

# Japan's Regulatory Initiative to promote Global Clinical Development

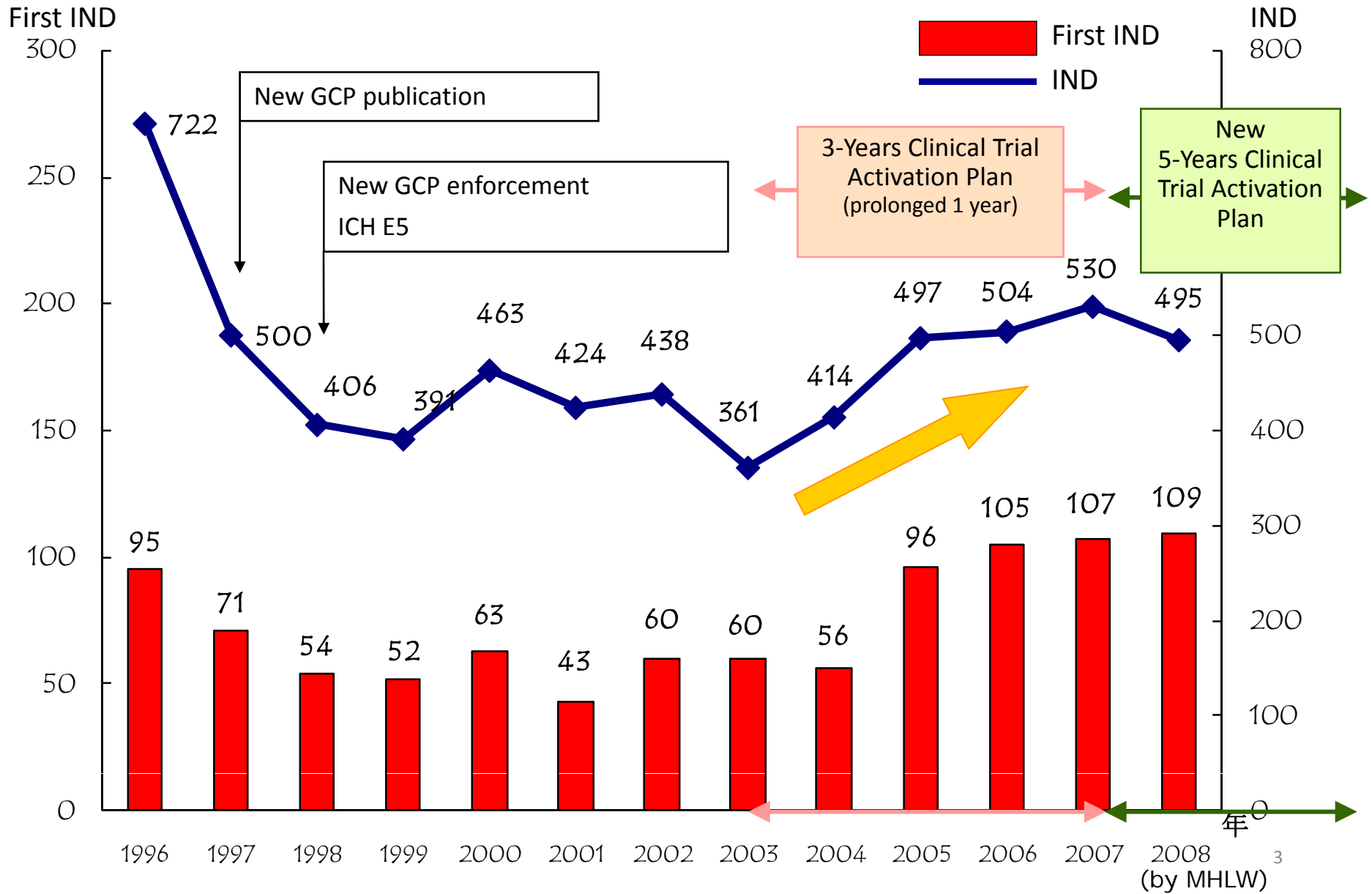
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Ministers' Secretariat, MHLW

# Contents

- Action plan for the promotion of clinical trials
- Global Clinical Trials & Drug Development Strategy in consideration of ethnic factors

# Number of IND Notifications

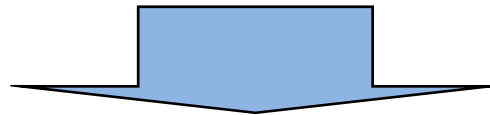


# Goals of New 5-Years Clinical Trial Activation Plan

Reinforce clinical research infrastructure to ensure safe and secured patients' access to new drug and devices

Build nationwide infrastructure to perform innovative and valuable clinical research in a smooth manner

Network core clinical research sites where research skills and resources are highly integrated



Enhance the level of Japan's medical quality

Penetrate Japan-originated clinical innovation in the world by enhancing Japan's contribution to international multi-centered trials

# New 5-Years Clinical Trial Activation Plan

MEXT / MHLW  
March 2007

## (1) Clinical Study Infrastructure Building

- 10 core clinical research centers that are able to plan and manage multi-center trials
- 30 major clinical trial institutions that are able to perform trials smoothly

## (2) Human Resource Development for Clinical Research

- Training provision for MDs, CRCs, Bio-statisticians, Data managers, etc.

## (3) Public Promotion of Clinical Trial and Encouraging Participation

- Improve patient volunteers' ease to participate in trials
- Improve patient's incentive to participate in trials

## (4) Efficient Clinical Research Management and Sponsors' Ease

- Harmonize administrative document formats
- Streamline administrative work share between hospitals and sponsors
- Improve transparency of hospitals' research capacity

## (5) Others

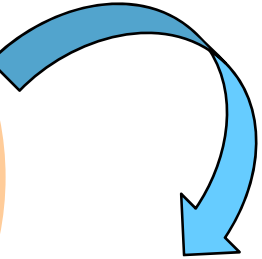
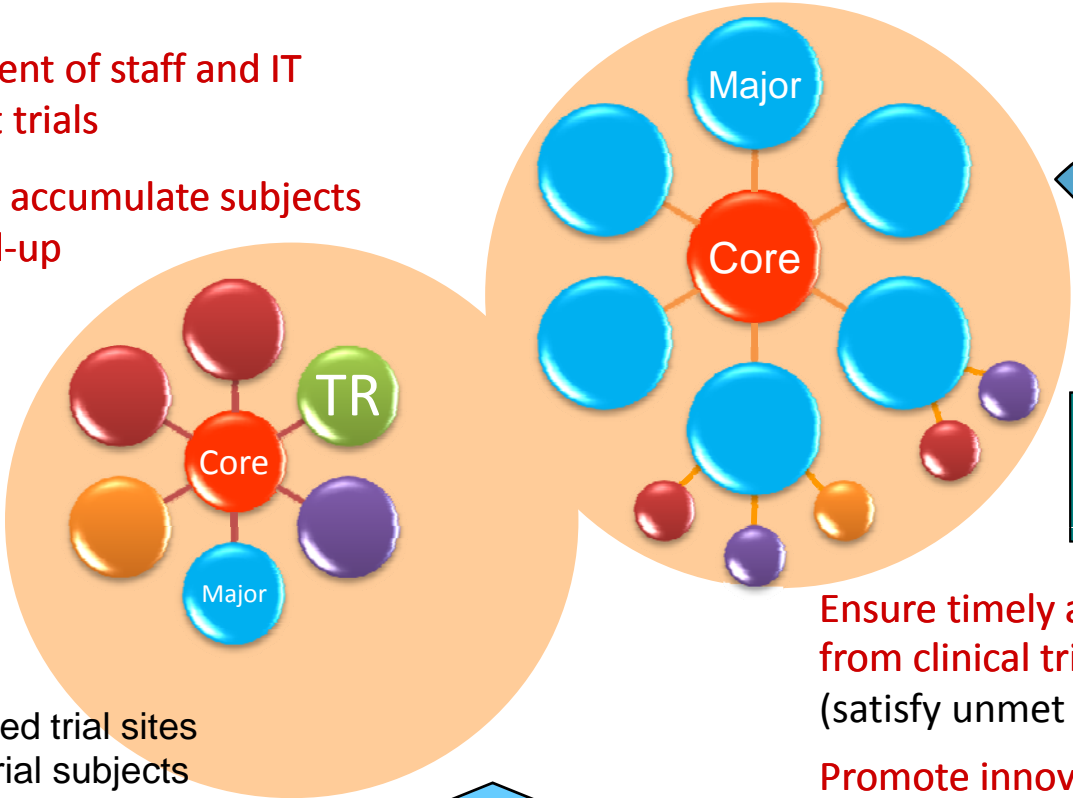
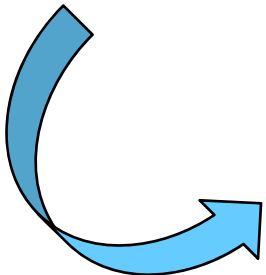
- Review GCP Ordinance and Clinical Research Guideline for international harmonization and patient protection

