2014 APEC LSIF Joint Multi-Regional Clinical Trials and Good Clinical Practice Inspection Workshop

# Risk-based approach on GCP inspection

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1. Trends in Improvement of the Efficiency in Clinical Trials
2. Risk-based Approach to GCP Monitoring
3. GCP Inspection Procedure in Japan
4. EDC Management Sheets

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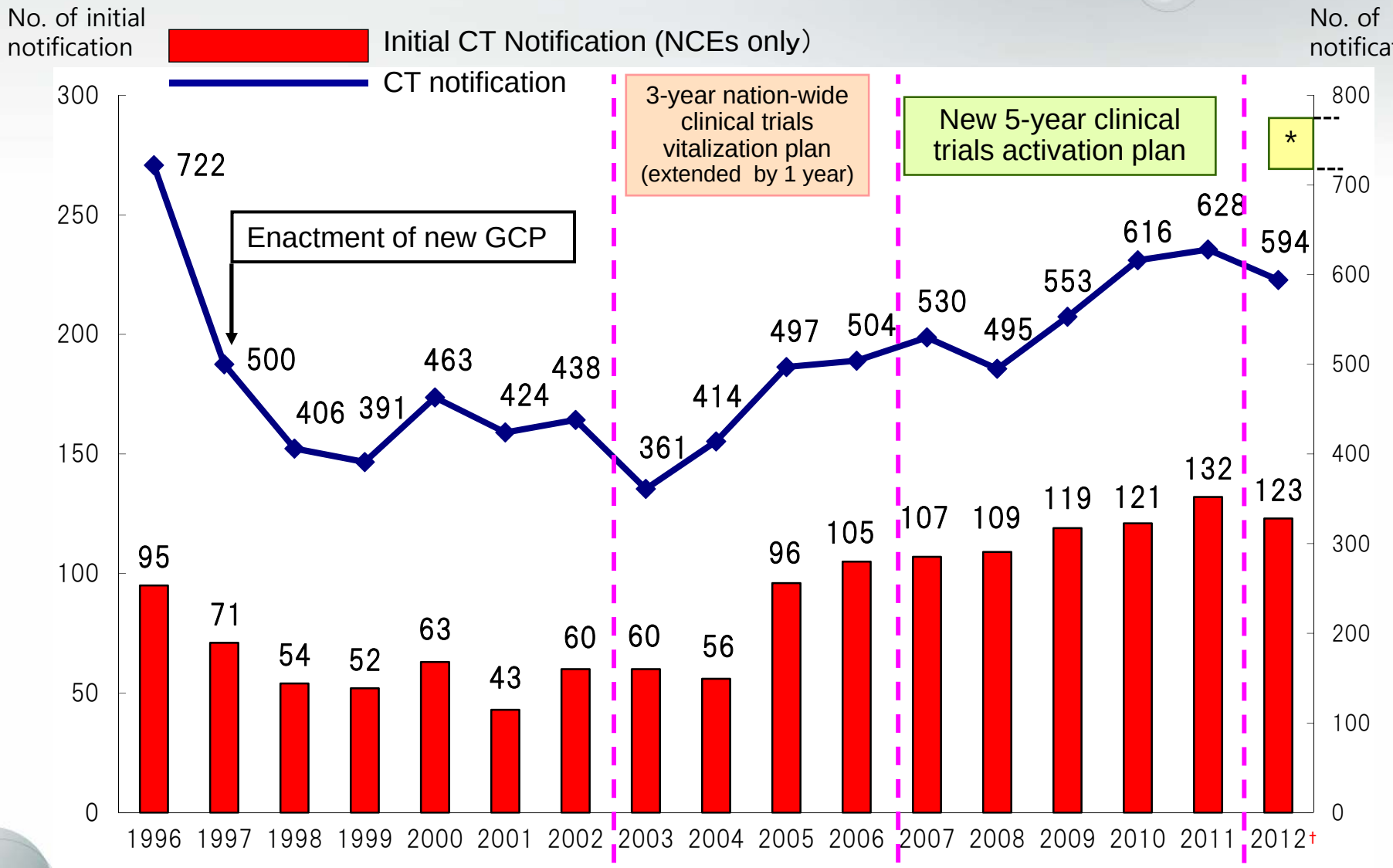
# Trend in Notified CTs in Japan






† 5-year clinical trials vitalization plan 2012 started in 2012

# Trends in Improvement of the efficiency in clinical trials (1)

## "5-year Clinical Trials Vitalization Plan 2012"

30 March, 2012 Notification 0330 No.33 MHLW/HSB

1. The next action forward based on the vitalization plans of the last 9 years
   - (1) Enrollment of subjects
   - (2) **Procedures for Implementation of Clinical Trials**
     **Improvement in efficiency of monitoring operations considering of sampling methods to select data for SDV**
   - (3) Human resources development (physicians etc.)
   - (4) Dissemination and education for patients and people
   - (5) Appropriate cost
   - (6) **Promotion of utilization of IT technologies, etc.**
2. Approach for Innovative pharmaceuticals and medical devices developed in Japan

