-clinical studies using human vascular model. If an additional risk is potentially raised (high novelty, different approaching route), the proposed medical device should be demonstrated to have the clinical efficacy and safety comparable or superior to those of the approved medical device. The above shall not apply to the following cases: The change causes differences in placement precision; comparability of the clinical efficacy and safety cannot be explained; and the change causes clinically significant differences or leads to different clinical positioning.

[Case 6] Catheter for intravascular optical tomography with different imaging modality

[Generic names, etc.] Catheters for intravascular optical tomography, OCT diagnostic imaging equipment

In cases where the proposed medical device is a catheter for intravascular optical tomography using the same fundamental principle and optical wavelength for photographing as those of the approved medical device; attachment of clinical trial results is not required if non-clinical studies in which blood flow environment or various intravascular pathological conditions are simulated can demonstrate that differences from the approved medical device (pull-back speed, imaging modality, etc.) have no impact on observation capability; and non-clinical studies can also demonstrate that the operability and safety are comparable or superior to those of the approved medical device. The above shall not apply to cases where the change causes clinically significant differences or leads to different clinical positioning.

[Case 7] Implantable cardiac pacemaker and defibrillator with additional functions

[Generic names, etc.] Implantable cardiac pacemakers, implantable ventricular synchronization pacemakers, and automatic implantable defibrillators

In cases where the proposed medical device is an implantable cardiac pacemaker or defibrillator with an additional function, evaluation based on clinical study results is necessary in principle, but if the addition function is related to detection of arrhythmia, and appropriate non-clinical studies such as one using simulated signals are feasible as substitute of clinical studies; attachment of clinical trial results is not required. If evaluation is made in studies using simulated signals, episode data in studies using simulated signals should appropriately reflect clinical conditions in patients who are to use the proposed medical device.

[Case 8] Medical device intended to relieve pain by dosing external energy

[Generic names, etc.] Pain relief equipment by dosing external energy (examples of generic names: implantable stimulators for pain relief, electric stimulation equipment for pain relief)

In cases where the proposed medical device is equipment that relieves pain by dosing energy to human body; attachment of clinical trial results is not required if the application site and operating principle are the same as those of the approved medical device, and the energy dosing parameters (output, pulse width, stimulation waveform, and stimulation mode, etc.) are comparable to those of the approved medical device.

[Case 9] Absorbable bone fixation implant used in orthopedic field using different raw materials or different compounding ratio from that of the approved medical device

[Generic names, etc.] Absorbable internal fixation plates, absorbable internal fixation screws, absorbable internal fixation systems, absorbable internal fixation cables, absorbable internal fixation staples, absorbable skull fixation clamps

In cases where the proposed medical device is an absorbable bone fixation implant used in orthopedic field, which has the same shape and structure, use method, indicated patients, and application site as those of the approved medical device but differs in raw materials or compounding ratio from the approved medical device; attachment of clinical trial results is not required only if the following requirements are met: Each of the raw materials has been used as a general material; the compounding ratio is comparable to that of the approved medical device; degradation medical devices are known substances; and animal studies demonstrate that the appropriate strength is maintained until bone union.

[Case 10] Medical devices manufactured by coating antimicrobial substances on the approved medical devices or comparable medical devices

[Generic names, etc.] Antimicrobial endotracheal tube for ventilation, antimicrobial catheter for use in the urinary tract..

In cases where the proposed medical device is a medical device manufactured by adding antimicrobial substances (silver, etc.) to the approved medical device to reduce infection risk factors, but definite reduction of the infection risk cannot be expected in clinical settings, and thus it is considered difficult to demonstrate the effect in clinical studies; attachment of clinical trial results is not required if the safety is comparable to that of the approved medical device. The above shall not apply to cases where addition of the antimicrobial substance is presumed to present risks such as appearance of resistant microorganisms, delay of healing, or reduced performance, and thus adequate safety comparability cannot be explained in non-clinical studies. If the antimicrobial substance used potentially led to the appearance of resistant microorganisms, the clinical benefit such as reduced infection risk should be demonstrated.

