Japan's Regulatory Initiative to promote Global Clinical Development

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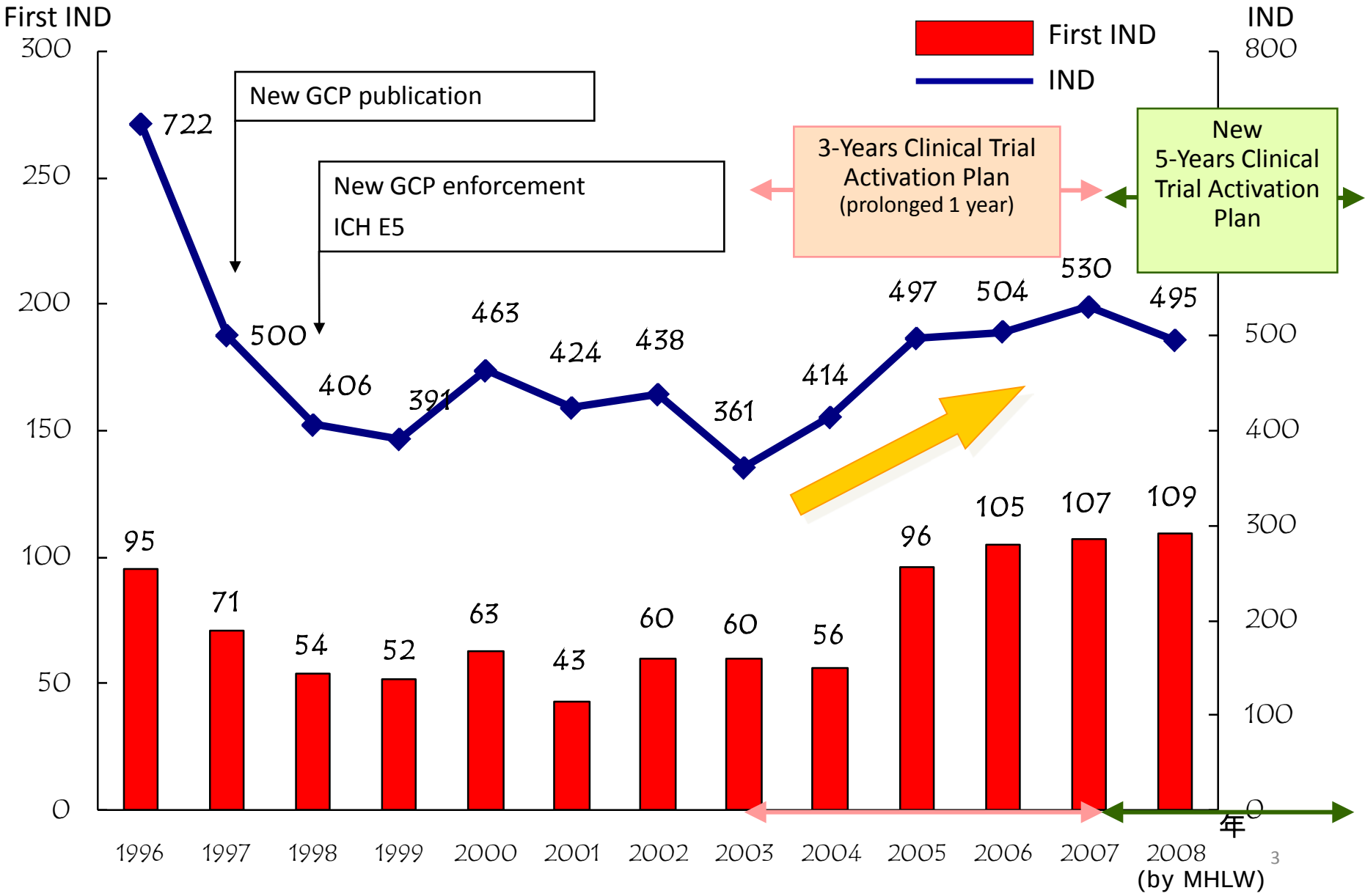
- Action plan for the promotion of clinical trials

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

Number of IND Notifications

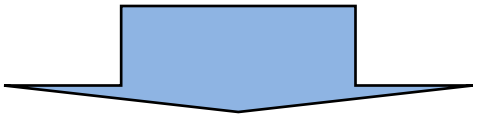


Goals of New 5-Years Clinical Trial Activation Plan

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

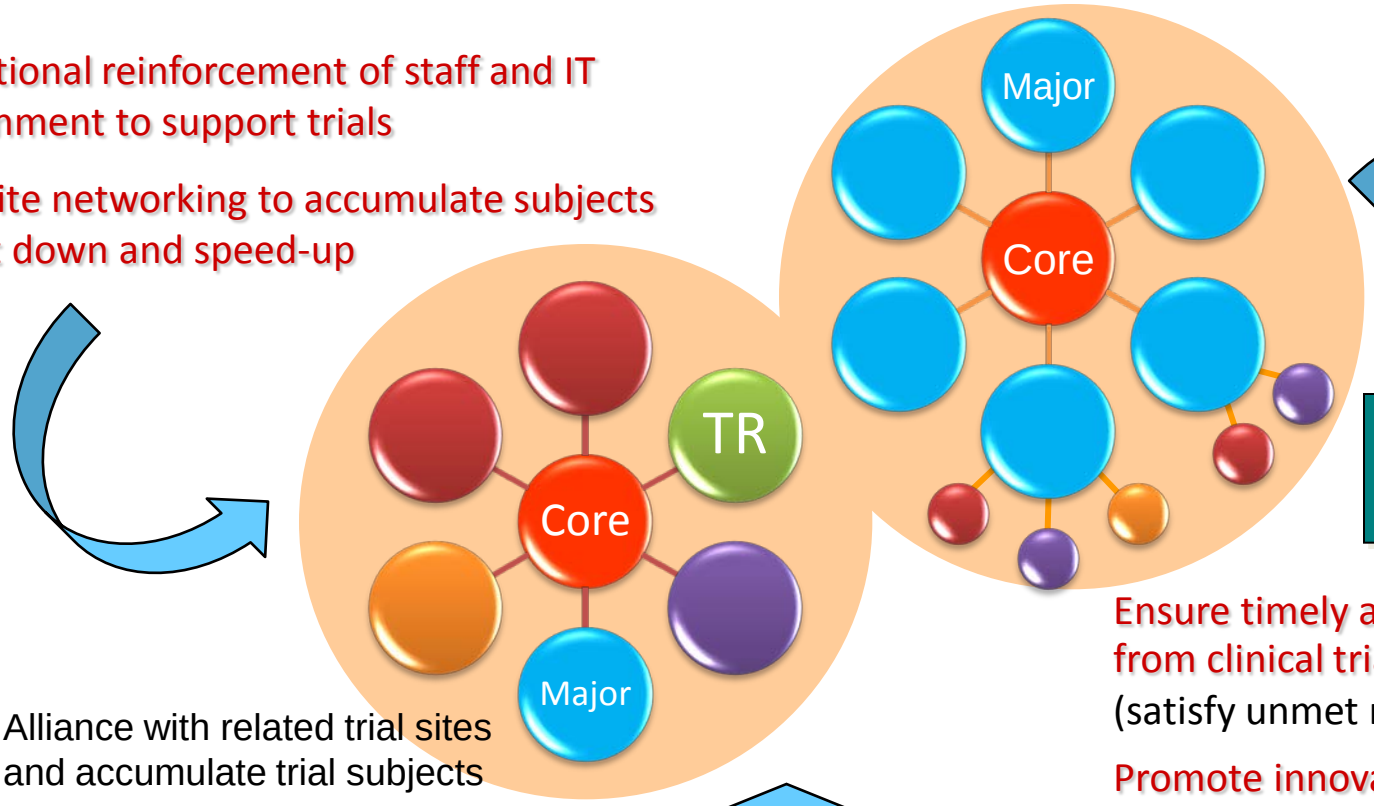
- Review GCP Ordinance and Clinical Research Guideline for international harmonization and patient protection