# Trends in Improvement of the efficiency in clinical trials (2)

"Research on the operations of the sponsor-investigator clinical trials"
FY2012 Health, Labour and Welfare Scientific Research Grants
for General Research on Drugs and Medical Devices Regulatory Sciences
The principal researcher, Professor Yuji Watanabe
(Faculty of Medicine, Hamamatsu Medical University)
**Contributor to the research,2012**

"The application of electromagnetic record to the Clinical Trial-related Documents for the conduct of a clinical trial"

↓

"Basic principles of Utilization of Electromagnetic Records In Clinical Trial Documents"
MHLW PFSB/ELD Notice, 1 July 2013

The advantages of electromagnetic method for recording can be maximized when the characteristics of the method (advantages and/or points of attention compared to those of paper documents) is fully understood

# Recent trend on Utilization of Electromagnetic Records

## ➢ Electromagnetic Documentation of Clinical trials

1. **Notification regarding utilization of electromagnetic record on clinical trial related documents**
   - † MHLW Administrative Notice(July 01, 2013)
2. **Project for Trial-related documents delivery by electromagnetic records**
   - † Electromagnetic Implement Task Force(JPMA, 2014)

## ➢ Electronic Data Capture (EDC) and Application Data

1. **Notification regarding inspection method for clinical trials which use EDC system**
   - † PMDA/CPE Notification No. 0327001(March 27, 2013)
2. **Electronic Clinical Study Data for Pilot Project**
   - † PMDA/CPE Notification No. 0902001(September 02, 2013)
3. **Project for 'Remote Data Monitoring' and 'EDC- EHR communication'**
   - † Health Labour Sciences Research Grant(2013)
4. **Project for clarifying inspection policy for clinical trials in which CDISC standard is applied**
   - † PMDA the current mid-term target(2014-2019)

# Trends in Improvement of the efficiency in clinical trials (3)

"Research on the operations of the sponsor-investigator clinical trials"

FY2012 Health, Labour and Welfare Scientific Research Grants
for General Research on Drugs and Medical Devices Regulatory Sciences
The principal researcher, Professor Yuji Watanabe
(Faculty of Medicine, Hamamatsu Medical University)
**Contributor to the research, 2012**

"Research about Risk-Based SDV approaches"

↓

"Basic principles of the Risk-Based Approach to Monitoring"

MHLW PFSB/ELD Notice, 1 July, 2013

Presenting basic principles of risk-based approach for monitoring and SDV

# Contents

# Background

- To conduct clinical trials, a great volume of operations and costs are required for monitoring
- Popularization of EDC (Electronic Data Capture) enables clinical trial data to be consolidated rapidly and centrally
- Centralized monitoring is accepted under GCP Ordinance, when the safety of the subjects is secured and the integrity of clinical trial data is assured

## Consideration of the risk-based approach to monitoring

"Basic principles of the Risk-Based Approach to Monitoring Clinical Trials" MHLW PFSB/ELD Notice, 1 July, 2013

# What is Risk-Based SDV approach ?

- A method to conduct SDV that verifies items selected in accordance with the pre-determined procedure, taking into consideration the impact of the data on the quality of the clinical trials, from the perspective of the safety of the subjects and importance of the data

＊Ministerial Ordinance on GCP Article 21 Paragraph 1 ; Guidance
If the clinical trials are operated appropriately in the core clinical trial hospitals, etc., not all data are required to be verified with source data

"Basic principles of the Risk-Based Approach to Monitoring Clinical Trials" MHLW PFSB/ELD Notice, 1 July, 2013

# Management of Clinical Trial Processes



Administration /controlling of electric medical record system

control/accountability of the IPs

Selection of IRB and Requesting of deliberation

Record keeping

Assigned duties

Selection of subjects and IC

Conducting a clinical trial

Reporting of ADRs

Medical records

Information sharing to involved parties

CRF etc.

Responsibilities for medical care of subjects

Investigator's Brochure

Control/accountability of the IPs
Supply of the IPs

Information on ADR etc.

Selection of medical institution and investigator

Clinical trial reports

Protocol

Pharma Company

Audits

Implementing/ controlling data capture system

Monitoring

Record keeping etc.

* Regarding risk-based monitoring, it is important to consider not only effectiveness of monitoring, but also process management in medical institutions, etc.

# Risk-based monitoring : Basic principles (1)

- It is essential for persons in charges in medical institutions to strive to submit data promptly, considering that monitoring could be conducted not by means of SDV
- It is essential that principal investigator/sub investigators and CRC etc. understand the aim and procedures of risk based monitoring adequately

  It is a requirement that the involved personnel are aware that it is their own responsibility to create accurate CRFs in medical institutions

- Emphasis must be placed on process management of clinical trials in the medical institution and it is essential that appropriate measures are in place to fill out CRFs accurately

"Basic principles of the Risk-Based Approach to Monitoring Clinical Trials" MHLW PFSB/ELD Notice, 1 July, 2013

# Risk-based monitoring : Basic principles (2)

- It is important that the sponsors ensure that the clinical trials (protocol, CRF, etc.) are designed concisely and clearly; for example, collecting only data those are fit for purpose

- The following items should be considered: the aim of the clinical trial, the trial design, the endpoints, the study population, and the experience of both the principal investigator and the medical institution, and the clinical trial implementation structure.