# (1) Clinical Study Infrastructure Building

# Network of clinical research centers

Institutional reinforcement of staff and IT environment to support trials

Build site networking to accumulate subjects  
→ cost down and speed-up



**Expedite trial performance**

Alliance with related trial sites and accumulate trial subjects

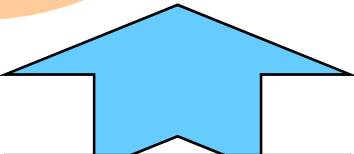
Ensure timely access to new drug from clinical trial stage (satisfy unmet needs)

Promote innovation of new drug

**10 Core** clinical research centers

Total 1,000M\ / year (approx. 10M\$ / year)

- Train human resources in-house and in the institutions in the net work
- Strengthen IRB capacity
- Consolidate data management system
- Plan, Do, Assess clinical research



**Infrastructure improvement**

**30 Major** clinical trial institutions

Total 750M\ / year (approx. 7.5M\$ / year)

- Secure Recruiting CRCs and other trial supporting staff
- Support promotion of common IT plat home

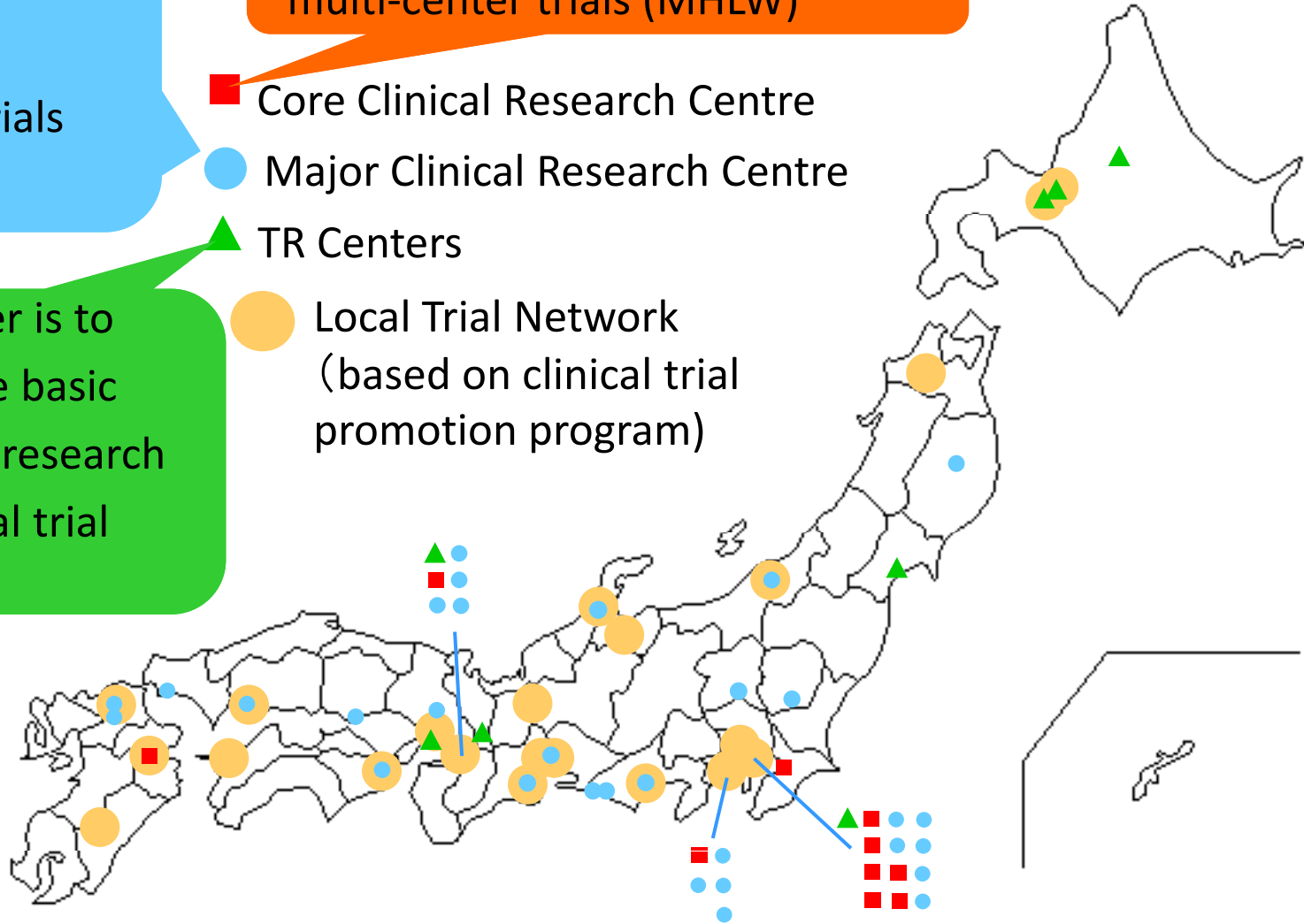
# Nation-wide network of TR/clinical trial centers

MCRC is a center to smoothly perform trials (MHLW)

CCRC is able to plan and manage multi-center trials (MHLW)

TR center is to translate basic medical research to clinical trial (MEXT)

- Core Clinical Research Centre
- Major Clinical Research Centre
- ▲ TR Centers
- Local Trial Network (based on clinical trial promotion program)



## (2) Human Resource Development for Clinical Research

### 1. Training Programs (FY 2009)

- CRC (basic, Advanced)
- Local Data Manager
- IRB member

### 2. e-Learning Systems for Clinical Researchers, CRC etc.



<http://icrweb.jp/icr/>



<https://etrain.jmacct.med.or.jp/>

# (3) Public Promotion of Clinical Trial and Encouraging Participation -Japan Primary Registries Network(JPRN)-

<http://www.mhlw.go.jp/topics/buk-yoku/isei/chiken/index.html>

Since Oct.2007

Public

WHO-ICTRP

MHLW

- Promotion
- Regulation and guidance

1. Keep public well informed
2. Avoid publication bias
3. Utilize negative data
4. Promote subject recruitment

National Institute of Public Health  
Search Portal Site

- Portal site management
- Promotion
- Coordination with 3 sites of clinical trial registry
- coordination with WHO-ICTRP