(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



Alliance with related trial sites and accumulate trial subjects

Expedite trial performance

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)

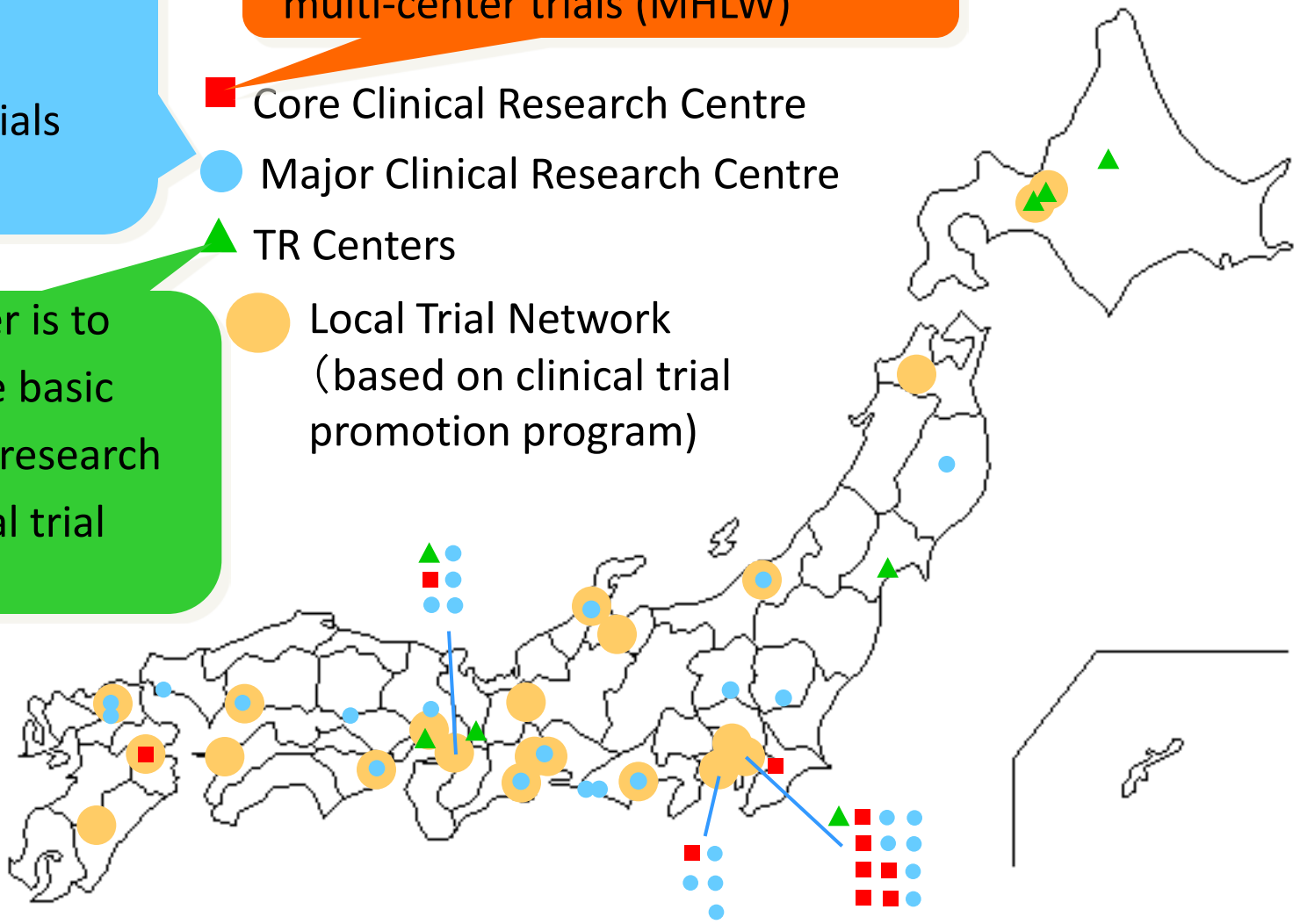
Core Clinical Research Centre

Major Clinical Research Centre

TR Centers

Local Trial Network
（based on clinical trial promotion program)

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



(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/bukyoku/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/ctrialr/