[Case 11] Dental bleaching agent containing the same active ingredient as that in the approved medical device

[Generic names, etc.] Dental bleaching agents

If differences between the proposed medical device and approved medical device both containing the same active ingredient are investigated in terms of release of the active ingredient over time, non-active excipient materials, clinical risk related to use method, and indications, and then impact of the differences on clinical use can be adequately evaluated in non-clinical studies, attachment of clinical trial results is not required.

Exhibit 2: Sample size of clinical trials (corresponds to Section 3.2)

The following pages provide information about sample size of clinical trials mainly of medical devices (including new medical devices and improved medical devices with clinical trials conducted) which were approved between FY 2010 and FY 2015 and of which information about pivotal clinical trials is available in review reports and package inserts. It should be noted that the information about sample size provided in the subsequent pages is positioned as a reference material because the sample size greatly differs depending on characteristics, novelty, history of development, and non-clinical study results.

In addition, the following note shows a summary of the sample size of clinical trials of medical devices in the cardiovascular field in this Exhibit 2.

[Medical devices in the cardiovascular field]

- Coronary stent
Comparative clinical trials including several hundreds of subjects were conducted for new medical devices, and single-arm clinical trials including 300 or fewer subjects were conducted. (The clinical trials were conducted for improved medical devices.)
- Peripheral vascular stent
Comparative clinical trials including more than 100 subjects or single-arm studies including 300 or fewer subjects were conducted for new medical devices, and single-arm clinical trials including 300 or fewer subjects were conducted. (The clinical trials were conducted for improved medical devices.)
- Aortic stent-graft
Single-arm clinical trials including approximately 50-130 subjects were conducted and comparisons with historical data were also conducted. (The clinical trials were conducted for new medical device and improved medical device.)
- Catheter for embolic containment in the central circulatory system
The medical device is filter used during carotid stent placement. Clinical trial including approximately 160-230 subjects was conducted for the medical device in question. The clinical trials were conducted for comparison with the previous data of the existing similar medical device group or the other treatment (without using the medical device in question) group. (The clinical trials were conducted for new medical device.)
- Prosthetic material for intravascular embolization in the central circulatory system
Clinical trials were conducted according to the intended use. A single-arm clinical trial for cerebral arterial aneurysm treatment medical device including approximately 100 subjects was conducted to evaluate late-post-procedure results. A single-arm clinical trial for vascular embolization beads including approximately 30 subjects was conducted to evaluate technical success of embolization. (The clinical trials were conducted for new medical devices.)
- Ablation catheter for cardiovascular system
Comparative clinical trials including approximately 70-100 subjects overall were conducted to evaluate treatment success and clinical usefulness of the proposed medical device. (The clinical trials were conducted new medical devices).