JPRN

UMIN  
Clinical Trial Registry

JMA  
Centre for Clinical Trials

JAPIC  
Trial Information System

- System management
- investigator initiated trials
- Promotion

<http://www.umin.ac.jp/ctr/index-j.htm>

- Sponsor-investigator trials
- Promotion

<https://dbcentre2.jmacct.med.or.jp/ctrtrial/>

- System management
- Company initiated trials
- Promotion

[http://www.clinicaltrials.jp/user/cte\\_main.jsp](http://www.clinicaltrials.jp/user/cte_main.jsp)

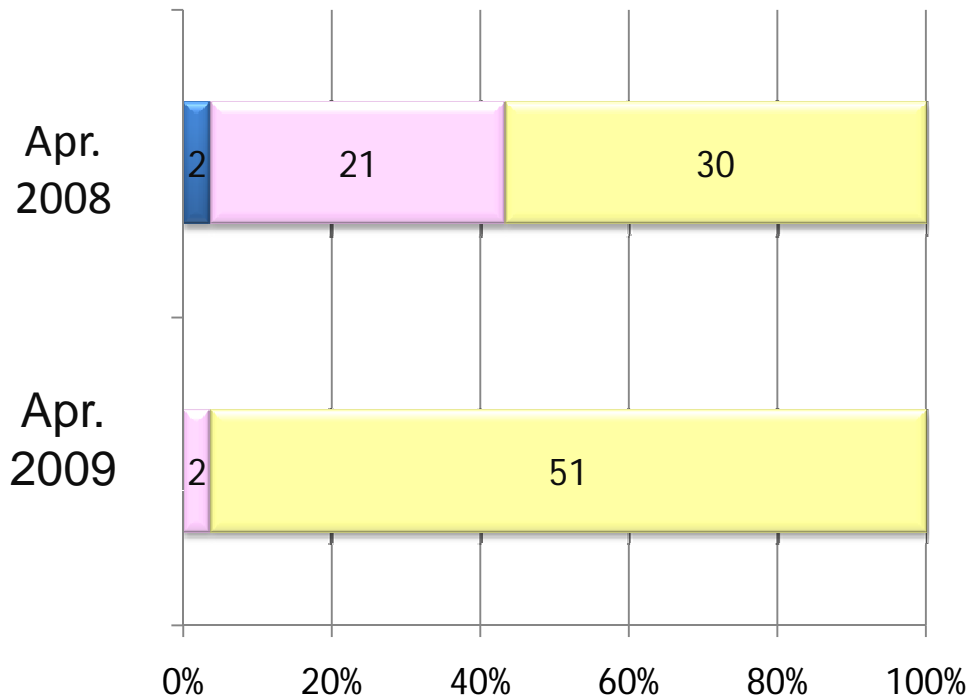
Investigator or  
company



**(4) Efficient clinical research  
management and sponsors' ease**

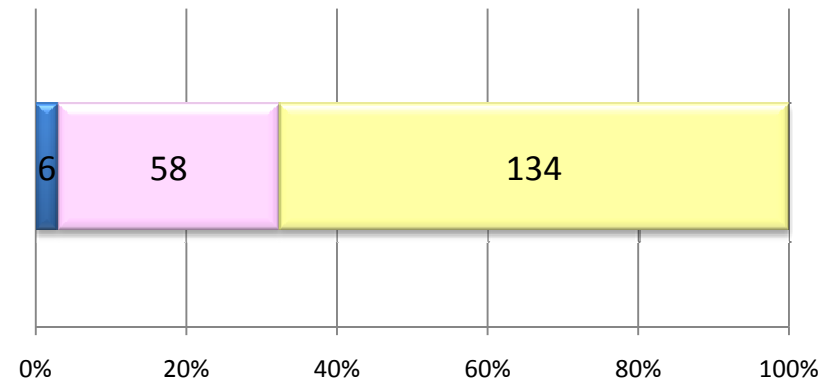
# Accept of common documentation format for clinical trials

Situation of accept in cores and majors



- undecided
- planning
- accepted

Cores, majors and other related 198 organizations



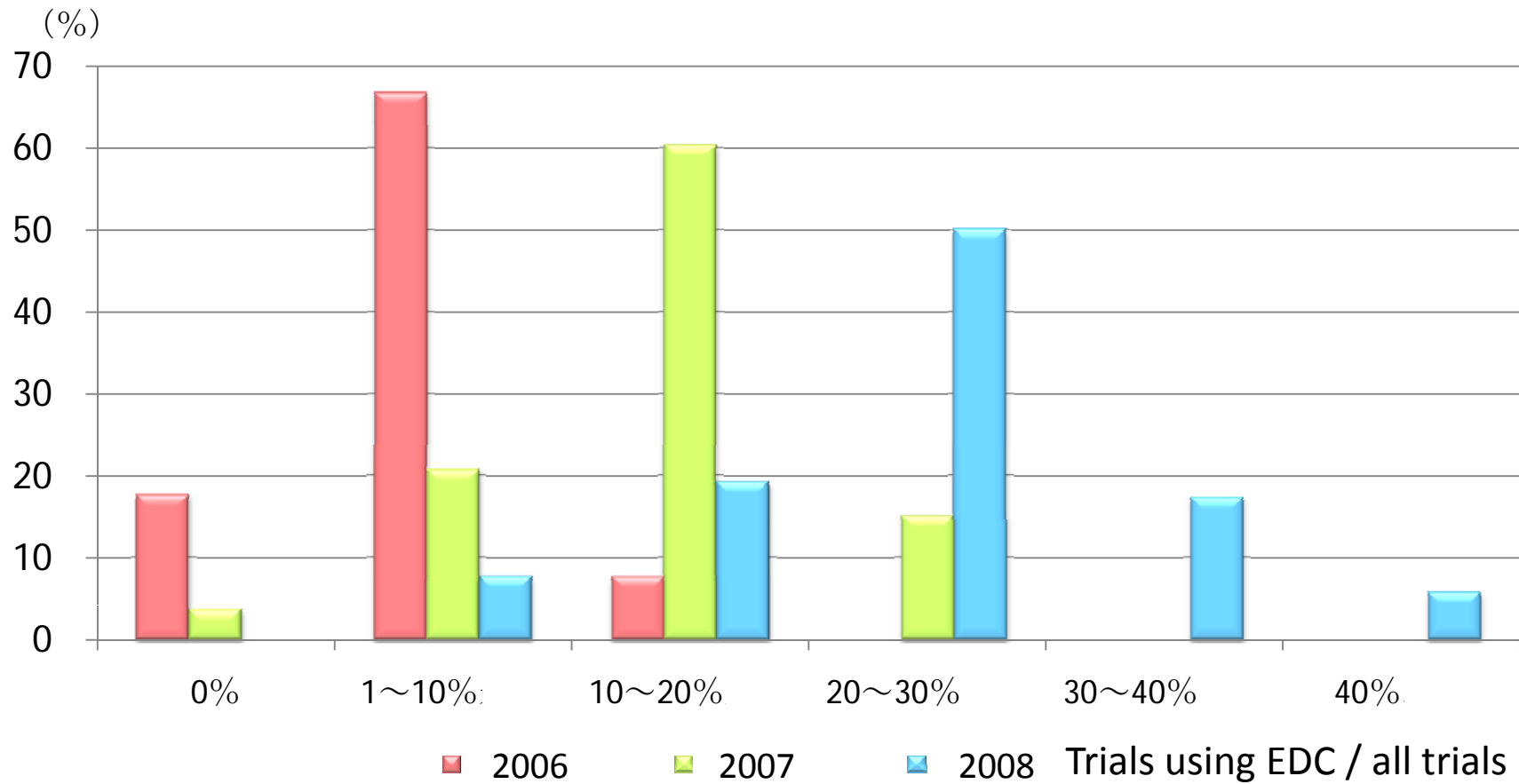
- undecided
- planning
- accepted

(Oct. 2008)