System management
- Company initiated trials
- Promotion

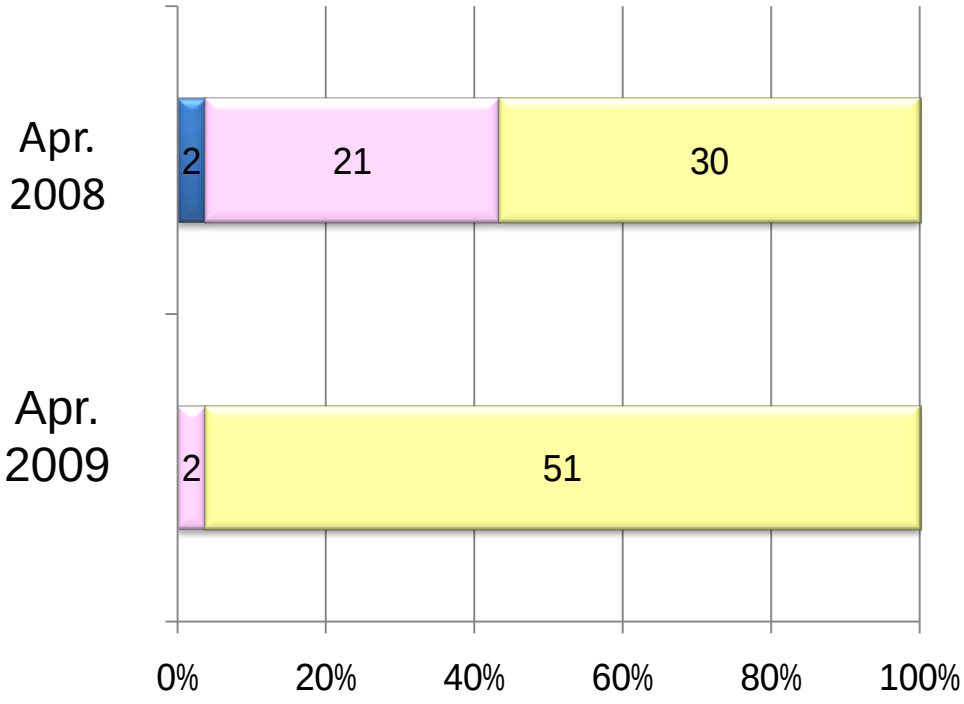
http://www.clinicaltrials.jp/user/cte_main.jsp

Investigator or company

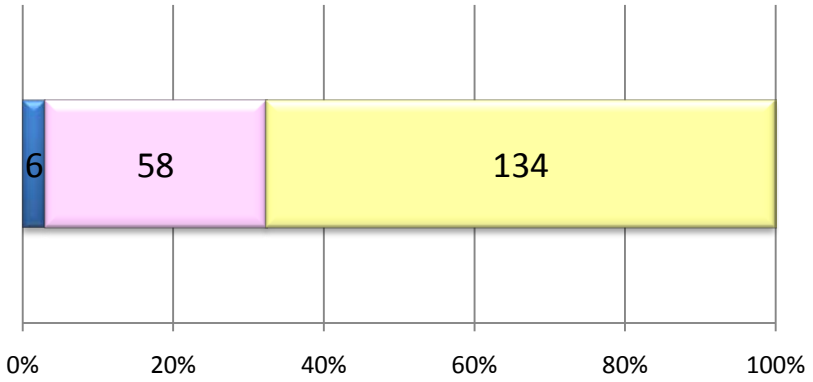
(4) Efficient clinical research management and sponsors' ease

Accept of common documentation format for clinical trials

Situation of accept in cores and majors



Cores, majors and other related 198 organizations

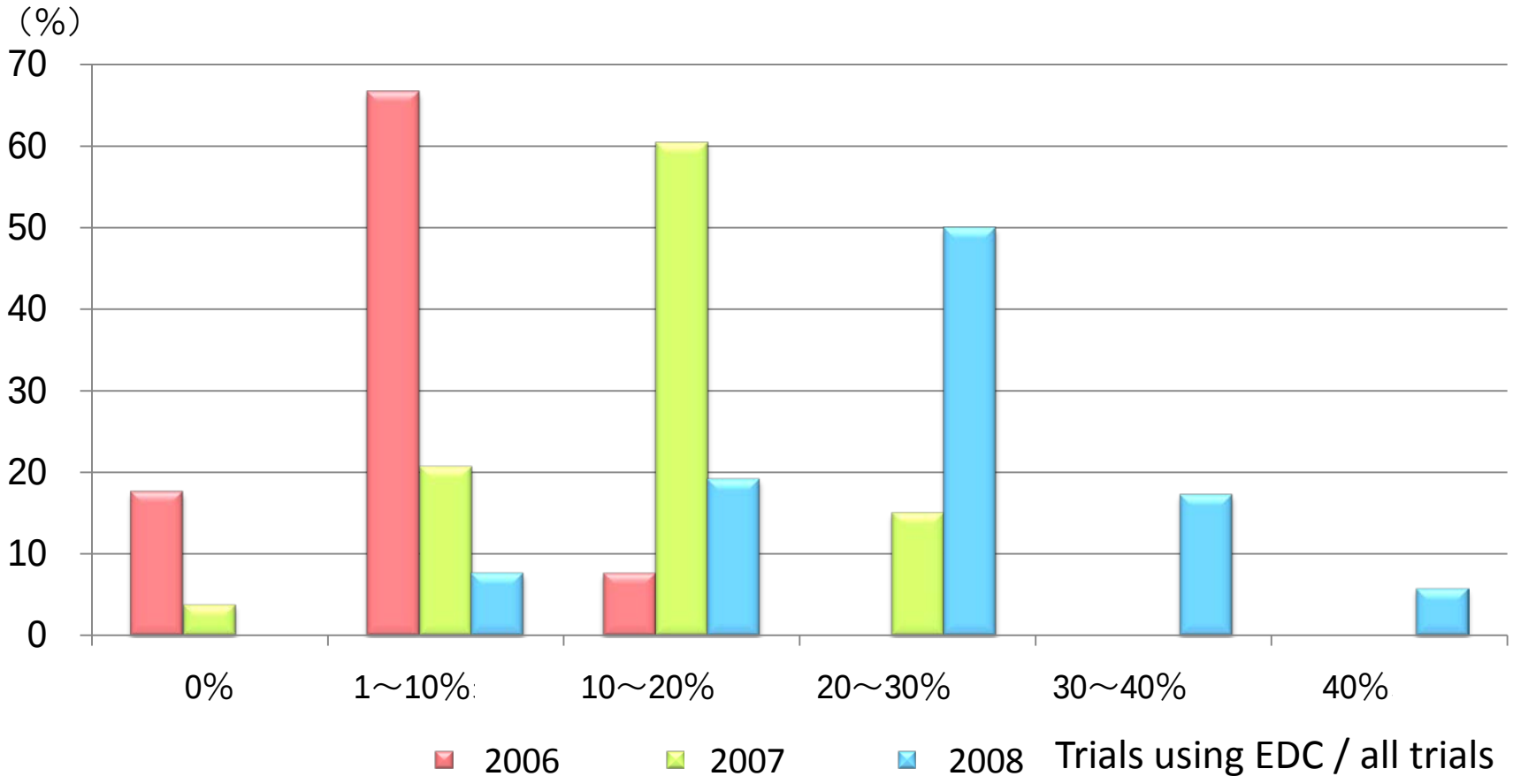


(Oct. 2008)