<<Medical devices in cardiovascular field>>

Generic name/ Class	Review category (results from either foreign or Japanese clinical study) <small>*Details of the study underlined are provided in the right column.</small>	Brand name	Intended use, Indications	Study design	Major endpoints	Sample size
Coronary stent/ Class IV	New medical device (global clinical trial and Japanese clinical study results)	PROMUS Element Plus stent system	The medical device is used for treatment for patients with symptomatic ischemic heart disease due to de novo lesions in coronary arteries 2.25 mm to 3.50 mm in reference vessel diameter in lesions ≤ 34 mm in length.	Comparative study (randomized single-blinded parallel-group comparative study) Control group: Existing stent	Target lesion failure rate 12 months post-procedure	Proposed medical device group 768, Control group 762
	New medical device (foreign and Japanese clinical study results)	Nobori	The medical device is used for treatment for patients with symptomatic ischemic heart disease due to de novo lesions in coronary arteries 2.5 mm to 3.5 mm in reference vessel diameter in lesions ≤ 30 mm in length.	Comparative study (randomized parallel-group comparative study) Control group: Existing stent	Target vessel failure rate 9 months post-procedure	Proposed medical device group 200, Control group 135
	Improved medical device (foreign clinical study results)	Kaname	The medical device is used for treatment for patients with symptomatic ischemic disease due to de novo or restenotic lesions in coronary arteries 3.0 mm to 4.0 mm in reference vessel diameter in lesions ≤ 25 mm in length (including treatment for acute or impending occlusion associated with intervention failure)	Single-arm study	Device success rate, procedure success rate, in-stent restenosis rate 6 months post-procedure, freedom rate from target vessel failure (TVF) 180 days post-procedure	282
	Improved medical device (Japanese clinical study results)	Byval coronary stent	The medical device is used for treatment for patients with symptomatic ischemic disease due to de novo or restenotic lesions in coronary arteries 3.0 mm to 4.5 mm in reference vessel diameter in lesions ≤ 25 mm in length (including treatment for acute or impending occlusion associated with intervention failure)	Single-arm study	Procedure success rate (residual stenosis rate in target lesion improved to < 50%, no major adverse cardiac events [MACEs] during hospital stay), and target vessel failure (TVF) rate and MACE rate 6 months post-procedure	95
Vascular stent/ Class III	New medical device (global clinical trials results)	Zilver Flex SF A Vascular stent	The medical device is intended for treatment for symptomatic vascular diseases in the above-the-knee femoropopliteal arteries 4 to 7 mm in reference vessel diameter under either of the following cases: - Treatment for acute or impending occlusion associated with intervention failure is indicated; and dissection occurs after placement of the maximum number of “Zilver PTX drug-eluting peripheral vascular stents”.	Comparative study (randomized comparative controlled study) Control group: Percutaneous transluminal angioplasty (PTA)	Primary patency rate at 1-year follow-up visit, 1-year event-free survival rate	Proposed medical device group 54, Control group 117
	New medical device; the original medical device under re-examination period (foreign and Japanese clinical study)	SMART stent	The medical device is used for treatment for symptomatic vascular diseases in superficial femoral arteries 4 mm to 7 mm in reference vessel diameter (including treatment for acute or impending occlusion associated with intervention failure)	Single-arm study	Comparison with the target value set based on results on plain old balloon angioplasty (POBA), the existing treatment	250
	Improved medical device (global clinical trials)	Innova Vascular Stent	The medical device is used for treatment for symptomatic vascular diseases in superficial femoral arteries or proximal	Single-arm study	Primary patency rate 12 months post-procedure	299

Generic name/ Class	Review category (results from either foreign or Japanese clinical study) *Details of the study underlined are provided in the right column.	Brand name	Intended use, Indications	Study design	Major endpoints	Sample size
	results)		femoropopliteal arteries 4 mm to 7 mm in reference vessel diameter in lesions ≤ 150 mm in length per leg (including treatment for acute or impending occlusion associated with intervention failure) In addition, treatment for acute or impending occlusion associated with intervention failure in the same site.			
	Improved medical device (foreign clinical study results)	Express SD Renal Artery Extension Stent System	The medical device is a stent delivery system used to assist in maintenance of vessel patency in atherosclerotic lesion at the ostium of the renal artery. Lesions to be treated shall be symptomatic renal artery stenosis with the stenosis rate ≥ 50% and meet any of the following conditions. - Peak systolic velocity (PSV) in renal artery, ≥ 180 cm/sec; - Maximum systolic pressure difference, ≥ 20 mmHg or mean pressure difference ≥ 10 mmHg	Single-arm study	Binary restenosis rate 9 months post-procedure (objective performance criterion [OPC], superiority to binary restenosis rate of percutaneous renal angioplasty [PTRA] using peripheral vascular balloon)	100
Aortic stent-graft/ Class IV	New medical device (Japanese clinical study results)	Kawasumi Najuta Thoracic Stent Graft System	The medical device is used for treatment for thoracic aortic aneurysm meeting all the following anatomical criteria. 1. Appropriate access route to iliac and femoral arteries. 2. Normal vessel on both central and peripheral sides of the arterial aneurysm (aortic vessels without aneurysm) for fixation that meets the following condition: - Length of the normal vessel between the bifurcation of the left common carotid artery and aortic aneurysm shall be ≥ 20 mm (if left subclavian artery is not occluded, the length of the normal blood vessel between the bifurcation of left subclavian artery and aortic aneurysm shall be ≥ 20 mm). - Length of the normal vessel between the bifurcation of the celiac artery and aortic aneurysm shall be ≥ 20 mm. - Diameters of the normal vessel at the fixation parts on both central and peripheral sides of the arterial aneurysm shall be ≥ 20 mm and < 38 mm.	Historical control study	Survival rate 12 months post-procedure for aneurysm (non-inferiority to historical control group registered in the Japan Adult Cardiovascular Surgery Database [JACVSD] [surgery group])	127
	New medical device (foreign clinical study results)	COOK Zenith Aortic Dissection Endovascular System	The medical device is used for intravascular treatment in patients with acute Stanford B aortic dissection with complication meeting the following anatomical criteria, who have not responded to internal treatment - Radius of curvature > 35 mm along the entire length of aorta intended to be treated with stent-graft or > 55 mm along the entire length of aorta intended to be treated with bare stent. - Non-dissection aortic part (fixation part) proximal to the entry fissure (most proximal to the left common carotid artery and dissection elongation) as follows: ≥ 20 mm in length Diameter measured outer wall to outer wall of the aorta ≥ 20 mm (total aortic diameter) and ≤ 38 mm (true lumen). -	Single-arm study	All-cause mortality 30 days post-procedure (comparison with the achievement criteria set based on historical data on surgical thoracotomy)	52