Completed to introduce at  
Cores, etc (July 2009)

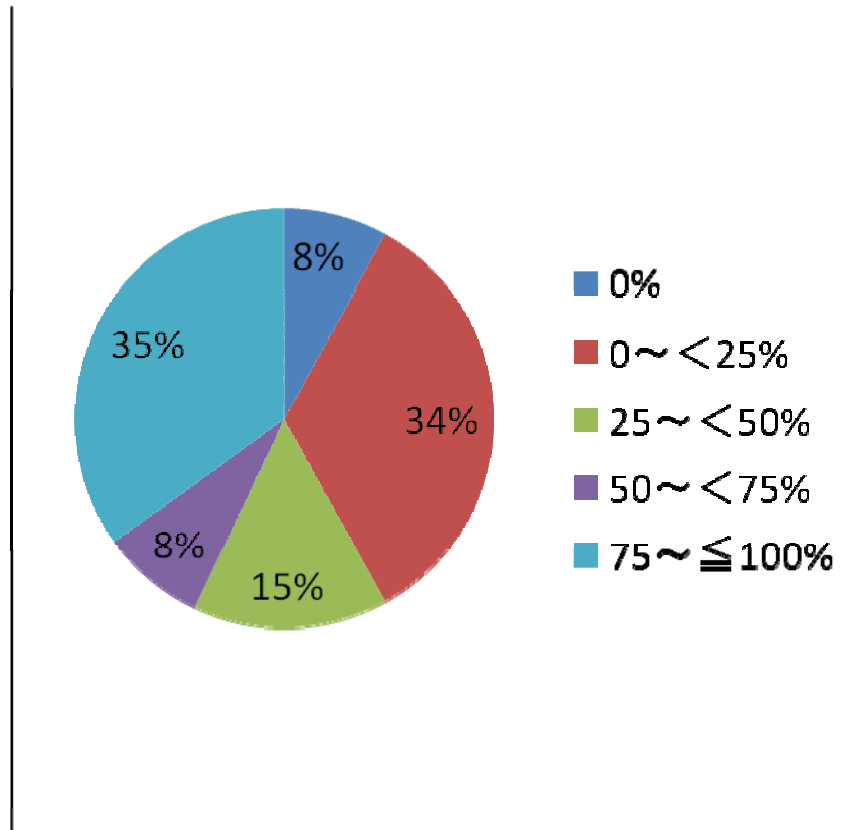
# Increase in the rate of clinical trials using EDC

in cores and majors for the past three years

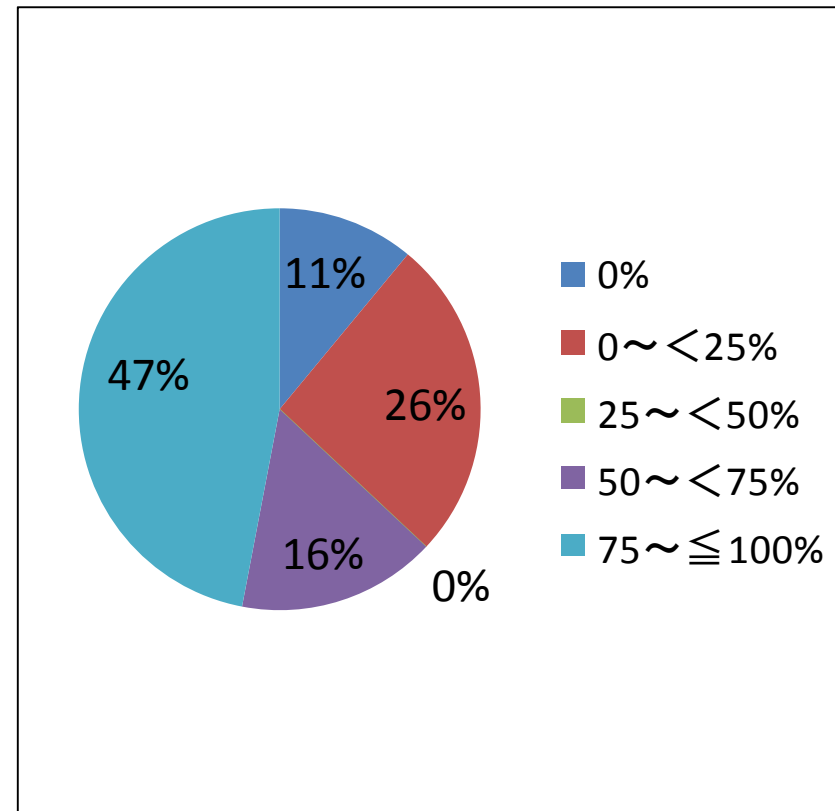


# The ratio of clinical trials using EDC (Domestic trials vs Global Trials) (Y.2008)

## Domestic Trials



## Global Trials



## (5) Others

### Amending Japan's GCP

1. Relaxed IRB rules, allowing a central IRB rather than each hospital's own IRB, with more Transparency
2. Introducing Periodical Safety Update (every 6 months)
3. Reducing "Essential Documents"
4. Relaxing some other procedures Ex. Clinical Trial Registration & Trial Substance Delivery

### Amending Clinical Research Ethical GL. Apr. 2009, etc-

1. Training for researchers
2. IRB (Annual Report, Utilizing IRB of other facilities)
3. Report of severe ADR

# Global Clinical Trials & Drug Development Strategy in consideration of ethnic factors

## Improvement of Global Study Bases (World-class clinical research sites)

### “5-year Strategy for creating innovative drugs and medical devices” 2008 Edition

Regarding clinical research/trials, we improve global clinical bases with central IRB functions, which can conduct high-level international joint research.