Completed to introduce at Cores, etc (July 2009)

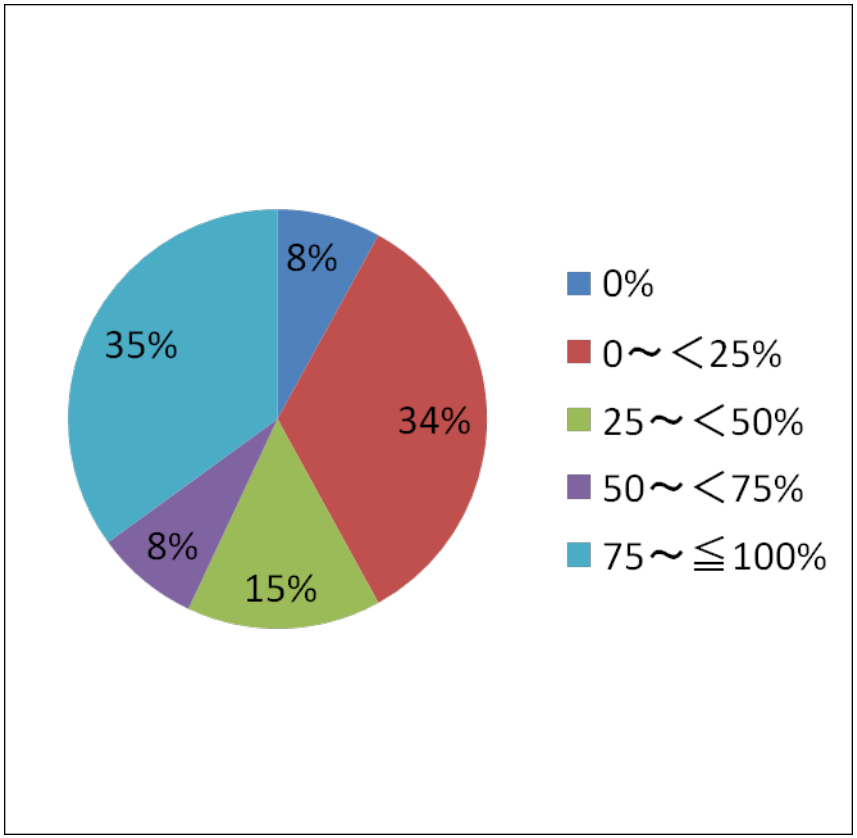
Increase in the rate of clinical trials using EDC

in cores and majors for the past three years

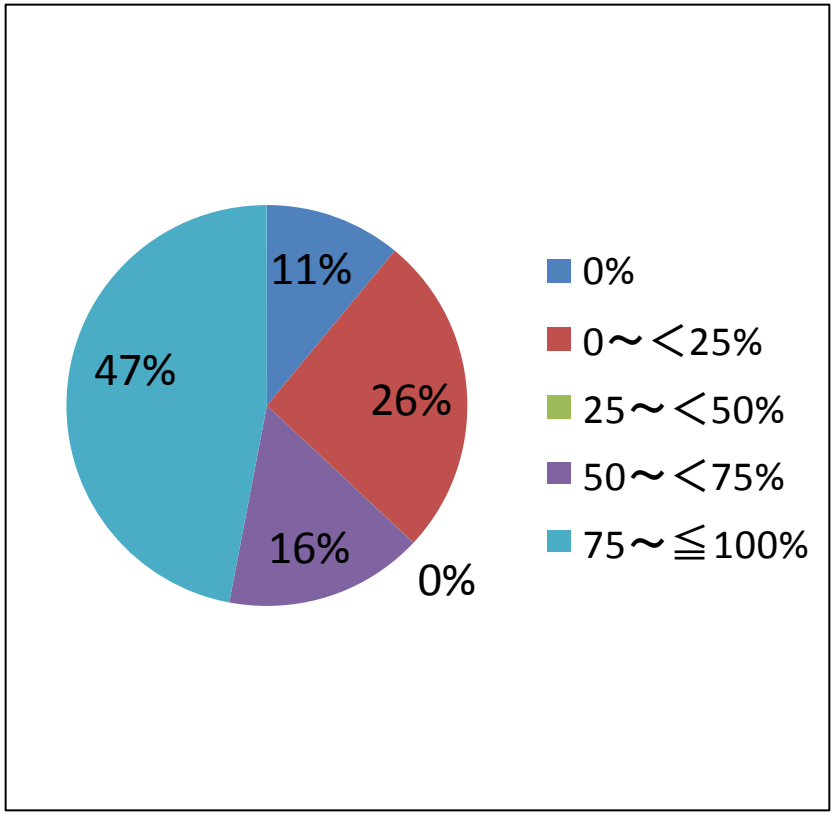


The ratio of clinical trials using EDC (Domestic trials vs Global Trials)（Y.2008）

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.

