Towards High-quality Clinical Trials And
Implementation Of Genomic Medicine

ATLAS Training Program

Course : CRC Training Course
Lecture Title : Support for multi-regional cancer clinical trials
Speaker : Emi YASUDA

ATLAS
ASIAN CLINICAL TRIALS NETWORK FOR CANCERS PROJECT

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Emi Yasuda

Clinical Research Coordinator, National Cancer Center Hospital

- Education
- Work Experience
  Apr 2016–present (National Cancer Center Hospital, Tokyo Japan)

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Multi-regional Cancer Clinical Trial

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What is Multi-regional Clinical Trial (MRCT)?

- Clinical trial targeting subjects in multiple regions and countries
- Clinical trial implemented at the same time based on a common protocol and are aimed at gaining approval for a drug

These trials are characterized by the ability to efficiently secure case numbers in a short timeframe, particularly for studies targeting rare diseases

Cited from: CRC Textbook. Multi-regional clinical trials - Background and Future - Osamu Komiyama

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What is MRCT?

To satisfy the approval conditions in each country using the same trial results, trials must be implemented

- Based on International Conference on Harmonization (ICH)-Good Clinical Practice (GCP)
- After satisfying the regulatory requirements in each country

Therefore, each medical institution must prepare a standard clinical trial implementation system not only for related regulations in their own country, but also internationally, and be able to flexibly manage various demands.

Cited from: CRC Textbook. Multi-regional clinical trials - Background and Future - Osamu KOMIYAMA

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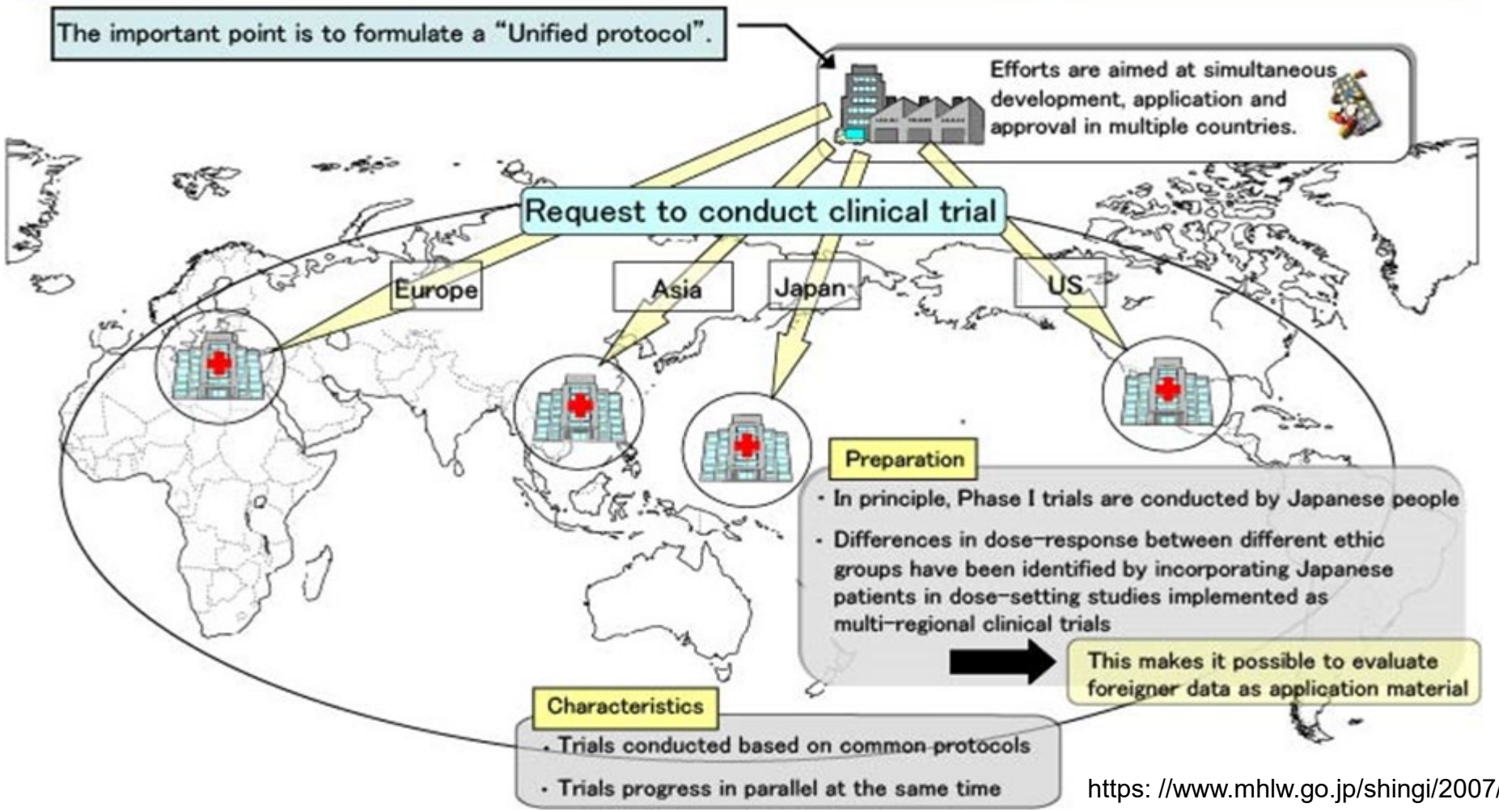
What is MRCT?