Generic name/ Class	Review category (results from either foreign or Japanese clinical study) *Details of the study underlined are provided in the right column.	Brand name	Intended use, Indications	Study design	Major endpoints	Sample size
			Localized angulation < 45 degrees for stent-graft or < 35 degrees for bare stent. - Adequate iliac/femoral access compatible with the required delivery system			
	Improved medical device (foreign clinical study results)	Relay Plus Thoracic Stent-Graft System	The medical device is used for treatment for thoracic descending aortic aneurysm in patients meeting all the following anatomical criteria. - Iliac/femoral artery suitable for insertion of delivery system, vascular access, and various concomitant devices - Non-aneurysmal normal aortic neck 19 to 42 mm in diameter - Non-aneurysmal normal aortic neck parts on both central and peripheral sides have a landing zone compatible with selected stent-graft diameter. The central-side edge of the stent-graft does not reach the origin of the left common carotid artery.	Comparative study (non-randomized open-label study) Control group: Surgical treatment	Efficacy endpoint is freedom from major device-related adverse events 1 year post-procedure, and safety is evaluated using composite endpoint based on major adverse events 1 year post-procedure (proposed medical device group vs. surgery group).	Proposed medical device group 120, Control group 60
	Improved medical device (Japanese clinical study results)	J Graft Open Stent-Graft	The medical device is used for treatment for diseases requiring replacement in the distal aortic arch to proximal descending artery that meet the following anatomical criteria. - Internal diameter of the vessel to be subjected to replacement on central and peripheral sides 15 mm to 37 mm. - Normal vessel \geq 20 mm on the peripheral side of the part be subjected to replacement.	Single-arm study	Incidence of major adverse events (MAEs) including death from procedure to hospital discharge (comparison with the target value set based on historical control)	60
Catheter for embolic containment in the central circulatory system/ Class IV	New medical device (foreign clinical study results)	MOMA Ultra	The medical device is an embolic protection device used to occlude the common carotid artery and external carotid artery with the device itself without passing any catheter through the internal carotid artery lesion so that embolic material (thrombus/debris) is prevented from entering the cerebral circulation and removed by suction during stent placement. Indicated for external carotid artery 3 mm to 6 mm in reference vessel diameter and common carotid artery 5 mm to 13 mm in reference vessel diameter.	Single-arm study	Comparison of major adverse cardiovascular and cerebrovascular events (MACCEs) reported until 30 days post-procedure with the achievement target (set based on the past carotid artery stent placement study results)	225
	New medical device (foreign clinical study results)	Angioguard XP	The medical device is distal embolic protection device to contain and remove embolic material such as thrombus during stent placement and to be used through percutaneous intravascular insertion and tentative placement distal to the lesion.	Comparative study (randomized comparative study) Control group: Surgical treatment (carotid endarterectomy)	MAE rate 30 days post-procedure and 360 days post-procedure *MAEs are defined as [1] events including death, all-cause cerebral stroke and/or myocardial infarction (MI) 30 days post-procedure, or [2] events including death and/or ipsilateral cerebral stroke between 31 days and 12 months post-procedure.	Proposed medical device group 167, Control group 167
Prosthetic material for intravascular embolization in the central	New medical device (foreign and Japanese clinical study results) * Medical device highly	Pipeline Flex Flow Diverter System	The medical device is used for intravascular treatment for intracranial arterial aneurysm from petrous part of the internal carotid artery to the superior hypophyseal artery in large (maximum aneurysm size 10 to 25 mm) or giant	Single-arm study	Efficacy endpoints are intact occlusion of the target arterial aneurysm 180 days post-procedure and percentage of arterial aneurysm assessed as \leq 50%	108