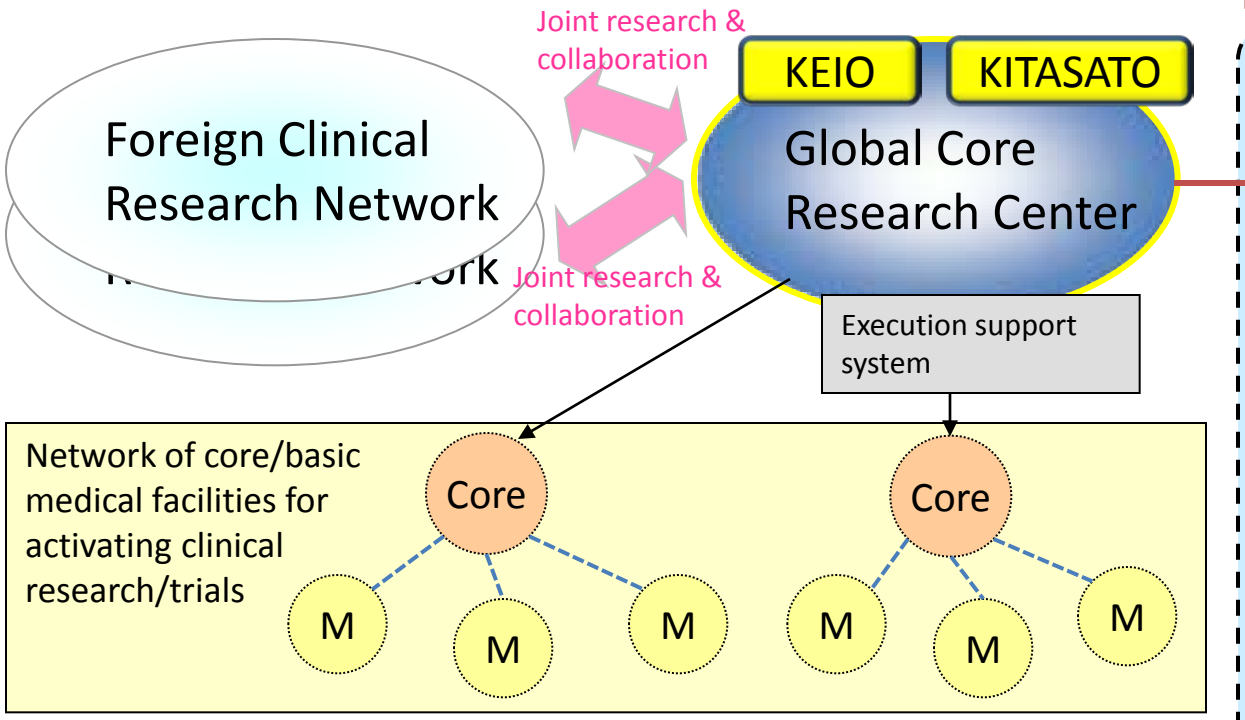
Purpose : In order to put Japan's basic research results into practical use, we have improved a system with higher expertise. While Global studies are increasing as a result of the improved base and sites for the studies, it has also become necessary to create a joint research system in Asia and its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



10 Core clinical research centers

Medical facilities able to conduct high-level clinical trial and research:

30 Major clinical trial institutions

Medical facilities able to smoothly conduct clinical trial and research in collaboration with core hospitals and other basic hospitals

Functions to be provided

- System for smoothly working out English contract and accounting based on international standards
- Central ethical review function
- International research planning/data analysis (Senior data managers and computer technicians can be secured)
- Setup as a domestic exploratory clinical research center (securing doctors, test technicians, radiologic technicians, etc.)
- Fostering of doctors to become international research support personnel and supply the personnel to the sites and bases
- To secure human resources for constructing systems and strategies for the management of intellectual property.
- Accumulation and organizational coordination of case information.

Guidance: Basic Principles On Global Clinical Trials

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

－One of Key Messages－

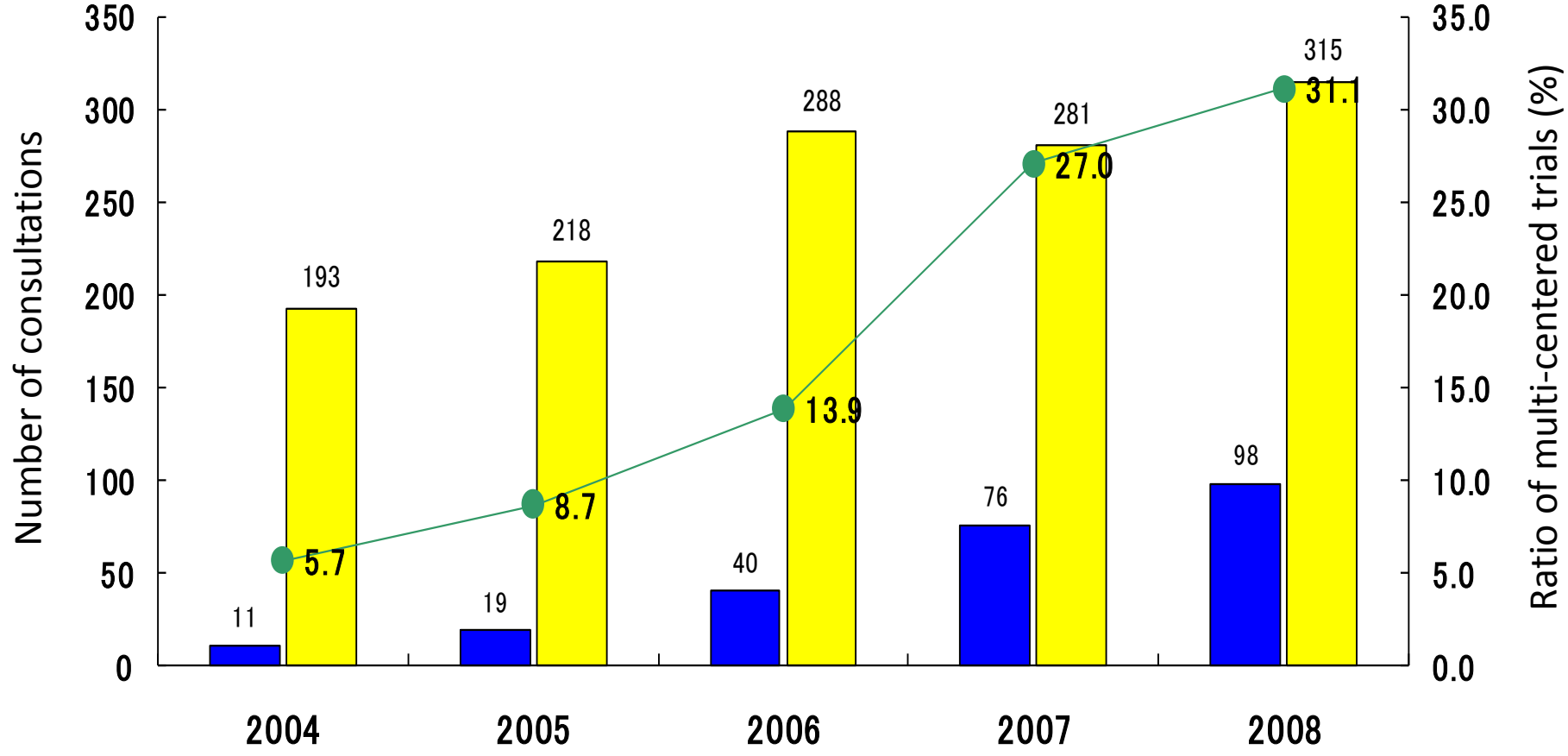
- Promote to conduct global clinical trials more appropriately in consideration of ethnic factors