Clinical trials planned for development and approval of new drugs on a global scale, with medical institutions in multiple countries and regions participating in a single trial, which is based on a common protocol and progresses in parallel at the same time. These trials mainly apply to Phase III trials.



https: //www.mhlw.go.jp/shingi/2007/07/dl/s0727-11d_0002.pdf

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Background of MRCT

Until the 1990s

- Clinical trials for drugs under development were mostly conducted in individual countries
- The rules for conducting clinical trials (regulations such as GCP) and trial implementation environment widely varied in each country

  -Transportation, postal service, telecommunications, and IT

- 1996
  - ➢ The foundations were laid for international mutual use of clinical trial data
- ICH-E6 Guideline for Good Clinical Practice agreement

Cited from: CRC Textbook. Multi-regional clinical trials - Background and Future - Osamu KOMIYAMA

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Background of MRCT

From the mid to late 1990s

Important ICH guidelines were established for both regulations and shared concepts

- ICH-E2: Clinical Safety Data Management: Elements and Specifications for Electronic Transmission
- ICH-MI (ICH-E9): International Medical Terms (Med-DRA)
- ICH-E8: General Considerations for Clinical Trials
- ICH-E9: Statistical Principles for Clinical Trials

Cited from: CRC Textbook. Multi-regional clinical trials - Background and Future - Osamu KOMIYAMA

ICH website URL: https: //www.ich.org/

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ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

ICH Trends

- 1998 ICH-E5 Ethnic Factors in the Acceptability of Foreign Clinical Data

≪Bridging studies≫

- Maximize the use of data from previous overseas trials
- Medical institutions: When accepting clinical trials, trials could be implemented in Japan after confirming the data on safety and efficacy from the investigator's brochure based on previous trials conducted overseas.

However…

This did not eliminate the drug lag, with the timing of drugs available to patients in Japan showing a delay compared to that of the drugs available overseas.

Cited from: CRC Textbook. Multi-regional clinical trials - Background and Future - Osamu KOMIYAMA

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ICH Trends

- 2006 ICH-E5 Ethnic Factors: Questions and Answers
- Guidelines for planning, implementation, and analysis of multi-regional clinical trials were established (E5 Q&A No.11)
- 2018 ICH-E17 General Principles for Planning and Design of Multi-Regional Clinical Trials

Cited from: CRC Textbook. Multi-regional clinical trials - Background and Future - Osamu KOMIYAMA

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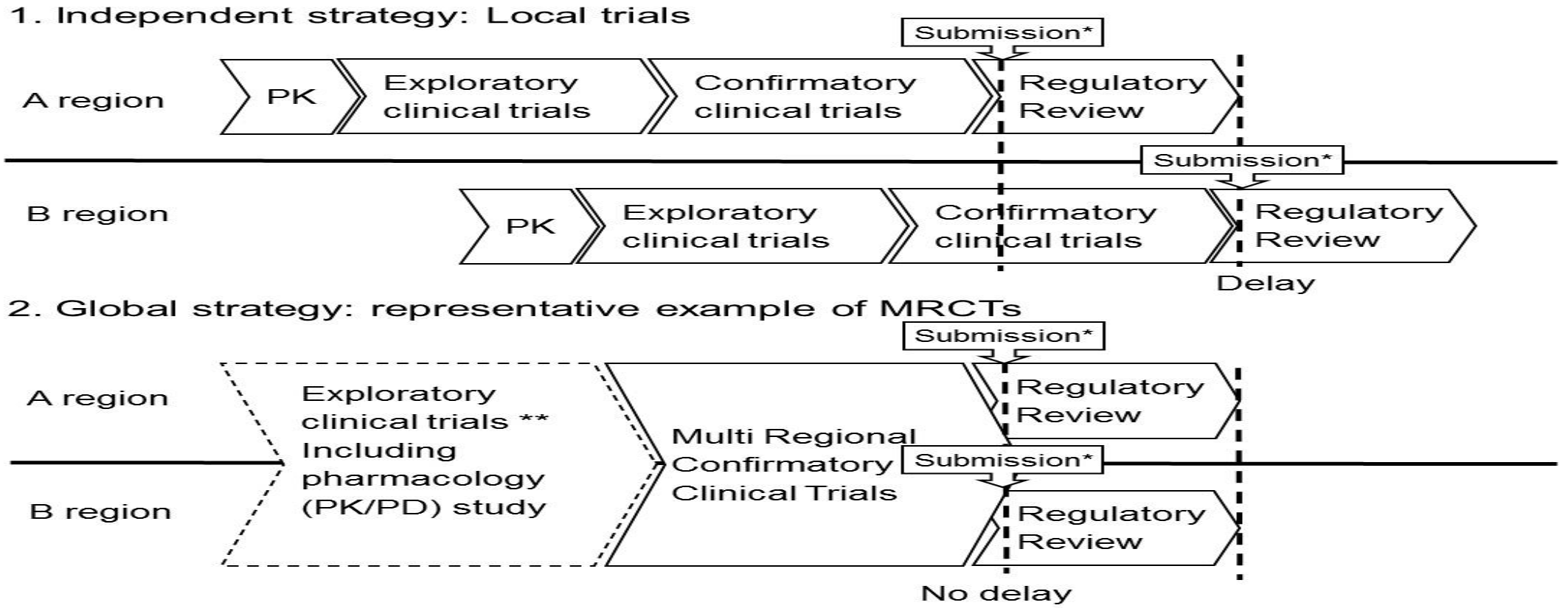
ICH-E17



