

Regulation on Clinical Trials in Japan

HBD East 2017 Think Tank Meeting

At National Institute of Global Health and Medicine

Tokyo, Japan: December 7, 2017

Introducing Innovative MDs

Previously...

CT is conducted in EU → Introduced in US/Japan

Future

Novel, Innovative MDs

are developed in US/Japan → Need for EFS

Acceleration measures for Innovative MDs

| Type | Area | Designation requirement |
|---|-------------------------------|---|
| Expedited review | Any product categories | <u>Designation is not needed</u> Needed to expedite the review |
| Priority review | | <u>Designation is needed</u> 1. Orphan 2. Apparent improvement of medical care and for severe diseases |
| SAKIGAKE (Forerunner designation) | | <u>Designation is needed</u> <ul style="list-style-type: none"> • Innovative medical products • For serious diseases • Development & NDA in Japan • being world's first or simultaneous with other countries • Prominent effectiveness expected on non-clinical and early phase clinical studies |
| Conditional Early Approval | Drugs | <u>Designation is not needed</u> Early application through confirmation of a certain degree of efficacy and safety through clinical trials other than confirmatory clinical trials. |
| | Medical Devices | <u>Designation is not needed</u> <ul style="list-style-type: none"> - MDs in high clinical needs - Balancing the pre- and post-market requirements |
| Conditional and Time-limited Authorization | Regenerative Medical Products | <u>Designation is not needed</u> |

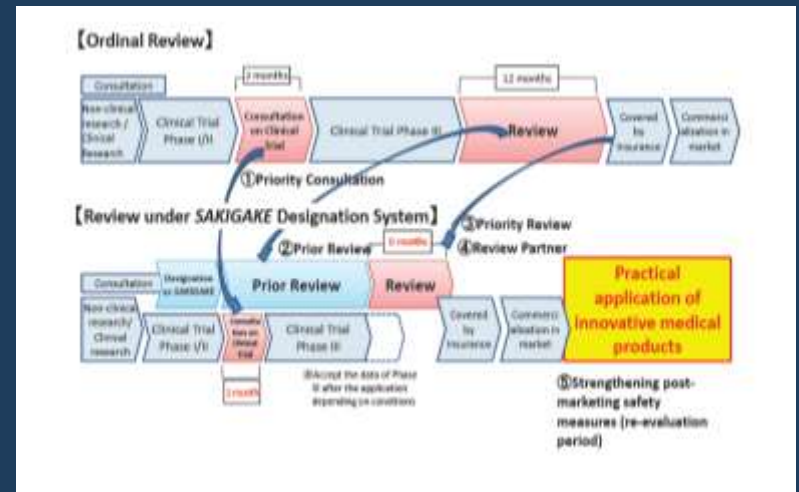
Strategy of Sakigake

An innovative MD/IVD for patients in urgent need of innovative therapy may be designated as a Sakigake Product if;

- 1) its premarket application will be filed in Japan firstly or simultaneously in some countries including Japan, AND
- 2) prominent effectiveness can be expected.

Once an MD/IVD is designated, its developer can enjoy such benefits as:

- A) Prioritized Consultation by PMDA
- B) Pre-application substantive review
- C) Prioritized Review (12 months → 6 months [MD])
- D) Review Concierge assigned by PMDA



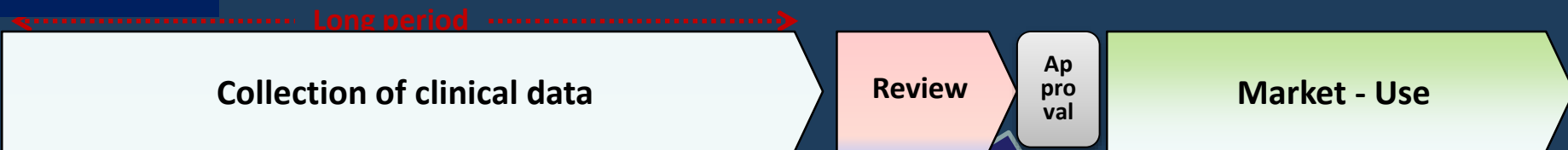
Fast Break Scheme

(Conditional Early Approval for Innovative MDs)