- 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

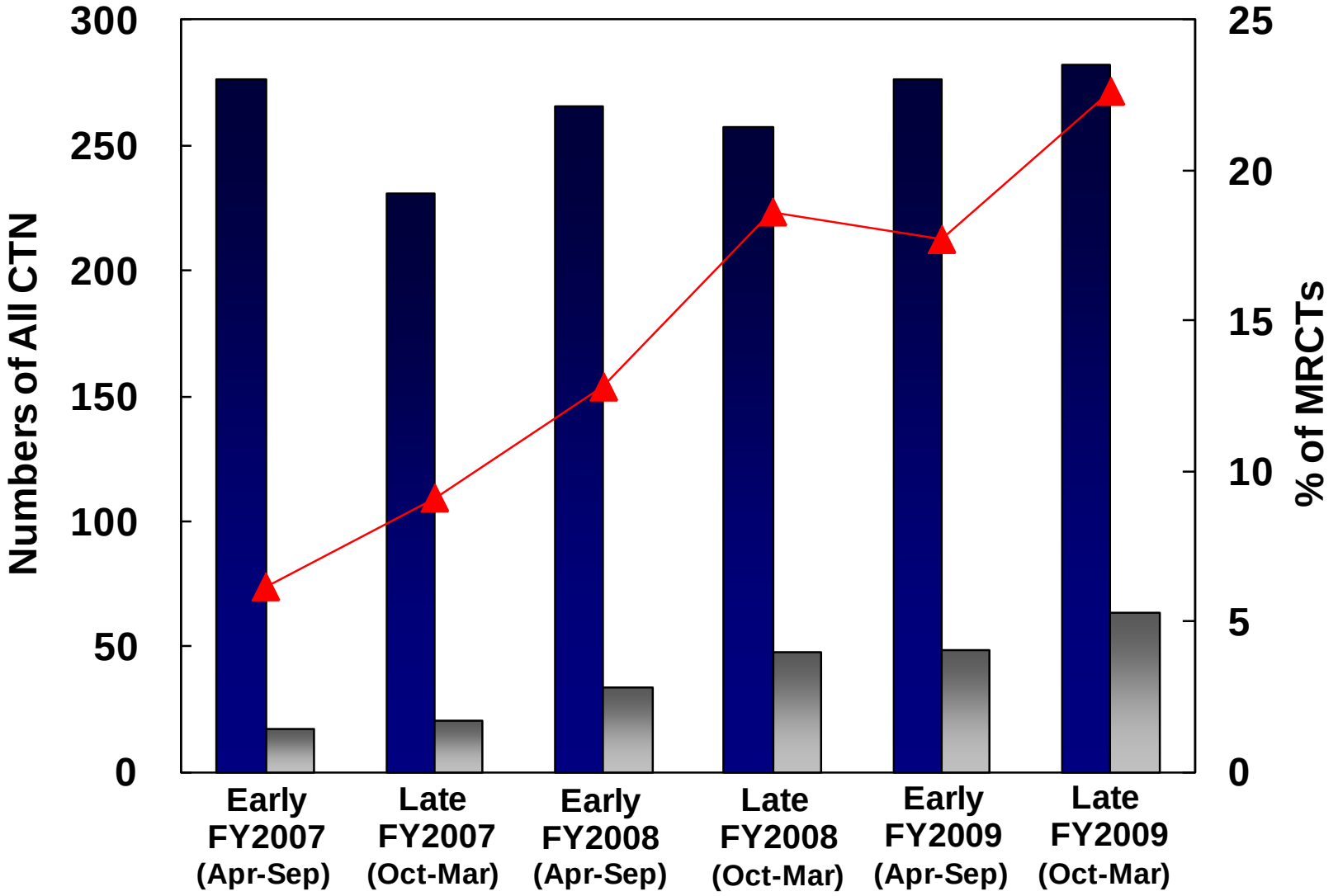


As of Apr. 27, 2009
(The figure in FY2008 is not fixed.)