ICH URL: https: //www.ich.org/

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Global Situation

- In the 2000s, a dramatic progress in the digitization, electronic transmission, and communication of data using EDC (electronic data capture) and information and communications technology, which gradually provided a technological foundation for clinical trials in distant countries.
- The number of multi-regional clinical trials with 3 or more participant countries began increasing starting in around 2004
- There was also an increase in participation by countries where clinical trials were inexpensive to implement (including countries unfamiliar with clinical trials), with a reduction of development costs as the main motivating factor.
- Currently, almost all clinical trials in the field of cancer research are conducted as MRCT.

Cited from: CRC Textbook. Multi-regional clinical trials - Background and Future - Osamu KOMIYAMA

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CRC Support In MRCTs

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Characteristics of MRCTs

- CRCs encounter a diverse range of people, such as study sponsor, CROs, and vendors, involved in MRCTs.

- Because of the large number of people involved in trials, the various adjustments required during the preparation period within the medical institution implementing the trial are often complex; therefore, it is important to understand these systems and their roles when starting clinical trials.

Cited from: CRC Textbook. Multi-regional clinical trials - Operating in medical institutions - Kaori Watanabe

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Sponsor Characteristics

- When a foreign-registered company headquartered overseas utilizes the functions of its branch in the country where the trial is conducted
- When an overseas venture company requests CROs to implement the trial
- When a domestic company conducts a trial in cooperation with an overseas company

Cited from: CRC Textbook. Multi-regional clinical trials - Operating in medical institutions - Kaori Watanabe

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Skill Required By CRCs in MRCTs

- IT support
- Ability to implement clinical trials based on ICH-GCP, and respond flexibly while satisfying the regulatory requirements of each country
  Example) Matters related to COI (conflict of interest), inspection certification, long term storage of essential documents, etc.
- Mutual understanding in various areas, as CRCs must often respond to problems caused by cultural differences, including differences in medical conditions, language, and interpretation of events.

It is essential for the trial to comply with ICH-GCP and the regulations in each country

Cited from: CRC Textbook. Multi-regional clinical trials - Operating in medical institutions - Kaori Watanabe

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Skill Required By CRCs in MRCTs

- Communication
  - A certain level of English language proficiency
  - Holidays in each country and time differences
- Understand the differences by the start of the trial
  - Feasibility check and institution selection by study sponsor
  - Clinical Trial Agreement

Cited from: CRC Textbook. Multi-regional clinical trials - Operating in medical institutions - Kaori Watanabe

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Document-related

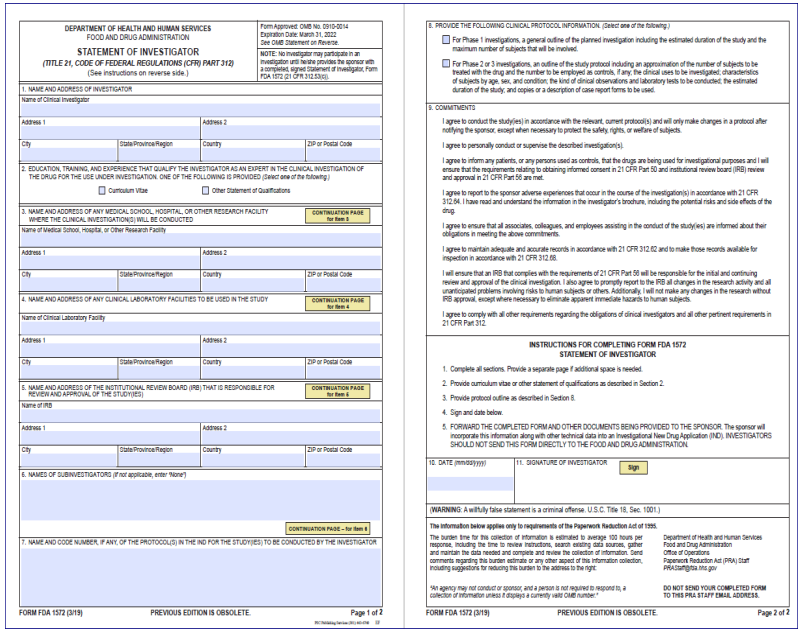
Document example (From 2021 Multi-regional Clinical Trials Pocket Reference Collection)＞

