Risk-based approach on GCP inspection

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Contents

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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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
<table>
<thead>
<tr>
<th>Year</th>
<th>Initial CT Notification (NCEs only)</th>
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Noted:
- **Enactment of new GCP**
- **3-year nation-wide clinical trials vitalization plan** (extended by 1 year)
- **New 5-year clinical trials activation plan**

* 5-year clinical trials vitalization plan 2012 started in 2012
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
devolved 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”

“The 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

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

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( ): The number of inspections in overseas
# Detail of Overseas Inspection

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<td>Spain 2, India 2</td>
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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)

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).

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

Compliance (no indication)
87 cases (88%)

A total of 99 cases ³)
Findings for Sponsors in JAPAN (FY 2012)

(N=21 cases)

Monitor’s responsibility
9 cases

Safety information reporting
8 cases

Others
4 cases

Details of findings for monitor’s responsibility
(N=9 cases)

Retention of Essential documents
4 cases

Discrepancy of CRF*
3 cases

Protocol deviation
2 cases

*CRF: Case Report Form
Findings for Sponsors in Overseas (FY 2009 - 2011)

- Monitor’s responsibility: 20 cases (N=23 cases)
- Protocol deviation: 7 cases
- Discrepancy of CRF: 8 cases
- Deficiency of Subinvestigator’s designate: 3 cases
- Others: 3 cases (N=20 cases)

Details of findings for monitor’s responsibility:
- Protocol deviation: 7 cases
- Discrepancy of CRF: 8 cases
- Deficiency of Subinvestigator’s designate: 3 cases
- Others: 2 cases
General Findings for Medical Institutions
(FY2012 for JAPAN, FY2009 – 2012 for Overseas)

JAPAN

- Investigational product control: 6 cases
- IRB’s review: 2 cases
- Contract of outsourcing: 5 cases
- Others: 1 case

(N=14 cases)

Overseas

- Investigational product control: 4 cases
- Subinvestigator’s designate: 4 cases
- Contract of clinical trial: 1 case
- Contract of outsourcing: 1 case

(N=10 cases)
Findings for Individual Subjects (Medical Institutions)
(FY2012 for JAPAN, FY2009 – 2012 for Overseas)

### JAPAN

- **Protocol deviations**: 34 cases
- **Informed consent**: 12 cases
- **CRF**: 7 cases
- **Record keeping**: 4 cases
- **Selection of subjects**: 4 cases

(N=61 cases)

### Overseas

- **Protocol deviations**: 28 cases
- **Informed consent**: 5 cases
- **CRF**: 15 cases
- **Record keeping**: 4 cases
- **Selection of subjects**: 3 cases

(N=55 cases)
Management of Clinical Trial Processes

- Administration /controlling of electric medical record system
- Selection of IRB and Requesting of deliberation
- Control/accountability of the IPs
- Record keeping
- Assigned duties
- Conducting a clinical trial
- Medical records
- CRF etc.
- Responsibilities for medical care of subjects
- Information sharing to involved parties
- Investigator’s Brochure
- Information on ADR etc.
- Clinical trial reports
- Audits
- Record keeping etc.

Selection of medical institution and investigator
Control/accountability of the IPs
Supply of the IPs
Protocol
Implementing/controlling data capture system
Monitoring
Contents

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4. EDC Management Sheet
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
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1. System overview

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2. Outsourcing contract (Construction/operation of the EDC System, operation of Help Desk, Etc.)
Thank you for your attention!