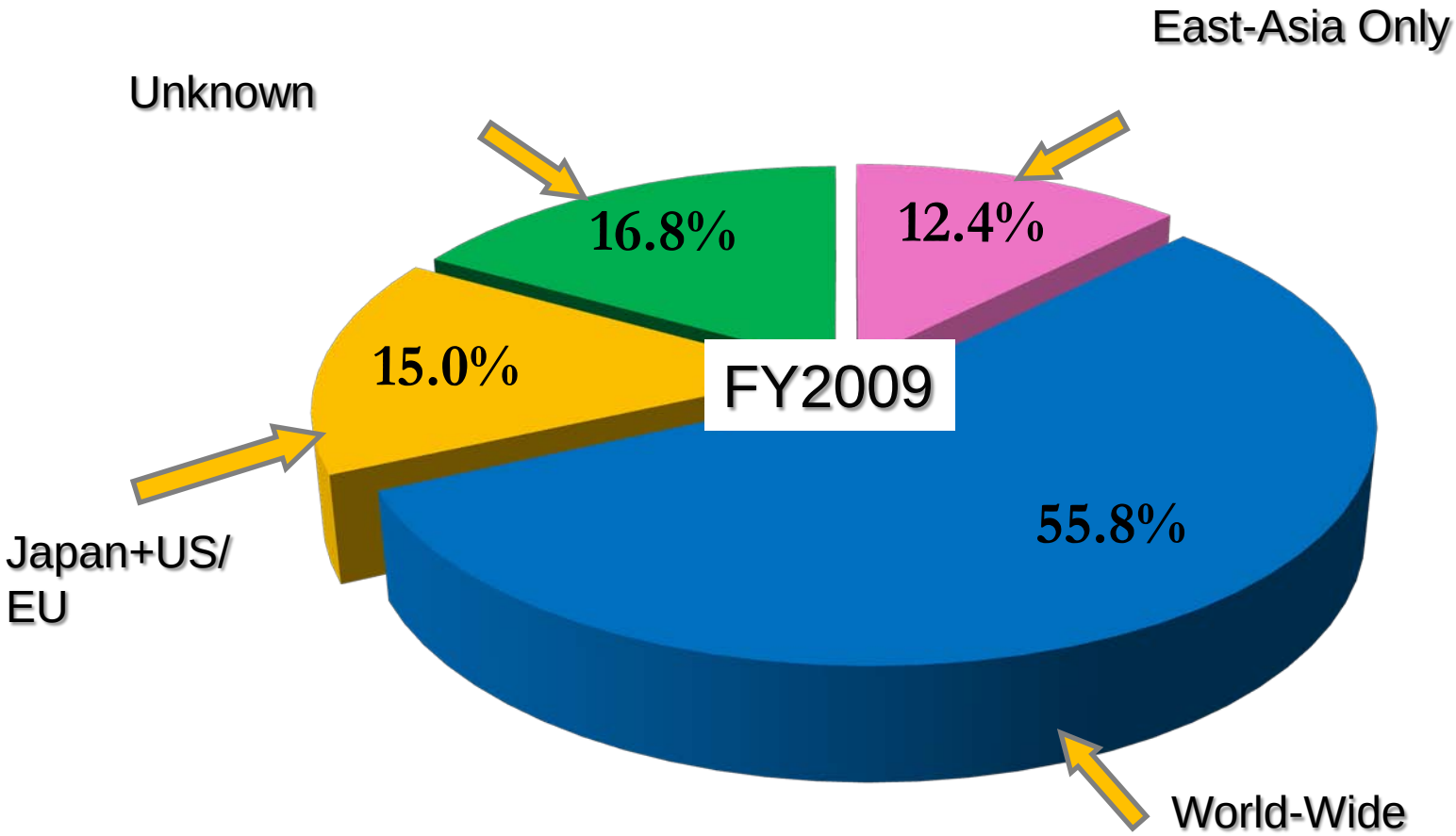
Source: PMDA

Trends of Global Clinical trials including Japan

-% of MRCTs in CTNs-



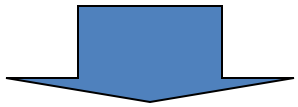
Operational Regions of Global Clinical trials in FY2009



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

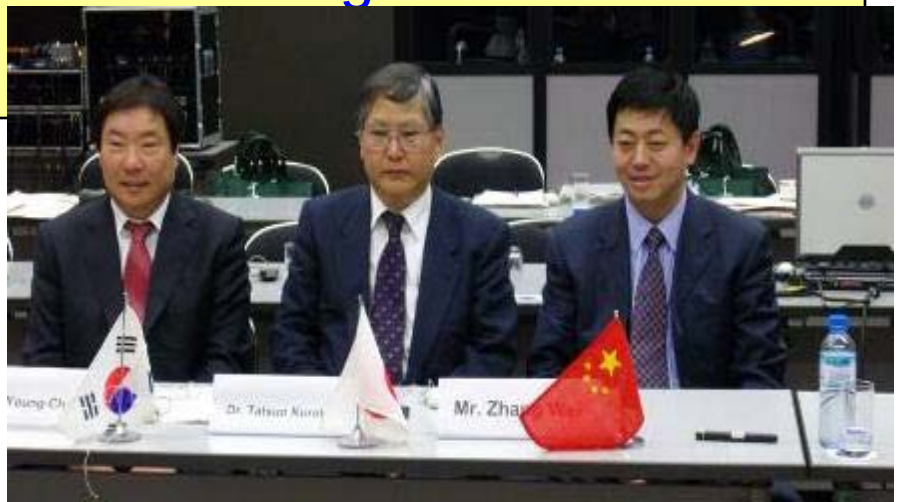
Tripartite Cooperation among China, Korea and Japan

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

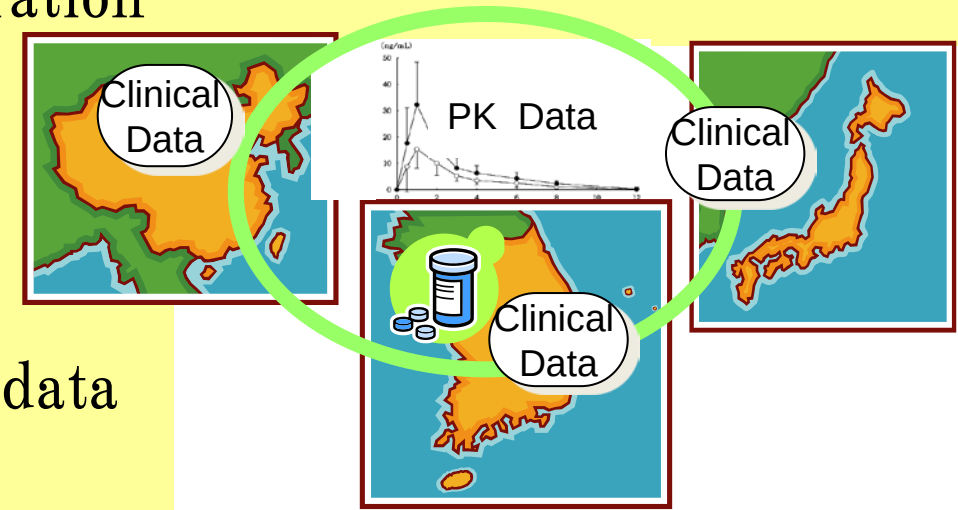
- FY2008 Collecting available PK data of Chinese, Korean and Japan and review the data
- FY2009-2010 Conducting Prospective PK study Including Chinese, Korean and Japanese in order to compare ethnic difference more precisely
  - Budget: approximately total 400M Yen (=4M $)
  - PK for several marketed 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