◎ Feasibility Assessment

◎ Confidentiality agreement

◎Form FDA 1572 is a document required for an Investigational New Drug Application (IND) in compliance with US-FDA Title 21 CFR Part 312 and is named as the Statement of Investigator.

Form FDA 1572



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

STATEMENT OF INVESTIGATOR
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)
(See instructions on reverse side.)

Form Approved: OMB No. 0910-0014
Expiration Date: March 31, 2022
See OMB Statement on Reverse.

NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).

1. NAME AND ADDRESS OF INVESTIGATOR
Name of Clinical Investigator
Address 1 | Address 2
City | State/Province/Region | Country | ZIP or Postal Code

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFY THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS PROVIDED (Select one of the following.)
☐ Curriculum Vitae ☐ Other Statement of Qualifications

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED — CONTINUATION PAGE for Item 3
Name of Medical School, Hospital, or Other Research Facility
Address 1 | Address 2
City | State/Province/Region | Country | ZIP or Postal Code

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY — CONTINUATION PAGE for Item 4
Name of Clinical Laboratory Facility
Address 1 | Address 2
City | State/Province/Region | Country | ZIP or Postal Code

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES) — CONTINUATION PAGE for Item 5
Name of IRB
Address 1 | Address 2
City | State/Province/Region | Country | ZIP or Postal Code

6. NAMES OF SUBINVESTIGATORS (If not applicable, enter "None")
CONTINUATION PAGE – for Item 6

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR

FORM FDA 1572 (3/19) PREVIOUS EDITION IS OBSOLETE. Page 1 of 2

8. PROVIDE THE FOLLOWING CLINICAL PROTOCOL INFORMATION. (Select one of the following.)
☐ For Phase 1 investigations, a general outline of the planned investigation including the estimated duration of the study and the maximum number of subjects that will be involved.
☐ For Phase 2 or 3 investigations, an outline of the study protocol including an approximation of the number of subjects to be treated with the drug and the number to be employed as controls, if any; the clinical uses to be investigated; characteristics of subjects by age, sex, and condition; the kind of clinical observations and laboratory tests to be conducted; the estimated duration of the study; and copies or a description of case report forms to be used.

9. COMMITMENTS
I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
I agree to personally conduct or supervise the described investigation(s).
I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.
I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64. I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.
I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.
I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR

1. Complete all sections. Provide a separate page if additional space is needed.
2. Provide curriculum vitae or other statement of qualifications as described in Section 2.
3. Provide protocol outline as described in Section 8.
4. Sign and date below.
5. FORWARD THE COMPLETED FORM AND OTHER DOCUMENTS BEING PROVIDED TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND). INVESTIGATORS SHOULD NOT SEND THIS FORM DIRECTLY TO THE FOOD AND DRUG ADMINISTRATION.

10. DATE (mm/dd/yyyy) | 11. SIGNATURE OF INVESTIGATOR — Sign

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

The information below applies only to requirements of the Paperwork Reduction Act of 1995.

The burden time for this collection of information is estimated to average 100 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the address to the right:

Department of Health and Human Services
Food and Drug Administration
Office of Operations
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number.

DO NOT SEND YOUR COMPLETED FORM TO THIS PRA STAFF EMAIL ADDRESS.