"Basic principles of the Risk-Based Approach to Monitoring Clinical Trials" MHLW PFSB/ELD Notice, 1 July, 2013

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# GCP Inspection Procedure in Japan

- ✓**Application-based**
- ✓**Conducted after the clinical trials (or surveys) have finished**

⇒ **By verifying the implementation status of the finished clinical trials (or surveys), we aim to secure the quality of ongoing clinical trials (or surveys), and/or trials (or surveys), scheduled in the future.**

- ✓**Timing**
  - **New-drug Application <Pre-approval>**
  - **Re-examination Application <Post-marketing>**

# Selection of Medical Institutions

## Current Procedure

- **The drugs with new active pharmaceutical ingredients**
  **(Excluding the drugs of quick/priority review, the orphan drugs)**

- **Others**

**Points to be considered**

- **Priority of clinical trials included in the application (ex; pivotal clinical trial)**
- **The number of subjects**
- **Results of previous inspections**

**…**

*** Additional inspections will be conducted if there are problems identified during review/inspection process.**

# Conducting GCP On-site Inspection in Overseas

## Current Procedure

- **Points to be considered**
  - **Pivotal clinical trials conducted in overseas ?**
  - **Already approved product in overseas ?**
  - **Already inspected trial/institution by foreign authorities ?**

    **…**
- **Selection of medical institutions**
  - **By the same way as in Japan**

# Conclusion of GCP On-site Inspection

**Compliance:**

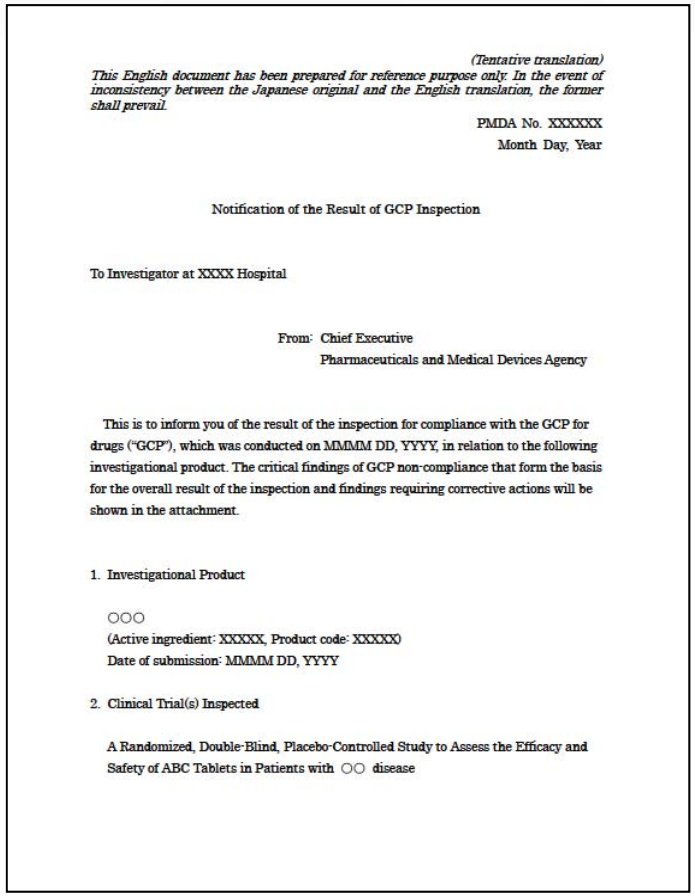
**Acceptable as application dossier**
**(indicate voluntary action, if necessary)**

**Compliance with condition:**

**Violation of GCP was found in a part of subjects**
**→ Acceptable as application dossier after excluding the data from NDA package**

**Non-compliance:**

**Violation of GCP was found generally and systematically**
**→ No reliability**
**→ Not acceptable as application dossier**



*(Tentative translation)*
*This English document has been prepared for reference purpose only. In the event of inconsistency between the Japanese original and the English translation, the former shall prevail.*

PMDA No. XXXXXX
Month Day, Year

Notification of the Result of GCP Inspection

To Investigator at XXXX Hospital

From: Chief Executive
Pharmaceuticals and Medical Devices Agency

This is to inform you of the result of the inspection for compliance with the GCP for drugs ("GCP"), which was conducted on MMMM DD, YYYY, in relation to the following investigational product. The critical findings of GCP non-compliance that form the basis for the overall result of the inspection and findings requiring corrective actions will be shown in the attachment.

1. Investigational Product

○○○
(Active ingredient: XXXXX, Product code: XXXXX)
Date of submission: MMMM DD, YYYY

2. Clinical Trial(s) Inspected

A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of ABC Tablets in Patients with ○○ disease

# Results of GCP On-site Inspection

## To sponsors

- **Finding(s) for preparation of clinical trials**
  **(preparation of protocol, investigator's brochure, etc.)**
- **Finding(s) for control of clinical trials**
  **(monitor's responsibility, provision of safety information, etc.)**

## To medical institutions

- **General finding(s)**
  **(control of investigational products, IRB, etc. )**
- **Finding(s) for individual subjects**
  **(informed consent, protocol deviations, etc.)**