Generic name/ Class	Review category (results from either foreign or Japanese clinical study) *Details of the study underlined are provided in the right column.	Brand name	Intended use, Indications	Study design	Major endpoints	Sample size
circulatory system/ Class IV	needed in medical practices		(maximum aneurysm size > 25 mm) and wide-necked (neck \geq 4 mm in length) lesion (except for acute rupture phase)		stenosis of the parent vessel; and safety endpoint is percentage of subjects in which ipsilateral severe cerebral stroke or cerebral neurological disorder-related death occurs within 180 days post-procedure. * OPC set based on review of literature on results from intravascular treatment for large and giant aortic aneurysms	
	New medical device (Japanese clinical study results) * Medical device highly needed in medical practices	HepaSphere	The medical device is used for arterial embolization in patients with plethoric tumors (except for uterine fibroid) or arteriovenous malformation	Single-arm study	Technical success (embolization or remarkable blood flow reduction in the target vessel: disappearance of densely stained tumor by \geq 90% or blood flow reduced by \geq 50% in the target vessel)	29
Ablation catheter for cardiovascular system/ Class IV	New medical device (foreign clinical study results) * Medical device highly needed in medical practices	1. Arctic Front Advance cryoablation catheter; 2. Freezor MAX cryoablation catheter	1. The medical device is a balloon catheter used for cardiac tissue cryoablation procedure, which is indicated for drug-resistant recurrent symptomatic paroxysmal atrial fibrillation 2. The medical device is used with balloon catheter in cryoablation procedure, which is indicated for patients with drug-resistant recurrent symptomatic paroxysmal atrial fibrillation, for the following purpose where necessary. 1. Gap cryoablation to complement pulmonary vein electric isolation 2. Cryoablation on locally evoked part to treat atrial fibrillation 3. Linear cryoablation between inferior vena cava and tricuspid valve	Comparative study (randomized comparative study) Control group: Drug therapy (drugs to treat atrial fibrillation)	Efficacy endpoint is treatment success (“acute procedure success” without “chronic treatment failure” in the investigational device group; and freedom from “chronic treatment failure” in the control group) Safety endpoints are [1] percentage of safety-analyzed subjects without cryoablation procedure events (CPEs) in the investigational device group; and [2] percentage of safety-analyzed subjects without major atrial fibrillation events (MAFEs) at 12-month follow-up visit in each group	Investigational device group 171, Control group 87
	New medical device (Japanese clinical study results)	SATAKE HotBalloon Catheter	The medical device is used for cardiac tissue radiofrequency ablation procedure, which is indicated for drug-resistant recurrent symptomatic paroxysmal atrial fibrillation.	Comparative study (randomized open-label comparative study) Control group: Drug therapy (antiarrhythmic drugs)	Chronic success rate (no documented atrial fibrillation that lasts \geq 30 seconds in 12-lead ECG, mobile ECG, or Holter ECG from the end of blanking period to post-procedure 48th week examination, and neither use of prohibited or restricted concomitant drugs nor implementation of restricted concomitant therapy in the investigational device group; No documented atrial fibrillation that lasts \geq 30 seconds in 12-lead ECG, mobile ECG, or Holter ECG from the end of	Investigational device group 100, Control group 43