FORM FDA 1572 (3/19) PREVIOUS EDITION IS OBSOLETE. Page 2 of 2

www.fda.gov/media/71816/download

Cited from: CRC Textbook. Multi-regional clinical trials - Operating in medical institutions - Kaori Watanabe

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Document-related

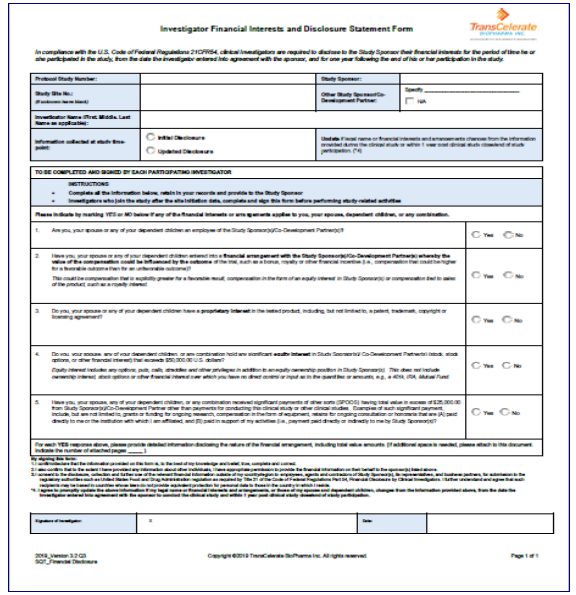
Document example (From 2021 Multi-regional Clinical Trials Pocket Reference Collection)＞

◎ The Financial Disclosure Form has been required since February 1999 for filing a drug approval application in the US, in compliance with FDA Title 21 CFR Part 54.

◎ Laboratory Certificate supports the eligibility of necessary testing equipment and reliability of the test data, and is certified by a third party

Cited from: Multi-regional Clinical Trials Pocket Reference Collection

Financial Disclosure Form (Example)


Investigator Financial Interests and Disclosure Statement Form

https: //www.transceleratebiopharmainc.com/

ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

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Document-related

Document example (From 2021 Multi-regional Clinical Trials Pocket Reference Collection)＞

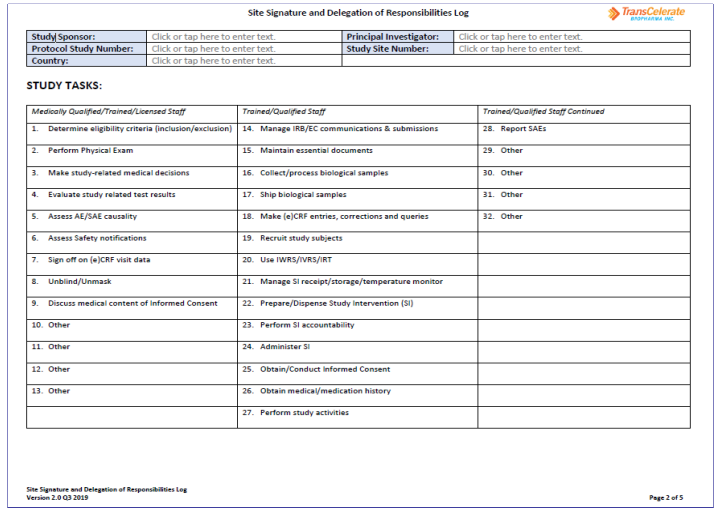
◎ The Delegation List is a document prepared describing how the principal investigator will be delegating subdivided clinical trial duties to appropriate individuals as the trial progresses.

◎ Investigator Agreement: In the US and Europe, a clinical trial agreement may be established directly between the principal investigator and sponsor. The Investigator Agreement may also contain content regarding the protocol agreement and clinical trial contract.

◎ Training log

Cited from: Multi-regional Clinical Trials Pocket Reference Collection

Delegation List (Example)



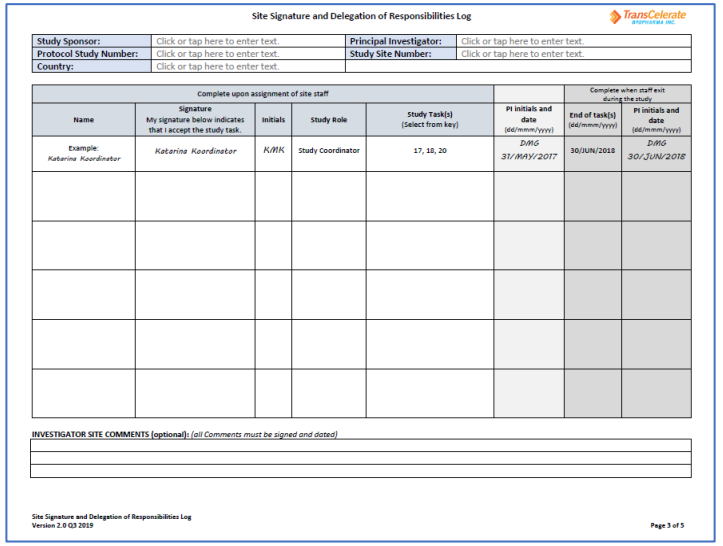
Site Signature and Delegation of Responsibilities Log

Study Sponsor:	Click or tap here to enter text.	Principal Investigator:	Click or tap here to enter text.
Protocol Study Number:	Click or tap here to enter text.	Study Site Number:	Click or tap here to enter text.
Country:	Click or tap here to enter text.		