# Trend in GCP On-site Inspections

| | FY' 08 | FY' 09 | FY' 10 | FY' 11 | FY' 12 |
|---|---|---|---|---|---|
| Number of drugs (NMEs) | 100 (3) | 84 (6) | 84 (7) | 83 (7) | 99 (5) |
| Number of sponsors | 100 (4) | 80 (6) | 78 (7) | 87 (7) | 99 (5) |
| Number of medical Institutions | 216 (6) | 180 (13) | 188 (14) | 180 (13) | 189 (9) |

( ): The number of inspections in overseas

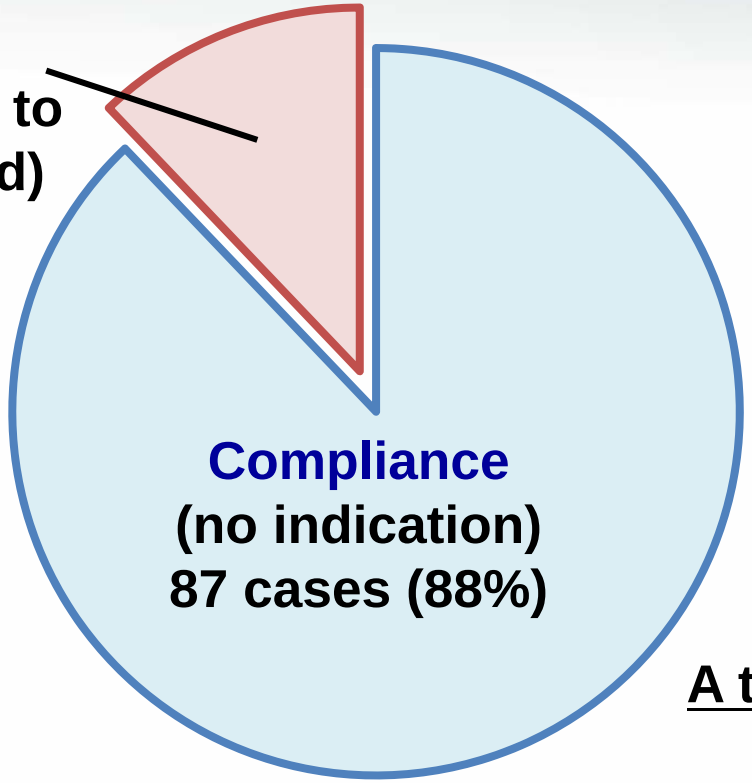
# Detail of Overseas Inspection

| | Accumulated total from April, 2007 to March, 2012[1)] | Country | | | |
|---|---|---|---|---|---|
| Number of inspection | 31 | | | | |
| Sponsors[2)] | 35 | USA | 10 | Netherlands | 1 |
| | | UK | 3 | China | 3 |
| | | Germany | 4 | Korea | 5 |
| | | France | 1 | Taiwan | 3 |
| | | Switzerland | 1 | Philippines | 1 |
| | | Belgium | 1 | Spain | 1 |
| | | India | 1 | | |
| Medical institutions | 55 | USA | 13 | Belgium | 1 |
| | | Canada | 2 | Netherlands | 1 |
| | | UK | 4 | China | 6 |
| | | Germany | 4 | Korea | 8 |
| | | France | 2 | Taiwan | 6 |
| | | Hungary | 2 | Philippines | 2 |
| | | Spain | 2 | India | 2 |

1) Number of Notices of results issued
2) Including the number of CRO

# Conclusion of GCP On-site Inspection for New Drugs (FY 2012) [1,2)]

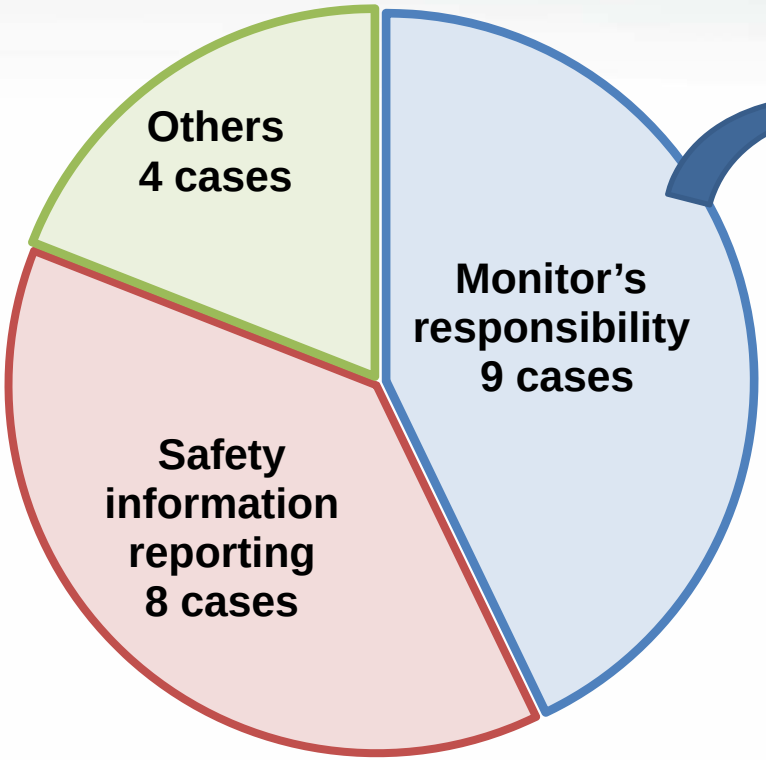
**Compliance**
**(voluntary actions to improve indicated)**
**12 cases (12%)**




**A total of 99 cases [3)]**

1) The products for which the inspection result notification was issued from Apr. 2012 to Mar. 2013.
2) There was no “Non-compliance” and ”Compliance with condition” cases in FY 2012.
3) Number of inspection result notifications issued (per applicant).