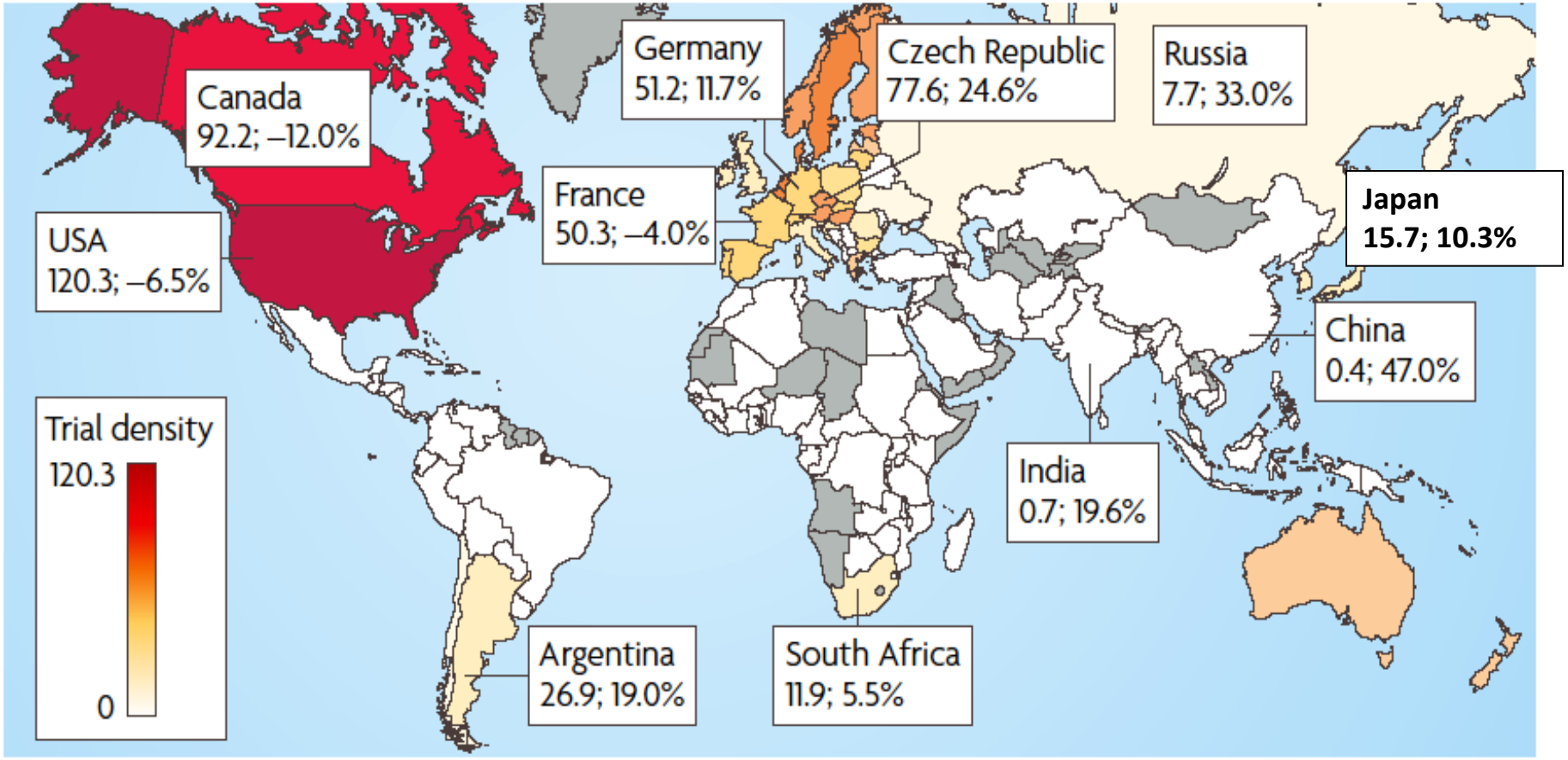
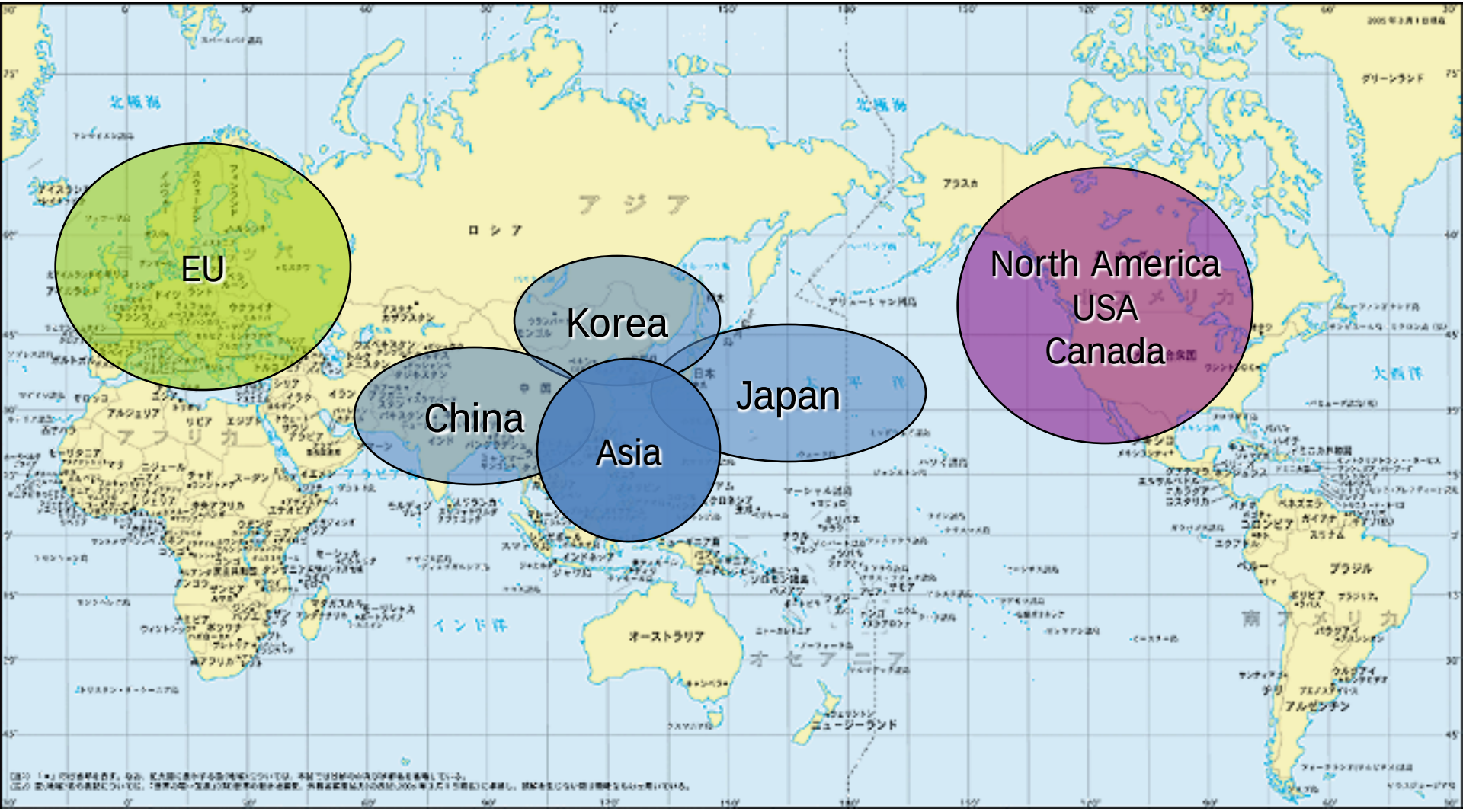


Figure 1 | **Density of actively recruiting clinical sites of biopharmaceutical clinical trials worldwide.** Density is in per country inhabitant (in millions; based on 2005 population censuses); darker orange/red denotes a higher density. The trial density and average relative annual growth rate in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

Nature Rev Drug Discovery, 7: 13, 2008

Drugs from Asia to the world



Importance of collaboration among China/Korea/Japan