STUDY TASKS:

Medically Qualified/Trained/Licensed Staff	*Trained/Qualified Staff*	*Trained/Qualified Staff Continued*
1. Determine eligibility criteria (inclusion/exclusion)	14. Manage IRB/EC communications & submissions	28. Report SAEs
2. Perform Physical Exam	15. Maintain essential documents	29. Other
3. Make study-related medical decisions	16. Collect/process biological samples	30. Other
4. Evaluate study related test results	17. Ship biological samples	31. Other
5. Assess AE/SAE causality	18. Make (e)CRF entries, corrections and queries	32. Other
6. Assess Safety notifications	19. Recruit study subjects	
7. Sign off on (e)CRF visit data	20. Use IWRS/IVRS/iRT	
8. Unblind/Unmask	21. Manage SI receipt/storage/temperature monitor	
9. Discuss medical content of Informed Consent	22. Prepare/Dispense Study Intervention (SI)	
10. Other	23. Perform SI accountability	
11. Other	24. Administer SI	
12. Other	25. Obtain/Conduct Informed Consent	
13. Other	26. Obtain medical/medication history	
	27. Perform study activities	

Site Signature and Delegation of Responsibilities Log
Version 2.0 Q3 2019 Page 2 of 5



Site Signature and Delegation of Responsibilities Log

Study Sponsor:	Click or tap here to enter text.	Principal Investigator:	Click or tap here to enter text.
Protocol Study Number:	Click or tap here to enter text.	Study Site Number:	Click or tap here to enter text.
Country:	Click or tap here to enter text.		

Complete upon assignment of site staff						Complete when staff exit during the study	
Name	Signature My signature below indicates that I accept the study task.	Initials	Study Role	Study Task(s) (Select from key)	PI initials and date (dd/mmm/yyyy)	End of task(s) (dd/mmm/yyyy)	PI initials and date (dd/mmm/yyyy)
Example: *Katarina Koordinator*	*Katarina Koordinator*	*KAK*	Study Coordinator	17, 18, 20	*DMG 31/MAY/2017*	30/JUN/2018	*DMG 30/JUN/2018*

INVESTIGATOR SITE COMMENTS (optional): *(all Comments must be signed and dated)*

Site Signature and Delegation of Responsibilities Log
Version 2.0 Q3 2019 Page 3 of 5

https: //myscrs.org/learning-campus/site-management-modules/#forms

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IRB Materials

- Informed Consent Form(s)

  Created in English as a study level ICF and translated into local language as country level ICF by sponsor.

  Modifications by institutions should be approved by sponsor.

  Time-consuming work for PI and CRC

Cited from: CRC Textbook. Multi-regional clinical trials - Operating in medical institutions - Kaori Watanabe

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Points To Note During Clinical Trials

- Maintenance of IT environment
- Confirmation of laboratory and imaging test requirements
- Management of lab kits/materials

Cited from: CRC Textbook. Multi-regional clinical trials - Operating in medical institutions - Kaori Watanabe

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Points To Note During Clinical Trials

- Management of the test materials

≪Important point≫

– A large volume of materials may be sent at once; therefore, confirm in advance how much material can be delivered and secure a storage location.
– When requesting materials, consider national holidays in the country preparing the material: For example, if the materials are made in China, they may not arrive in time if the request coincides with the long break at the commencement of the Chinese New Year.

Cited from: CRC Textbook. Multi-regional clinical trials - Operating in medical institutions - Kaori Watanabe

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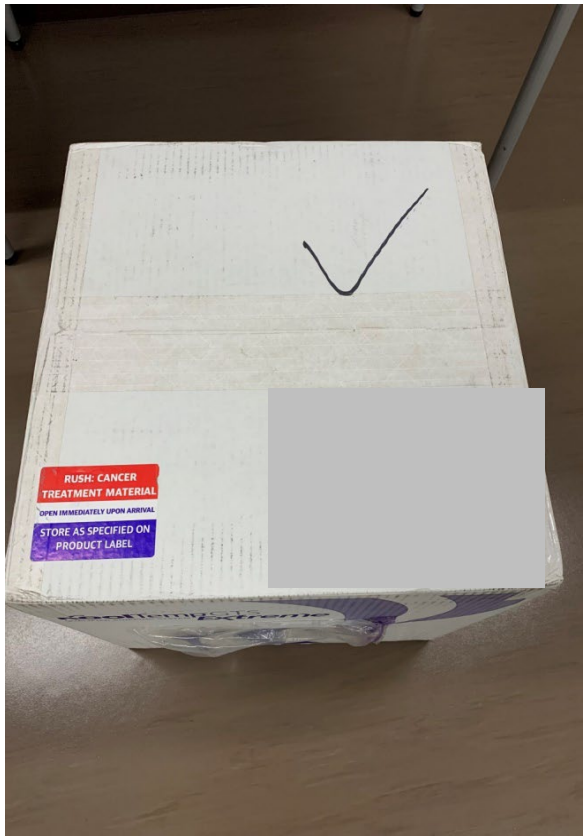
Points To Note During Clinical Trials