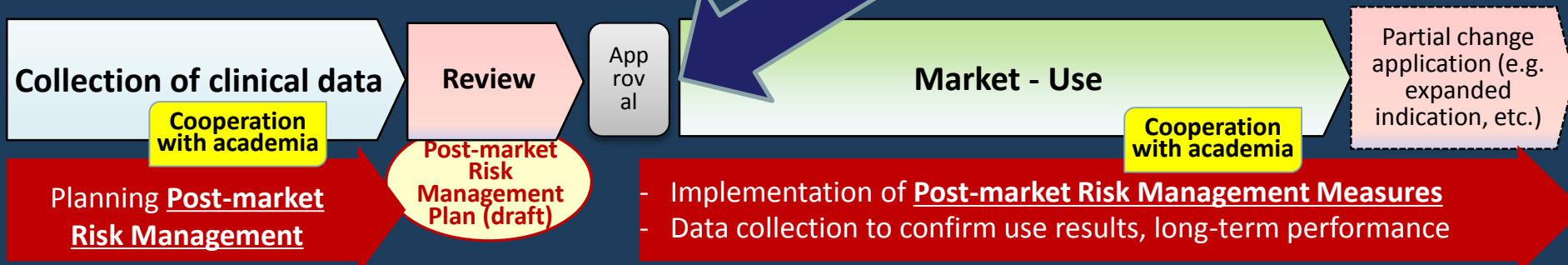
<Implemented on 31 July 2017>

Accelerate approval of MDs in high clinical needs by balancing the pre- and post-market requirements, based on the lifecycle management of the MDs.