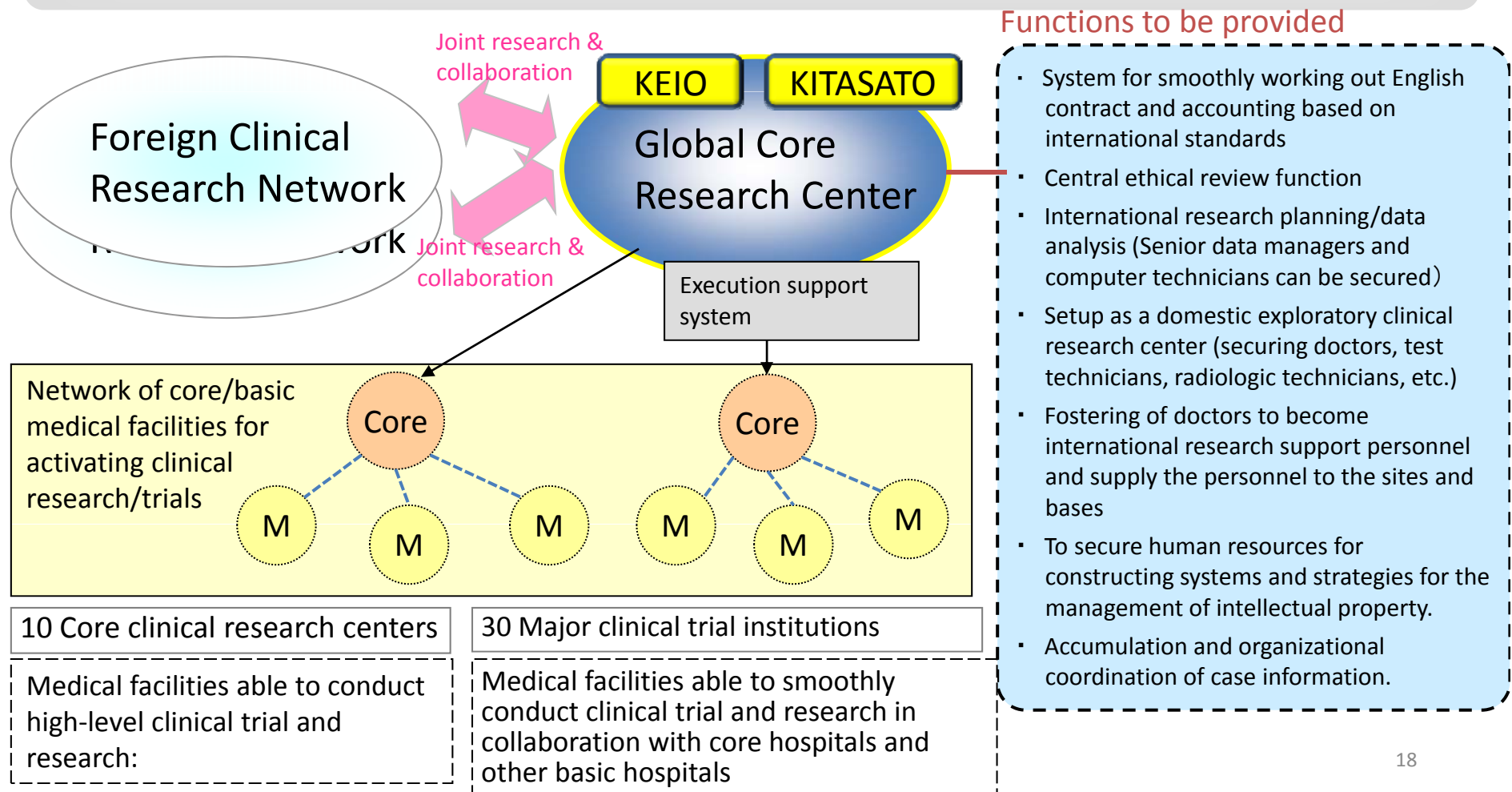
**Purpose:** In order to put Japan’s basic research results into practical use, we have improved a system with higher expertise. While Global studies are increasing as a result of the improved base and sites for the studies, it has also become necessary to create a joint research system in Asia and its bases.

**Effect:** We can reduce execution time-lag with foreign countries by planning international joint research programs and proceeding with the development of ethical review procedures and contract in an integrated manner. Smooth implementation is made possible through the use of medical staff capable of communicating with foreign organizations at any time.

# Global Core Research Center for Clinical Trial

Started in 2009 with budget of \400 million

Goal: Reinforcement of clinical trial institution in Japan and promotion of simultaneous global development of innovative drugs



# Guidance: Basic Principles On Global Clinical Trials

English : <http://www.pmda.go.jp/operations/notice/2007/file/0928010-e.pdf>

## — One of Key Messages —

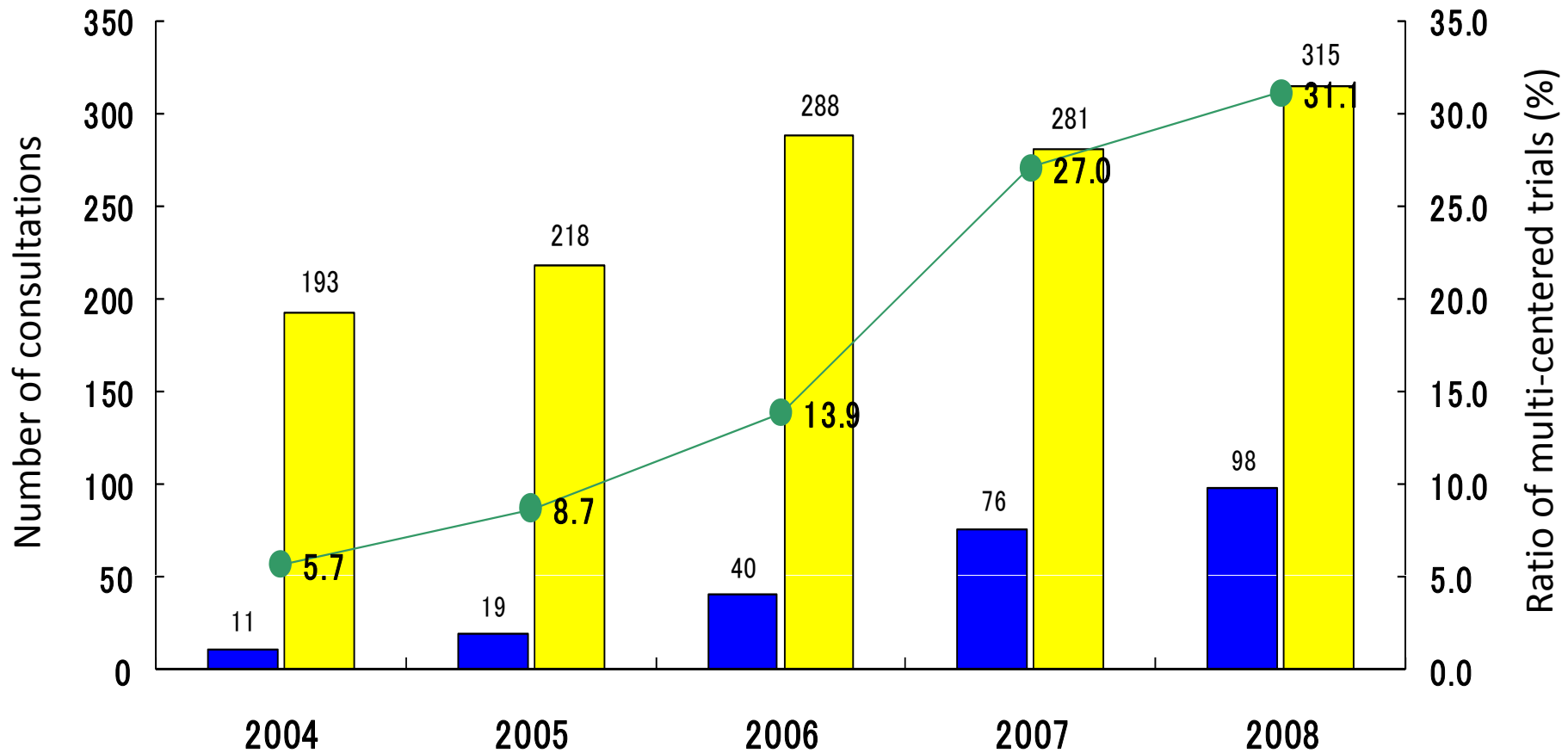
- Promote to conduct global clinical trials more appropriately in consideration of ethnic factors

### - Impacts -

- ✓ Markedly increase numbers and % of clinical trial notification (CTN) of MRCTs including Japan
- ✓ Promotion of sample size considerations in scientific arena
  - Kawai, N et al, An Approach to Rationalize Partitioning Sample Size Into Individual Regions in a Multiregional Trial, *Drug Info. J.* 42, 139-147 (2008)
  - Quan, H et al, Sample size considerations for Japanese patients in a multi-regional trial based on MHLW guidance. *Pharmaceut. Statist.* Published Online: Jun 4 2009 4:09AM 10.1002/pst.380 (2009).