- Delivery and management of the investigational product



Logger

Cited from: CRC Textbook. Multi-regional clinical trials - Operating in medical institutions - Kaori Watanabe

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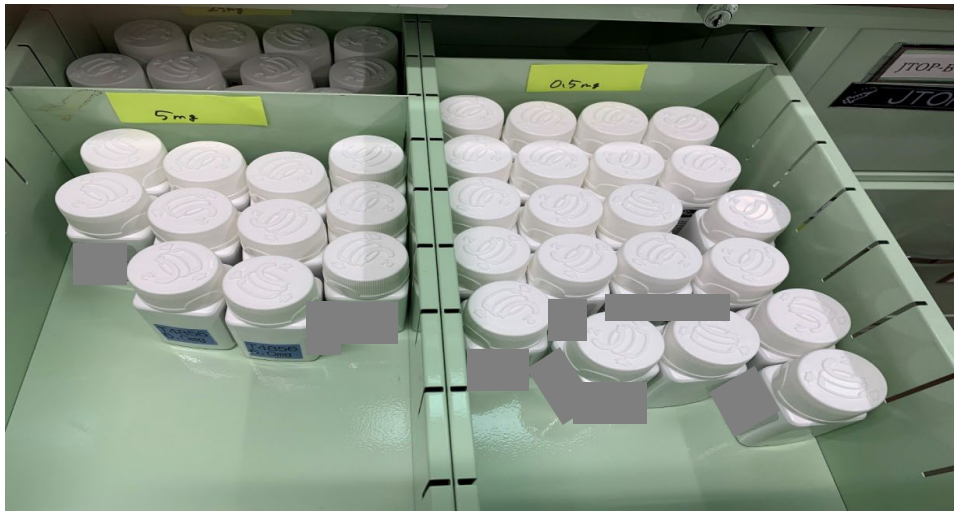
Points To Note During Clinical Trials

- Investigational product temperature control

Oral medication: Cold storage 2–8℃

Oral medication: Room temperature 1~30℃



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Points To Note During Clinical Trials

- Investigational drug temperature control

Oral medication: Thermostat chamber 20℃

Thermostat chamber
The internal temperature is controlled at a constant temperature for long periods of time
In this hospital, the temperature is set at 20ºC (changes between 19–21ºC)

Why is a thermostat chamber needed?
Room temperature in Japan is 1–30ºC
Room temperature overseas is 15–25ºC
The temperature in the dispensing room of this hospital (room temperature) is 22–28ºC

The temperature of the room exceeds 25ºC, and therefore this is a case of temperature deviation!

↓

Investigational products that cannot be stored under refrigerated conditions (2–8ºC), but must be stored at 25ºC or lower, are stored in a thermostat chamber

Cited from Pharmacy Department student training materials

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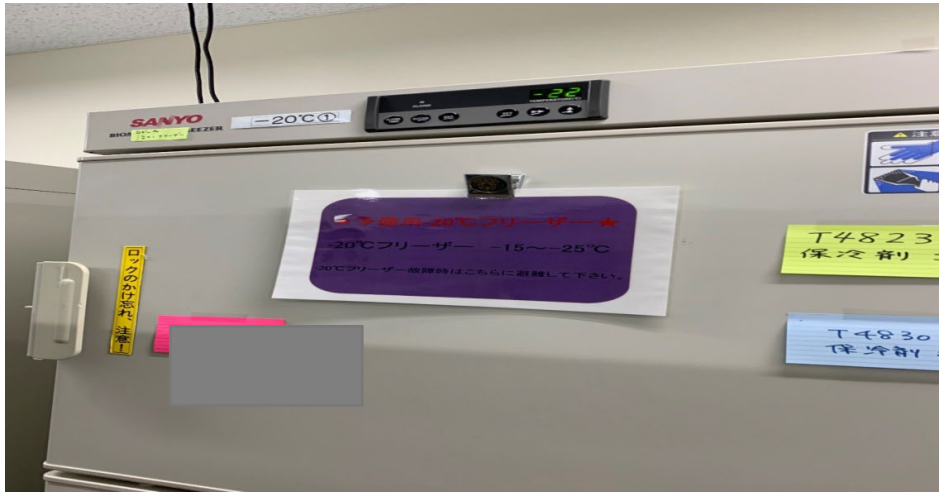
Points To Note During Clinical Trials