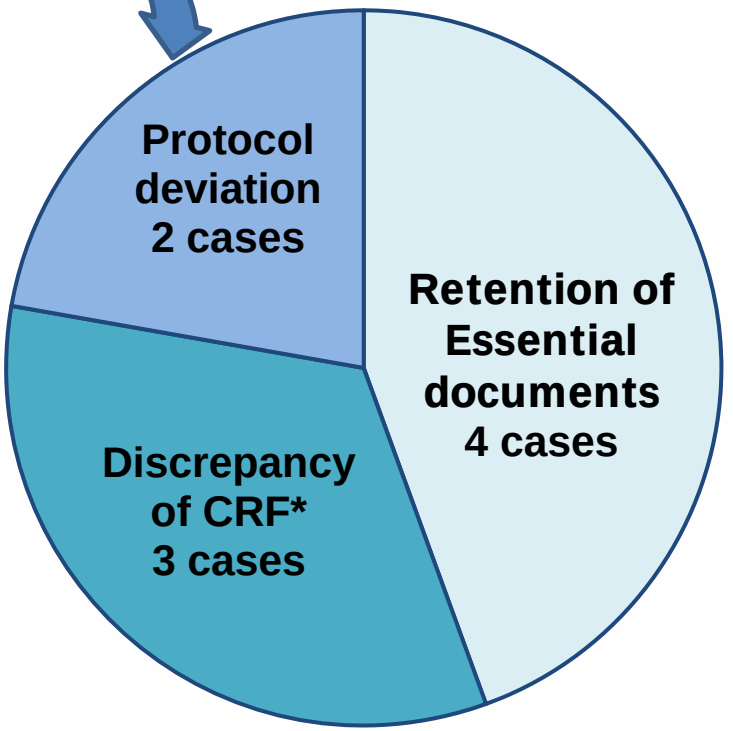
# Findings for Sponsors in JAPAN (FY 2012)




(N=21 cases)

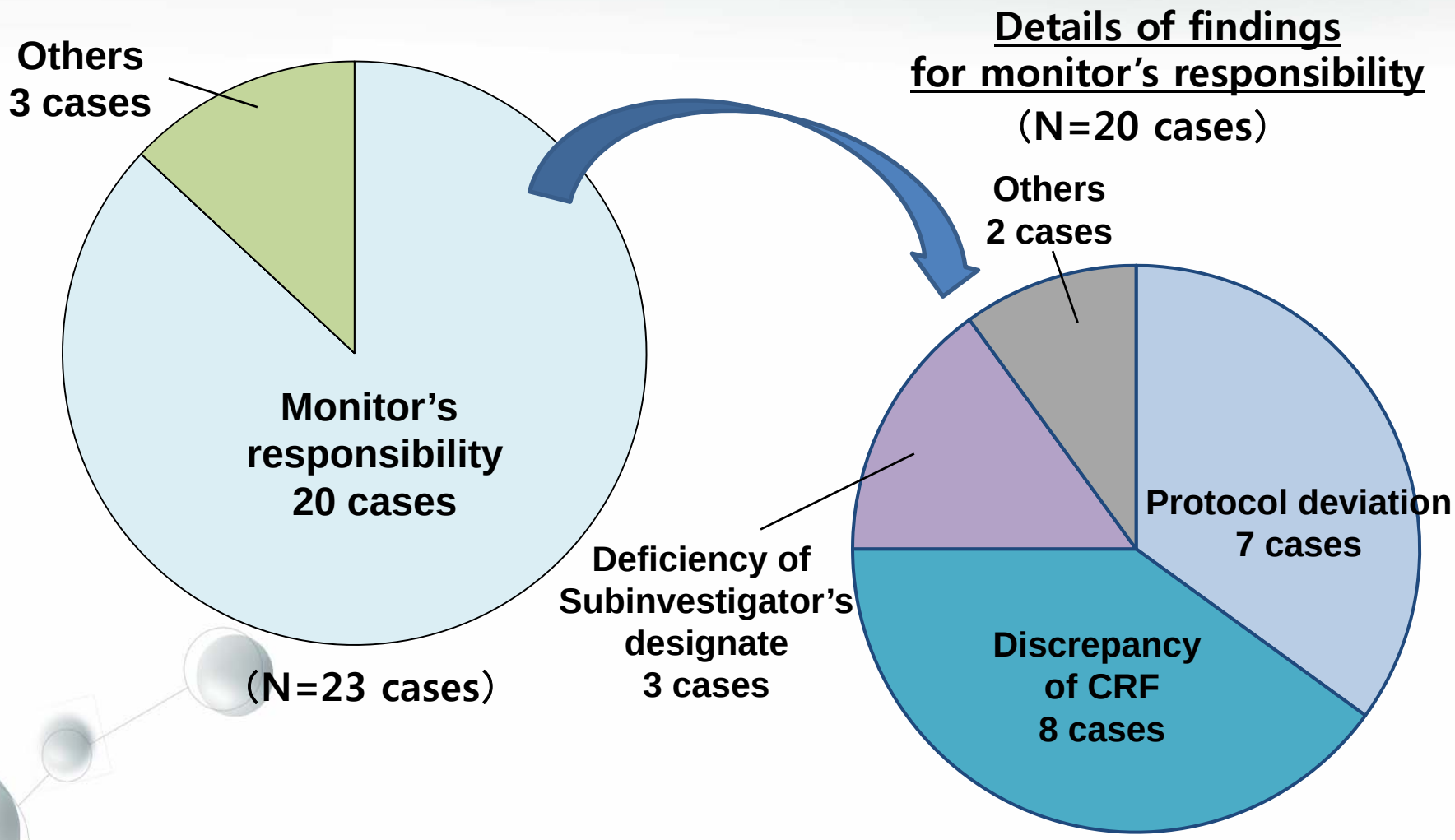
**Details of findings for monitor's responsibility**