# Increasing trend toward multi-centered trials

## PMDA's trial consultation basis

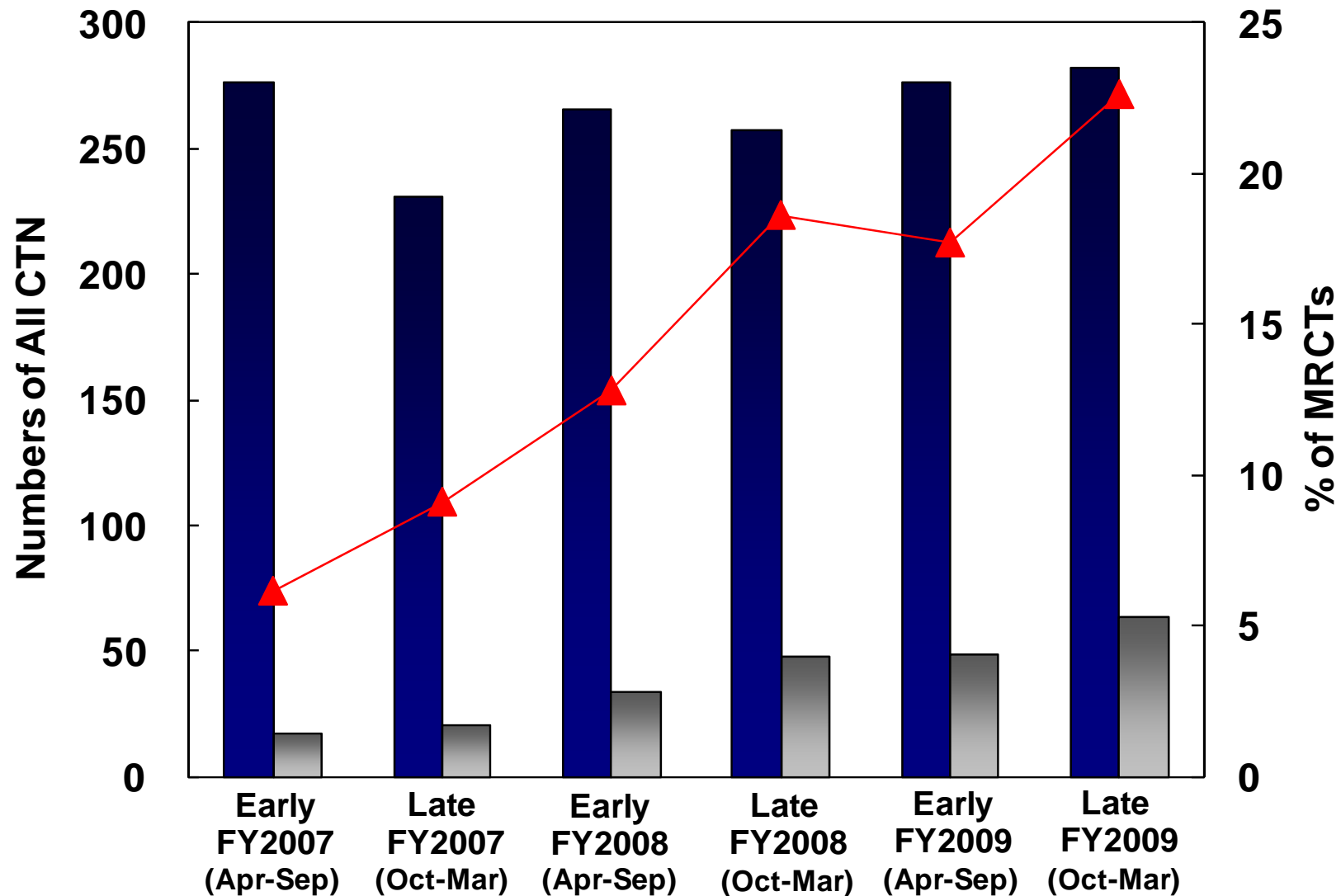


Source: PMDA

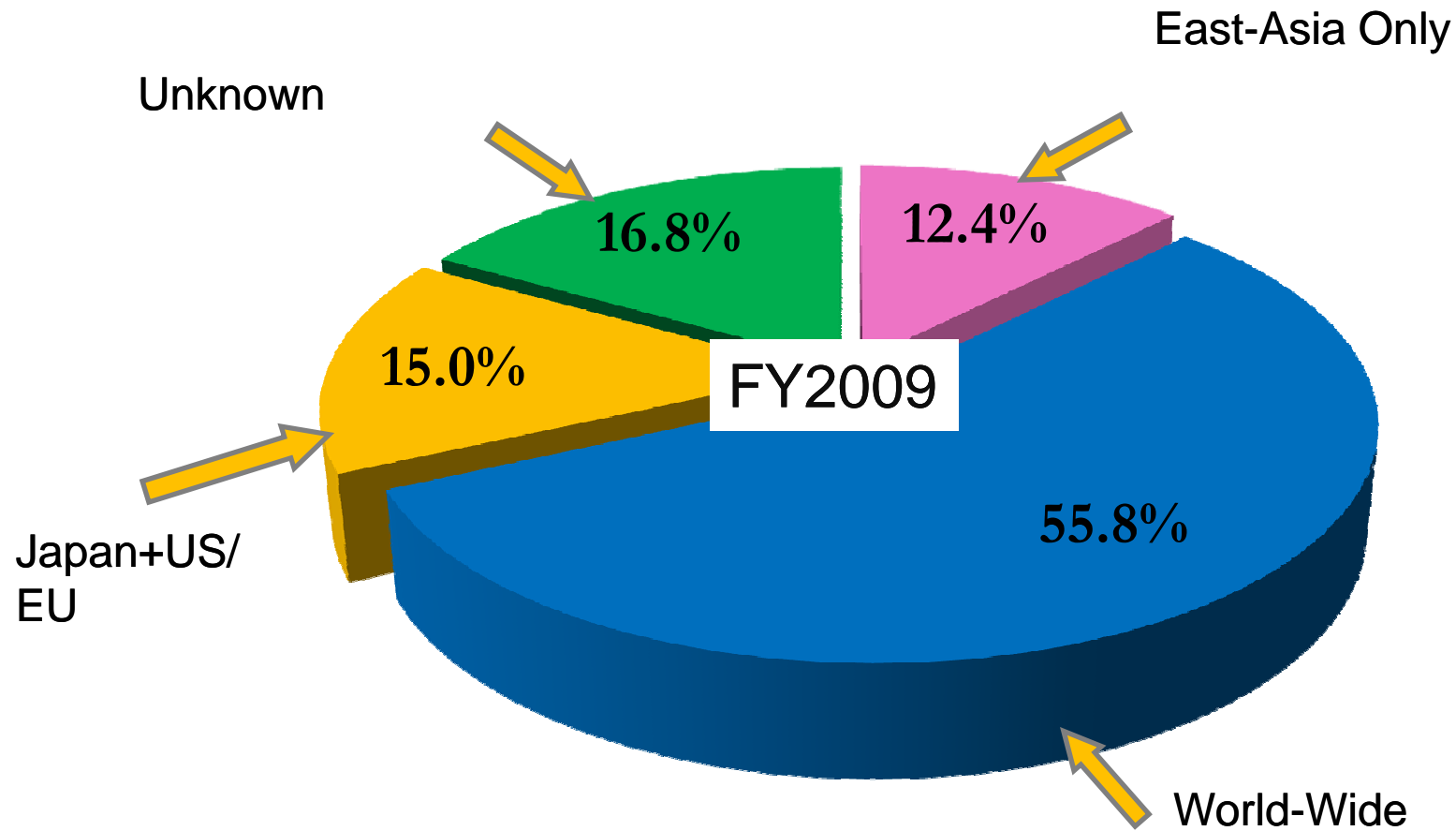
As of Apr. 27, 2009  
(The figure in FY2008 is not fixed.)