Generic name/ Class	Review category (results from either foreign or Japanese clinical study) *Details of the study underlined are provided in the right column.	Brand name	Intended use, Indications	Study design	Major endpoints	Sample size
					drug titration period to 40th week examination after the first dose, and neither use of prohibited or restricted concomitant drugs nor implementation of restricted concomitant therapy in the control group)	
	New medical device (Japanese clinical study results)	1. NaviStar RMT, 2. NaviStar RMT ThirmoCool	1. The medical device is an electrode catheter intended to perform myocardial ablation and cardiac electrophysiological examination with radiofrequency current to treat supraventricular tachycardia, and operated with the magnetic navigation system. For myocardial ablation, the medical device is used in combination with dedicated radiofrequency generator, and for electric physiological examination (electroanatomical mapping), it is used concurrently with dedicated 3D mapping system for electric physiological examination. 2. Th medical device is an electrode catheter intended to perform myocardial ablation and cardiac electrophysiological examination with radiofrequency current to treat drug-resistant symptomatic paroxysmal and persistent atrial fibrillation, atrial flutter, and ventricular tachycardia refractory to the other therapies, and operated with the magnetic navigation system. In addition, it has an irrigation function with an irrigation hole at the tip of the chip electrode, from which physiological saline outflows. For myocardial ablation, the medical device is to be used in combination with dedicated radiofrequency generator and irrigation equipment, and for electric physiological examination (electroanatomical mapping), it is used concurrently with dedicated 3D mapping system for electric physiological examination.	Comparative study (randomized open-label comparative study) Control group: Existing ablation catheter for cardiovascular system	Efficacy major endpoint: Is the time required to perform cardiac electric physiological examination (Electro Physiological Study) on 5 predetermined intracardiac sites (non-inferiority verification according to the non-inferiority limit, the examination time with the investigational device is twice that with the control device)	Investigational devices group 52, Control group 17
Cerebral artery stent/ Class IV	New medical device (Japanese clinical study results) * Medical device highly needed in medical practices	Wingspan Stent	The medical device is to be used in percutaneous transluminal angioplasty with balloon-expandable angioplasty catheter to treat intracranial arterial stenosis in the following case: - Retreatment after angioplasty as emergency treatment or only one effective option for vascular dissection, acute occlusion, or impending occlusion occurring during angioplasty	Single-arm study * Investigator-initiated clinical trial	Ipsilateral cerebral stroke or death until 6 months post-procedure (including death of which causal relationship to the proposed medical device only)	20

<<Medical devices in orthopedic field>>

Generic name/ Class	Review category (results from either foreign or Japanese clinical study) <small>*Details of the study underlined are provided in the right column.</small>	Brand name	Intended use, Indications	Study design	Major endpoints	Sample size
Absorbable ligament anchor/ Class IV	Improved medical device (Japanese clinical study results)	HEALICOIL RG Suture Anchor	The medical device is to be used to anchor soft tissues such as tendon, ligament, and muscle to bones. Multiple anchors are implanted in the bone and connected to the soft tissues using surgical suture.	Single-arm study	Comprehensive evaluation based on Japan Shoulder Society - Shoulder Instability Score (JSS-SIS), CT, and conventional MRI 6 months post-procedure	62
	Improved medical device (Japanese clinical study results)	GRYPHON BR Anchor	The medical device is to be used to anchor soft tissues such as ligament to bones in the shoulder, leg/ankle, elbow, and hip.	Single-arm study	Surgery success and clinical function evaluation (JSS-SIS score and Rowe score 12 weeks post-procedure)	24
Acetabular component for hip joint prosthesis/ Class III	Improved medical device (Japanese clinical study results)	Aquala Liner	The medical device is to be used in hip replacement arthroplasty to treat joint disorders due to osteoarthritis.	Single-arm study	Comprehensive assessment based on JOA score and X-ray findings. Presence or absence of reimplantation or removal, safety evaluation, and QOL evaluation using SF-36®	80
	Improved medical device (Japanese clinical study results)	Trabecular Metal Modular Acetabular System	The medical device is an acetabular shell directly anchored to the pelvis during hip replacement arthroplasty (including reimplantation) and to be used to substitute hip joint functions. Indications: Traumatic or disease-related hip injury	Single-arm study	JOA score and 4-grade evaluation on X-ray image (clear zone) 12 months post-procedure	96
Total hand joint replacement/ Class III	New medical device (Japanese clinical study results)	D A R T S Hand Joint Prosthesis	The medical device is to be used for replacement of dysfunctional hand joint severely damaged due to the primary disease such as rheumatoid arthritis. It is intended to function as a substitute of hand joint.	Single-arm study * Investigator-initiated clinical trial	JOA score 18 months post-implantation and percentage of subjects in whom the scores of Wrist Scoring System by Figgie and Range of Motion achieved ≥ 70 and ≥ 10 , respectively, 18 months post-implantation	20