(N=9 cases)



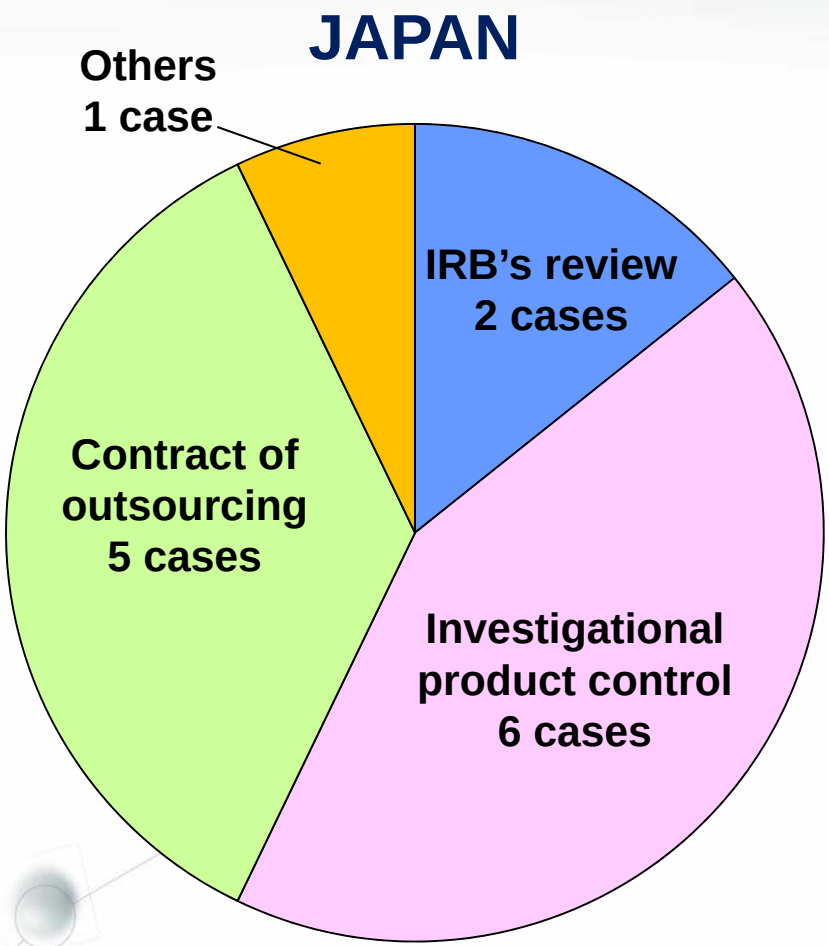

*CRF: Case Report Form

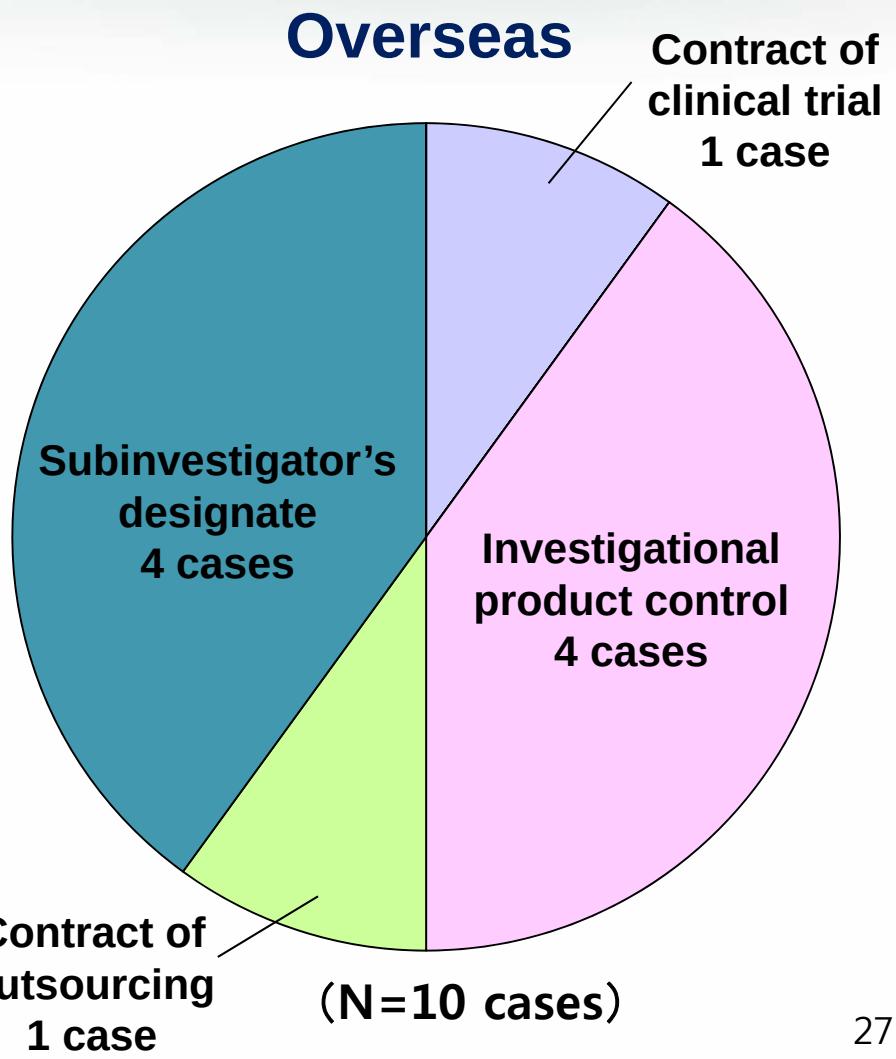
# Findings for Sponsors in Overseas (FY 2009 - 2011)



# General Findings for Medical Institutions

(FY2012 for JAPAN, FY2009 – 2012 for Overseas)