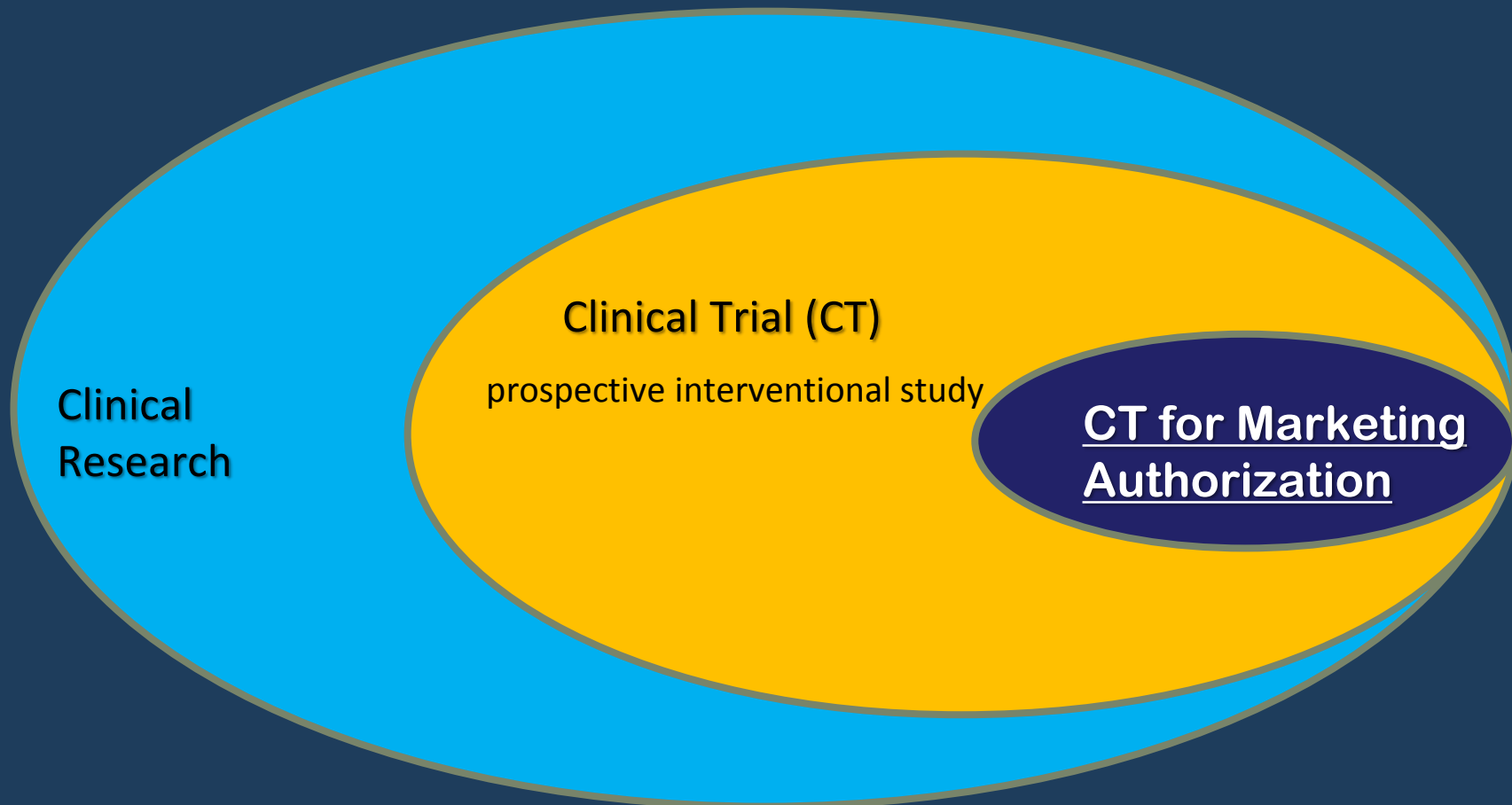
Present



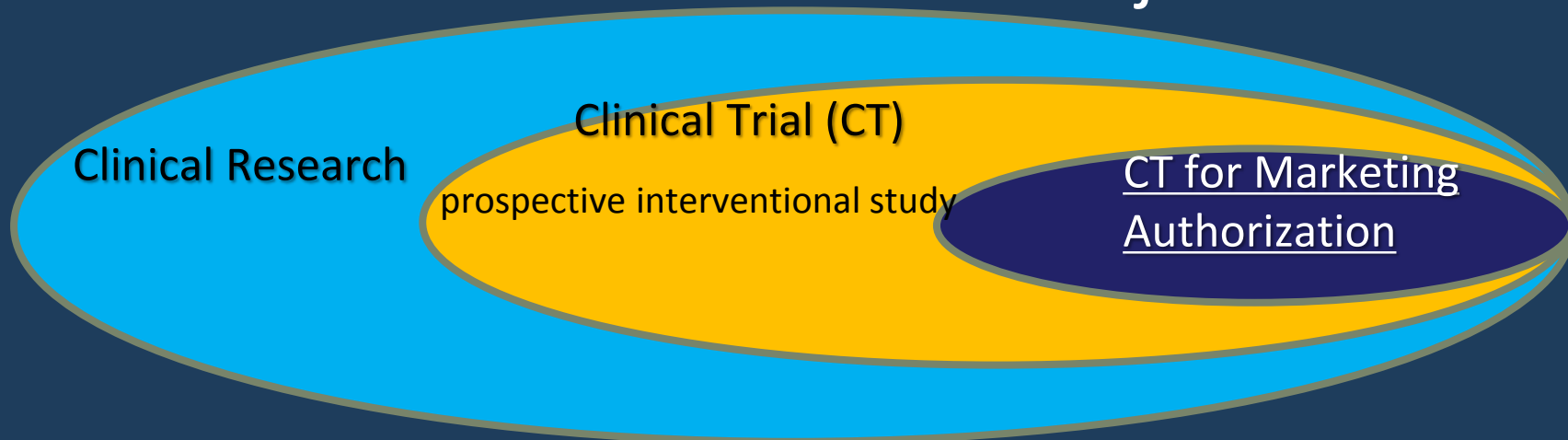
Conditional Early Approval for Innovative MDs



Clinical Research on Human Subjects



Research on Human Subjects



Study purpose is other than Marketing Authorization (academic purpose)

Ethical Guidelines for Medical and Health Research Involving Human Subjects

The studies are conducted as a part of daily medical practice. In addition to mutual trust between patient and doctor, requirement of ethical consideration is stipulated by ministerial announcement.

Study purpose is to file for MA

Good Clinical Practice (GCP)

The study sponsors conduct trials for profit (product development). Therefore operating procedures and system are stipulated by ministerial ordinance (GCP) in order to protect study subjects and ensure data reliability.

Ethical Guidelines for Medical and Health Research Involving Human Subjects

The Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare established joint committee for reviewing 2 guidelines on 2013 Feb.