# Trends of Global Clinical trials including Japan

-% of MRCTs in CTNs-



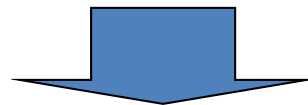
# Operational Regions of Global Clinical trials in FY2009



# Collaboration in East-Asia

## Background:

- In the era of globalization of Drug Development
- The necessity of evaluation on ethnic factors
- East Asian Advantage
  - Ethnic Similarities in China/Korea/Japan East-Asia
    - Genetic similarities
    - Cultural similarities (e.g.; chopsticks countries)
  - Improvement of clinical trial environment in East-Asia
  - Emerging drug market in East-Asia



To develop better drugs through collecting clinical data efficiently in East-Asia, **Regulatory collaboration** among China/Korea/Japan is important

# Tripartite Cooperation among China, Korea and Japan

Apr. 2008 1st Tripartite Director-Generals Meeting in Tokyo  
Agreement on 1)ethnic factor research among east Asia,  
2)information exchange, 3)establishment of WG

Aug. 2009 1st WG in Tokyo

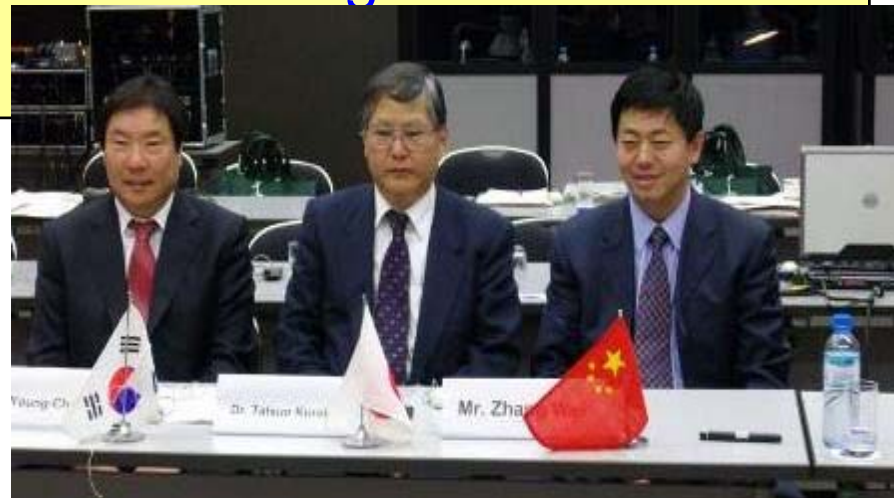
Discussion on TOR of WG

Dec. 2009 2nd WG & Tripartite Director-Generals Meeting in  
Beijing

Agreement on TOR of WG

2010 3rd Tripartite Director-Generals Meeting in Seoul  
(planned)

Apr. 2008 1st Tripartite Director-  
Generals Meeting in Tokyo



# Activities on ethnic factor research in East Asia

## 1 Activities of Japan

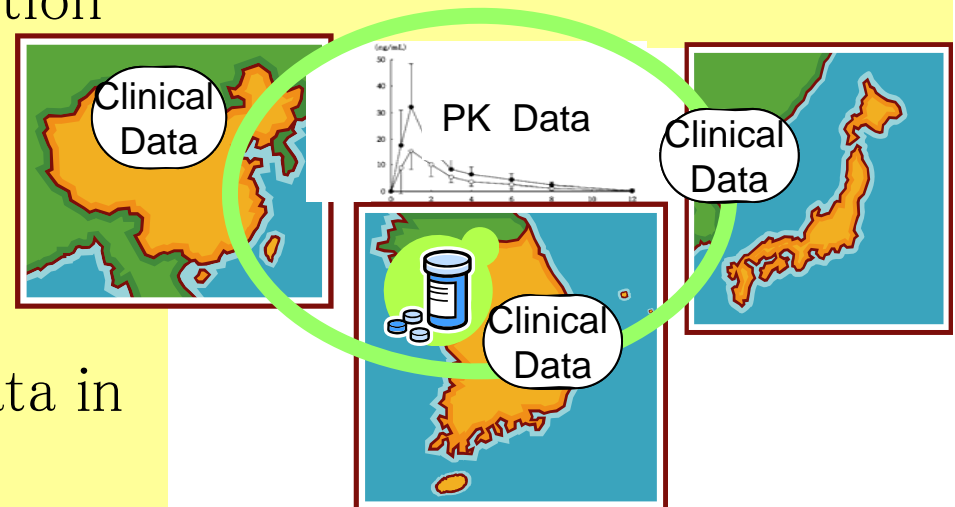
- FY2008 Collecting available PK data of Chinese, Korean and Japan and review the data
- FY2009–2010 Conducting **Prospective PK study Including Chinese, Korean and Japanese** in order to compare ethnic difference more precisely
  - Budget: approximately total 400M Yen (=4M \$ )
  - PK for several marketed drugs is planned to measure
  - PK is measured by use of validated methods

## 2 Activities of Tripartite Cooperation

Collecting available data and discussing ethnic factors

## 3 Japanese Perspective

To develop consideration for collecting East Asian clinical data in MRCT



## Cooperation with other regulatory authorities etc.

### 1 SFDA

- Jan. 2009 MOU for the cooperation on pharmaceuticals with SFDA
- Bilateral meetings for related matters every year

### 2 EU/EMA & FDA

- Bilateral meetings for related matters

### 3 APEC LSIF/RHSC

MRCT Seminar is being planned in this year under the cooperation with KFDA, SFDA, JPMA and PhRMA.