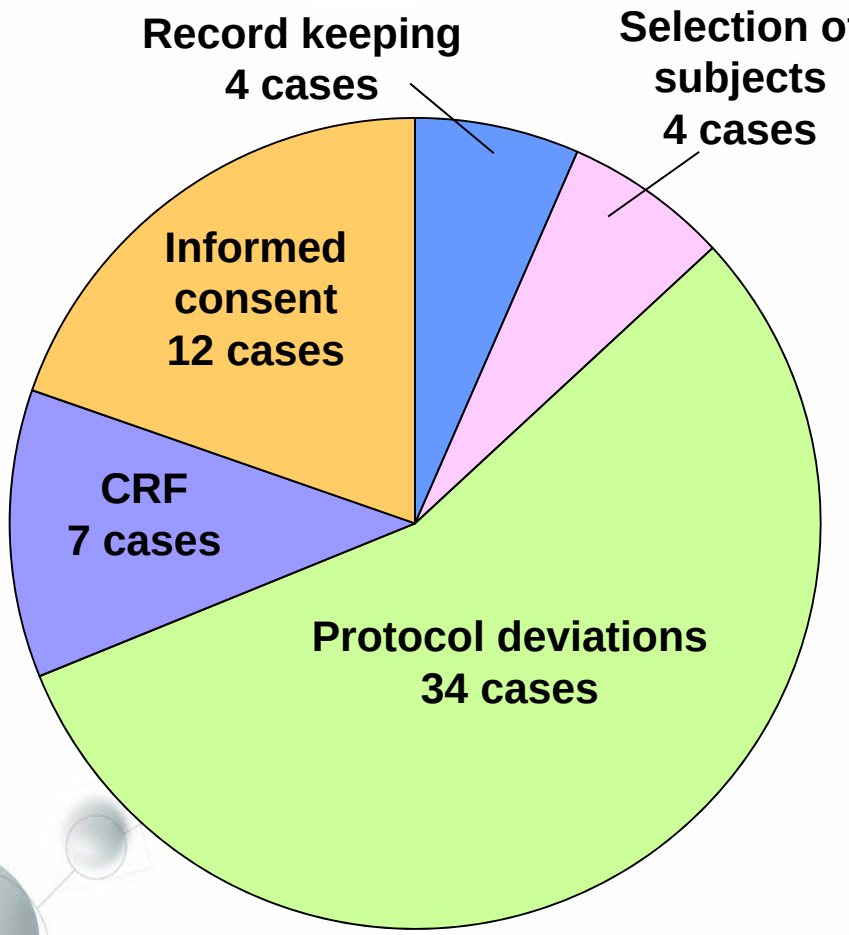


# Findings for Individual Subjects (Medical Institutions)

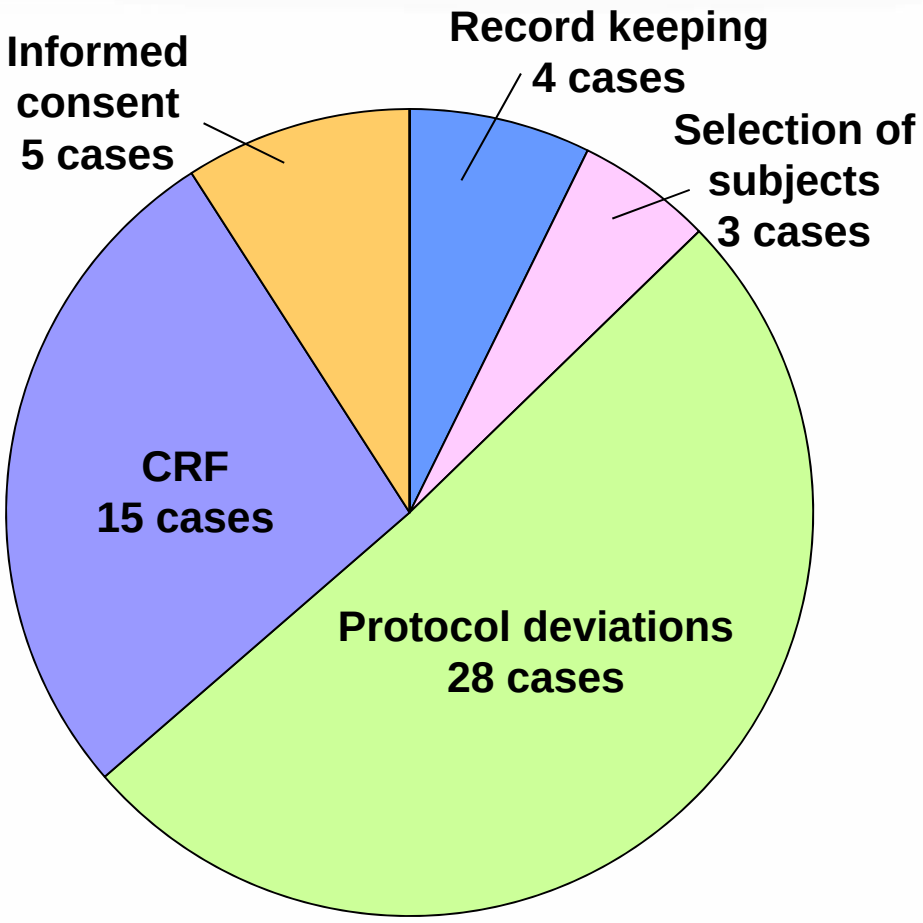
(FY2012 for JAPAN, FY2009 – 2012 for Overseas)

## JAPAN




（N=61 cases）

## Overseas




（N=55 cases）

# Management of Clinical Trial Processes

Administration /controlling of electric medical record system

control/accountability of the IPs

Selection of IRB and Requesting of deliberation

Record keeping

Assigned duties

Selection of subjects and IC

Conducting a clinical trial

Reporting of ADRs

Medical records

Information sharing to involved parties

CRF etc.

Responsibilities for medical care of subjects

Investigator's Brochure

Control/accountability of the IPs
Supply of the IPs

Information on ADR etc.

Selection of medical institution and investigator


Clinical trial reports

Protocol

Audits

Implementing/ controlling data capture system

Monitoring

Record keeping etc.

# Contents

# EDC Management Sheet (1)

- Notification regarding inspection method for clinical trials which use EDC system

  PMDA/CPE Notification No. 0327001(March 27, 2013)

- Basic Concept
  - For the clinical trials using EDC system, similar inquiries among trials could be avoided in GCP inspection.
  - For sponsors, it could be useful tool for self-inspection by updating appropriately.

- Composition

  EDC Management Sheet consists of two kinds of sheets:
  1) Operational Procedure Sheet
  2) Operating Experience Sheet

# EDC Management Sheet (2)

1. Operational Procedure Sheet
   - EDC system overview
   - Outsourcing contract
   - Requirements for the Use of Electromagnetic Records
   - Requirements for the Use of Electronic Signatures
2. Operational Experience Sheet