Ethical guidelines for
epidemiology research

2002 in force (revise in 2007)

Ethical Guidelines for
Clinical Research

2003 in force (revise in 2008)

Ethical Guidelines for Medical and Health Research
Involving Human Subjects

2015 April 1st in force

Recent scandal in the field of clinical trial

- Diovan (Valsartan)
 - Kyoto Heart Study
 - Jikei Heart Study
 - SMART (the Shiga Micro albuminuria Reduction Trial)
 - VART (The Valsartan Amlodipine Randomized Trial)
 - Nagoya Heart Study
- Tasigna (Nilotinib)
 - SIGN Trial
- Bropress (Candesartan)
 - CASE-J

Movement to new regulation

**Review Committee for clinical trials of
hypertension Drug (Diovan)**
(2013.Aug. ~ 2014.Mar.)

**Review of Ethical
Guidelines for Clinical
Research**
(2014.Dec.)

**Committee for clinical trial
regulation**
(2014.Spr. ~ 2014.Dec.)

Clinical Trial Act

Summary of the report on the Committee for clinical trial regulation①

1 . Necessity of establishing new act

- ◆ Overviewing based on the globalization of drug and medical device development over the 5 years, 10 years
- ◆ Current guideline is not enough to recover the confidence
- ◆ Establishing excess regulation leads to shrink the study activity.
- ◆ Balance is needed between the self regulation and legal framework.
- ◆ New regulation is expected for the clinical trial to some degree.

Summary of the report on the Committee for clinical trial regulation②

2. Main target of the act

- ◆ Clinical trial intending to evaluate Non-Approved drugs and medical devices etc.
- ◆ Clinical trial planned to use the data for advertising the drugs and medical devices etc.

3. Summary content of the act

- ◆ Ethical Review Committee
 - Requirement of the membership
 - Guarantee of the quality of the committee

Summary of the report on the Committee for clinical trial regulation③

- ◆ Information disclosure related to the clinical trial
 - Guarantee of transparency by the information disclosure
 - Considering the intellectual property
- ◆ Practice standards of clinical research
- ◆ Corresponding at the time of adverse events
- ◆ Monitoring and guidance by government authorities
- ◆ Penalty to the investigator
- ◆ Ensure transparency, such as pharmaceutical companies

Regulation on Clinical Research

Clinical Research of Medical Products

| Clinical Research of Medical Products | | | |
|---------------------------------------|--------------------------------|---|---|
| CT Type | CT for Marketing Authorization | Designated Clinical Research <ul style="list-style-type: none"> ● Clinical Research of unapproved products or Off-label use ● Clinical Research with funding from company | Other Clinical Research |
| Regulation | PMD Act GCP Ordinance | Clinical Research Act (CRA) CRA Ordinance | Ethical Guidelines for Medical and Health Research Involving Human Subjects |

Content of Clinical Trial Act

Chapter 1 general provision

article 1 , article 2

Chapter 2 conducting clinical trials

article 3 ~ article 22

Chapter 3 accredited clinical research review committee

article 23 ~ article 31

Chapter 4 providing the funds for clinical trials

article 32 ~ article 34

Chapter 5 Miscellaneous provision

article 35 ~ article 38

Chapter 6 Penal provision

article 39 ~ article 43

Supplementary provision

Major issue of ministry order of Clinical Trial Act

平成29年8月2日 第1回 臨床研究部会 参考資料6より

| | Article | Title of the article |
|------------|------------------|--|
| Chapter 1 | Article 2 | Definition |
| Chapter 2 | Article 3 | Clinical trial implementation standards |
| | Article 5 | Submission of clinical trial plan |
| | Article 9 | Informed Consent |
| | Article 12 | Record of specific clinical trials |
| | Article 13 | Adverse event report to the accredited clinical research review committee and MHLW |
| | Article 14 | |
| | Article 17 | Annual Report to the accredited clinical research review committee and MHLW |
| Article 18 | | |
| Chapter 3 | Article 23 | Accreditation of clinical research review committee by MHLW |
| Chapter 4 | Article 32 | Conclusion of the contract |
| | Article 33 | Publication of information related to the provision for the specific clinical trials |
| Chapter 5 | Article 38 | Delegation to ministry order |

Early Feasibility Study

- Necessary for Early Access of Innovative MDs
- Need for Protection of Patients
- Improving Environment for Patient Protection would encourage EFS, Innovative MD development, and Early access for Innovative MDs!

Thank You !