# Globalization of Clinical Trials

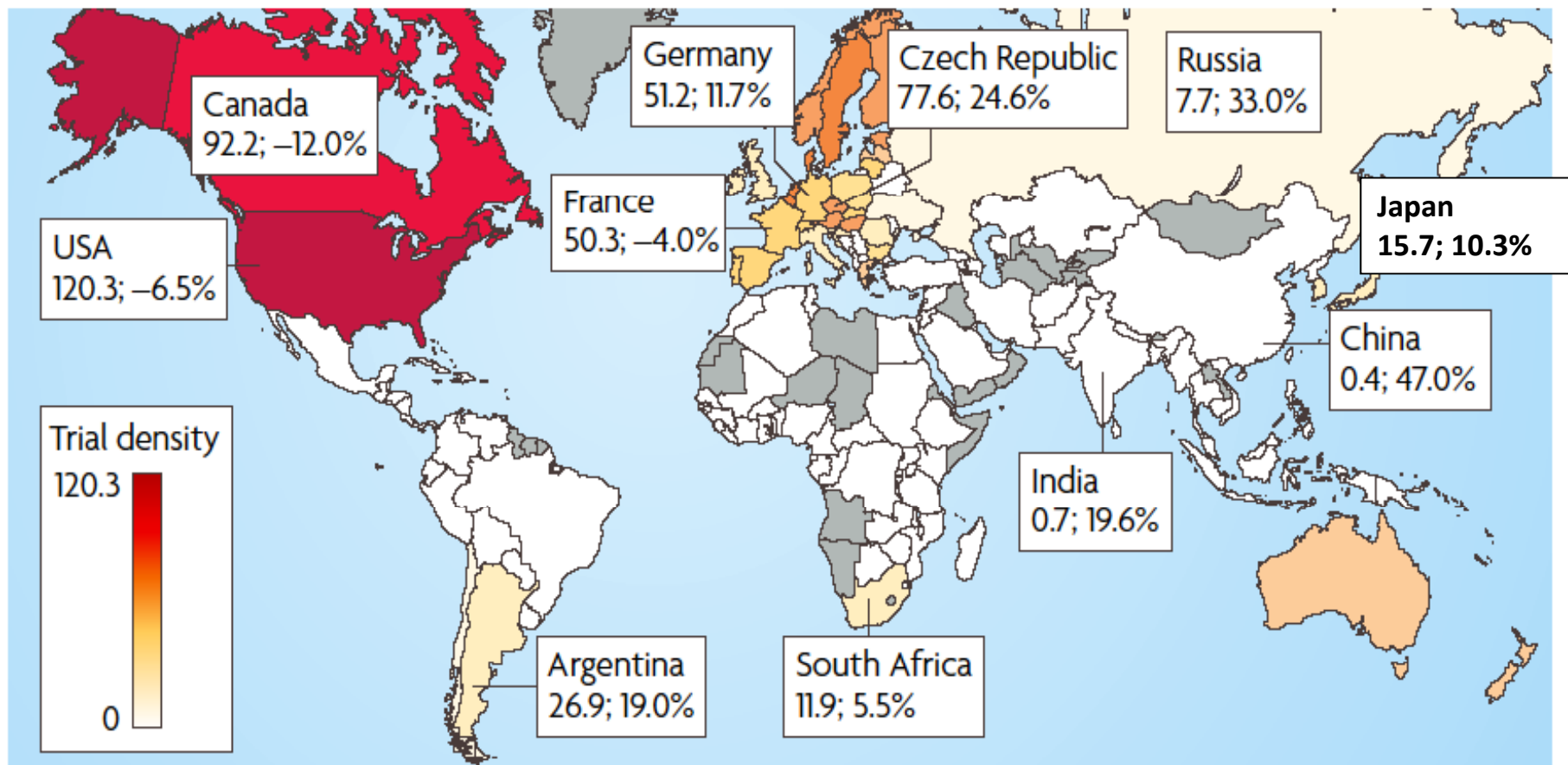
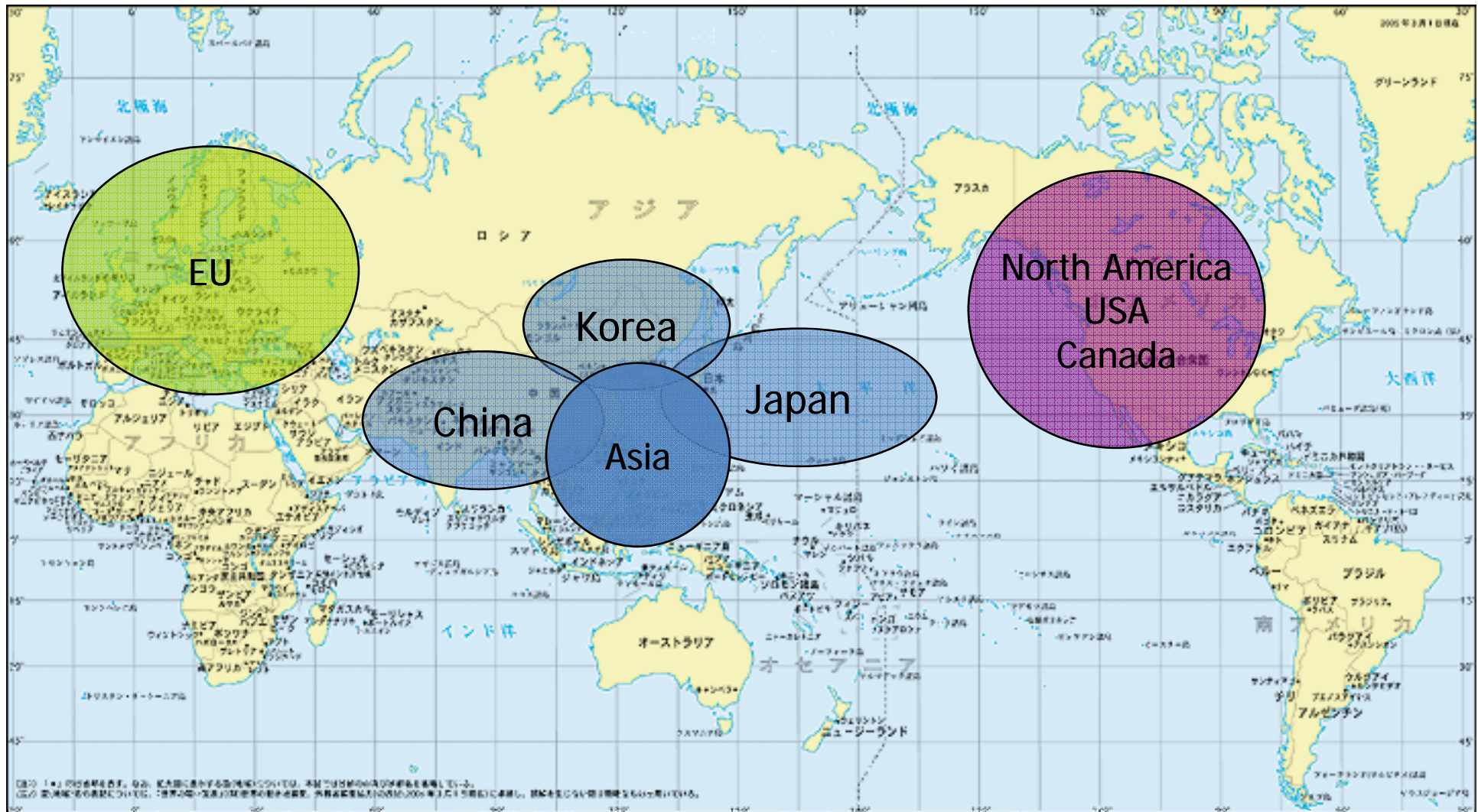


Figure 1 | **Density of actively recruiting clinical sites of biopharmaceutical clinical trials worldwide.** Density is in per country inhabitant (in millions; based on 2005 population censuses); darker orange/red denotes a higher density. The trial density and average relative annual growth rate in percent is shown for selected countries. The countries in grey had no actively recruiting biopharmaceutical clinical trial sites as of 12 April 2007.

# Drugs from Asia to the world



Importance of collaboration among China/Korea/Japan