For details, please see
http://www.jpma.or.jp/information/evaluation/allotment/translation_edc.html

# EDC Management Sheet (3)



## EDC Management Sheet (for Sponsor/Marketing Authorization Holder (MAH)) Operational Procedure Sheet (JPMA Translation)

| | |
|---|---|
| **Name of the sponsor or the MAH** | |

※In this sheet, "Clinical trials, etc." means "clinical trials, post-mar

### 1. System overview

| | |
|---|---|
| **Name of the EDC System** | |
| **System category (System development type)** | ☐ ASP (Application Service Provider) service (Company name: )<br>☐ In-house development<br>☐ Other ( ) |
| **Intended purpose (Collected information etc)** | ☐ 01 Case report form (CRF) used in clinical trial<br>☐ 02 Patient diary<br>☐ 03 CRF used in Post-marketing surveillance<br>☐ 04 Other ( ) |
| **Security measures for the overall system** | ☐ ASP service security policy/procedure is used<br>☐ Internal security policy/procedure is used<br>☐ Other ( ) |

| | Entry column | | |
|---|---|---|---|
| | [1] | [2] | |
| **Version of the EDC system** (Only major upgrades such as adding functions to be specified) | | | |
| **Duration of use (20xx/xx/xx ~ 20xx/xx/xx)** | ~ | ~ | |
| **Release declaration (20xx/xx/xx)** | | | |
| **Differences from the previous version** * Briefly summarize the release notes of the version obtained internally or from a vendor. Can be left blank in case of a newly introduced system. | | | |
| **Status of conduct or confirmation of the computer system validation at the time of system introduction or system update** | | | |

### 2. Outsourcing contract (Construction/operation of the EDC System, operation of Help De

# Thank you for your attention !