<<Other medical devices>>

Generic name/ Class	Review category (results from either foreign or Japanese clinical study) <small>*Details of the study underlined are provided in the right column.</small>	Brand name	Intended use, Indications	Study design	Major endpoints	Sample size
Diode laser /Class III	New medical device (Japanese clinical study results)	ELVeS Laser	The medical device is to be used for blockade of blood flow at the saphenous vein stem in patients with primary varicose vein (varicose greater saphenous vein or varicose small saphenous vein ≤ 20 mm in diameter).	Comparative study Control group: Surgical treatment (stripping surgery)	For efficacy, superiority in AUC obtained from changes over time in CIVIQ2 total score for noninvasiveness and non-inferiority in decreases in VFI value for treatment effect	Proposed medical device group 62, Control group 30
	Improved medical device	LSO1470 Laser	The medical device is to be used for treatment at the	Single-arm study	For verification of the clinical efficacy	75

Generic name/ Class	Review category (results from either foreign or Japanese clinical study) <i>*Details of the study underlined are provided in the right column.</i>	Brand name	Intended use, Indications	Study design	Major endpoints	Sample size
	(Japanese clinical study results)		saphenous vein stem for primary varicose vein (varicose greater saphenous vein or varicose small saphenous vein ≤ 20 mm in diameter).		and safety, non-inferiority to clinical study results of the approved medical device, “ELVeS Laser”	
PDT semiconductor laser /Class III	New medical device (Japanese clinical study results) <i>* Medical device for rare diseases</i>	PD Laser BT	The medical device is a laser device to be used for photodynamic therapy (PDT) with photosensitizer, talaporfin sodium. Indications: Primary malignant brain tumor (limited to cases undergoing tumor resection)	Single-arm study <i>* Investigator-initiated clinical trial</i>	Overall survival 12 months after PDT	27
Bronchial filling material/Class III	New medical device (Japanese clinical study results) <i>* Medical device for rare diseases, medical device highly needed in medical practices</i>	Bronchial filling material EWS	The medical device is to be indicated for patients with inoperable secondary intractable pneumothorax for which bronchial occlusion is indicated, prolonged air leak after pneumonectomy, and the other fistula, and is to be used to occlude fistula by filling the bronchus.	Single-arm study	Evaluation was made for removal or not of chest drainage in patients with it placed; or presence or not of additional treatment in patients without chest drainage placed until 90 days after bronchial filling procedure. Patients with chest drainage removed or those treated additionally were considered as responders (response rate was compared with predicted responder rate from Japanese clinical researches).	25
Body temperature adjustment system/ Class II	New medical device (Japanese clinical study results)	Coopdech iCool	The medical device is to be used to reduce brain temperature in patients for whom induced hypothermia is indicated by attaching to the pharyngoesophageal part the cuff in which cooled physiological saline is circulated. <i>* This medical device is not intended for systemic hypothermia. It should be used prior to systemic hypothermia.</i>	Single-arm study	Cooling effect within 2 hours after arrival at hospital (change in tympanic temperature) <i>* Efficacy criterion was set as follows: The change in tympanic temperature in the Japanese investigational device group shall be greater than that in the control group (without using the proposed medical device) in the preceding clinical research.</i>	24
Artificial synthetic dura mater/ Class IV	Improved medical device (Japanese clinical study results)	Dura Wave	The medical device is a prosthetic material for cerebral dura mater defects Indicated for the following patients [1] Patients with cerebral dura mater defect requiring restoration; and [2] Patients in whom the primary suture of cerebral dura mater is not possible or sufficient with the existing methods.	Single-arm study	[1] Intraoperative closure performance; [2] Preventive effect rate against cerebrospinal fluid leak or subcutaneous cerebrospinal fluid effusion during the whole post-procedure period.	57
Non-absorbable topical hemostatic material for central circulatory system/ Class IV	New medical device (Japanese clinical study results)	Matsudaito	The medical device is used for auxiliary hemostasis at the anastomosis site of blood vessel prosthesis associated with replacement of thoracic aorta or branching artery of aortic arch where hemostasis is not achieved with conventional surgical procedures including ligation.	Comparative study (randomized open-label comparative study) Control group: Existing hemostasis treatment	Presence or absence of bleeding at the vascular anastomosis site just before administration of protamine sulfate (for each anastomosis site) and presence or absence of bleeding at the vascular anastomosis site 15 minutes after	Proposed medical device group 60, Control group 30

Generic name/ Class	Review category (results from either foreign or Japanese clinical study) *Details of the study underlined are provided in the right column.	Brand name	Intended use, Indications	Study design	Major endpoints	Sample size
					administration of protamine sulfate (for each anastomosis site); hemostasis rate	
Anti-adhesive absorbable barrier/ Class IV	Improved medical device (Japanese clinical study results)	AdSpray	The medical device is used to injured peritoneal area under abdominal incision (injured sites of the abdominal wall, abdominal organs, uterus, and adnexa uteri) in patients undergoing abdominal or pelvic cavity to alleviate post-procedure adhesion in terms of frequency, area, and severity.	Comparative study (open-label comparative study) Control group: Without treatment	Laparoscopic assessment of post-procedure adhesion under laparotomy incision at the time of colostomy closure (presence or absence of adhesion, area of adhesion, and severity of adhesion)	Proposed medical device group 55, Control group 43
Hyaluronic acid-contained soft-tissue injection material/Class IV	Improved medical device (foreign clinical study results)	Juvederm Vista Voluma XC	The medical device is used to be injected subcutaneously or superperiosteally in adults to restore mesoprosopic, submaxilla, or temple part in volume.	Comparative study (randomized open-label comparative study, assessment physicians blinded) Control group: Without treatment	MFVDS (mesoprosopic facial volume decrease scale) assessment on mesoprosopic face overall at 6 months	Proposed medical device group 208, Control group 36
Gastroduodenal stent /Class III	Improved medical device (foreign clinical study results) * Medical device highly needed in medical practices	WallFlex Duodenal Stent	The medical device is a stent to be endoscopically inserted to resolve gastroduodenal occlusion caused by malignant tumor and maintain the patency in patients who have difficulty undergoing palliative gastrectomy or are unlikely to respond to the other therapies.	Single-arm study	Assessment of GOOSS (ColoRectal Obstruction Scoring System) score at 6 months post-procedure	43

Study Group Members Contributing to the Clinical Trial Guidance

(Research Representative)

Shohei Nakano, Executive Director of the Japan Association for the Advancement of Medical Equipment

(Research Collaborators)

Kiyoshi Okada, Lecturer, Department of Medical Innovation, Osaka University Hospital

Munehiro Sugiyama, Chief Physician, Department of Radiology, Kitamura Hospital

Shuichi Mochizuki, Adjunct Professor, Center for Advancing Clinical Research, University of Yamanashi

Takahiro Uchida, Company Executive Officer, Japanese Organization for Medical Device Development, Inc.

Hiroko Tanioka, Clinical Evaluation Committee, Japan Federation of Medical Devices Associations

Noriko Yasuda, Clinical Evaluation Committee, Japan Federation of Medical Devices Associations

Shiho Tanaka, American Medical Devices and Diagnostics Manufacturers' Association in Japan

Kaoru Moriwaki, European Business Council in Japan

Shin-ichi Takae, Director of Office of Medical Devices I, Pharmaceuticals and Medical Devices Agency

Kensuke Ishii, Director of Office of Medical Devices II, Pharmaceuticals and Medical Devices Agency

Yuka Suzuki, International Coordination Officer in charge of Medical Devices, Office of International Programs, Pharmaceuticals and Medical Devices Agency

Mami Ho, Specialist (in charge of clinical affairs), Office of Medical Devices III, Pharmaceuticals and Medical Devices Agency

Haruki Shirato, Reviewer, Office of Medical Devices III; Pharmaceuticals and Medical Devices Agency

(Observers)

Soichiro Isobe, Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare

Hiroshi Yanaginuma, Director of Regenerative Medicine Evaluation Division

Akihide Konishi, Coordinator for Advanced Medical Devices

(Secretariat)

Medical Device Strategy Institute, Japan Association for the Advancement of Medical Equipment