- Investigational product temperature control

Injection: Refrigerator

Injection: Freezer -80℃

Injection: Freezer -20℃



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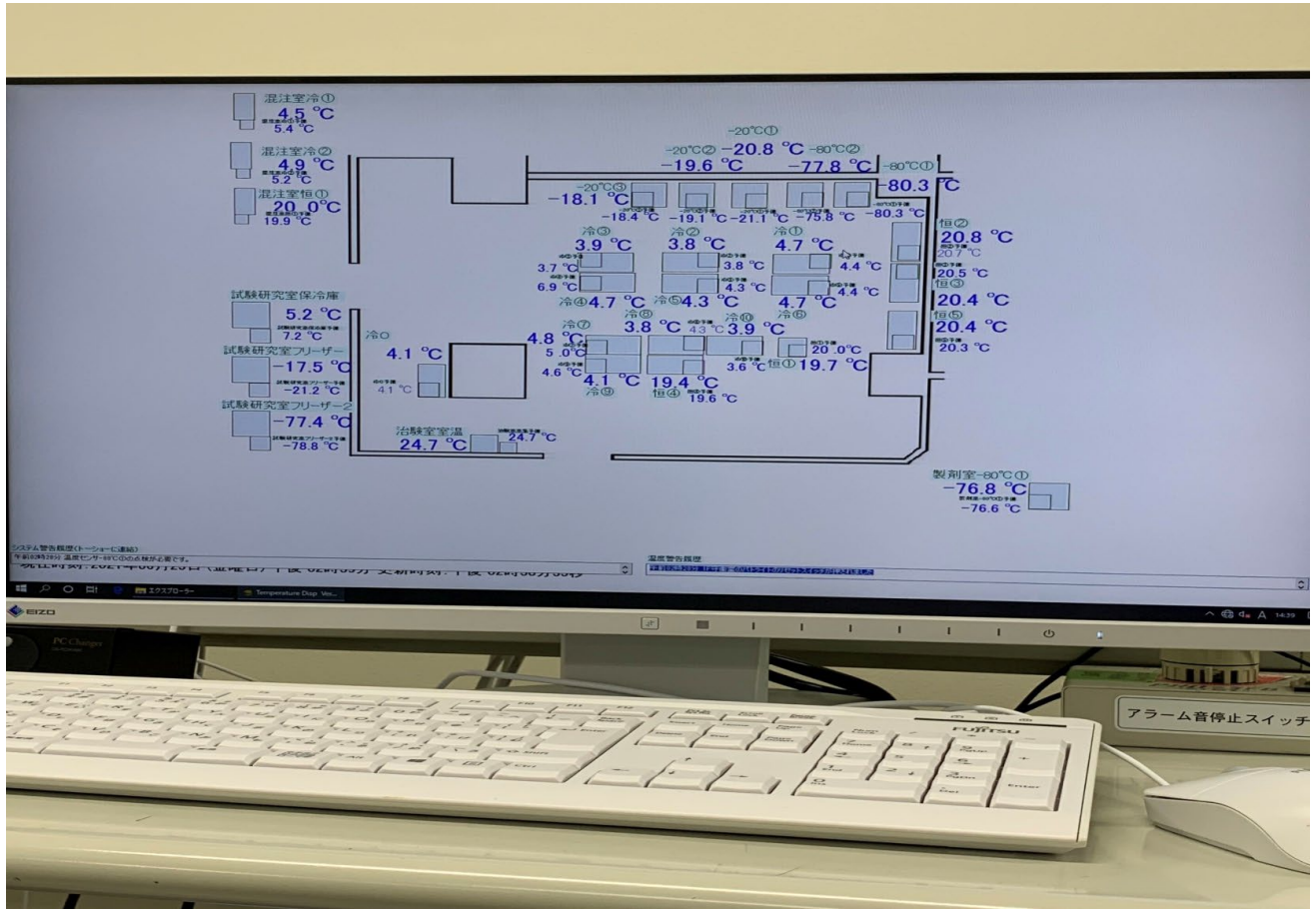
Points To Note During Clinical Trials

- Investigational product temperature control



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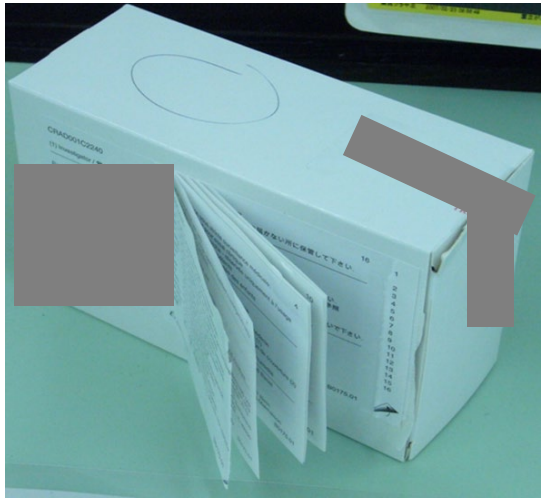
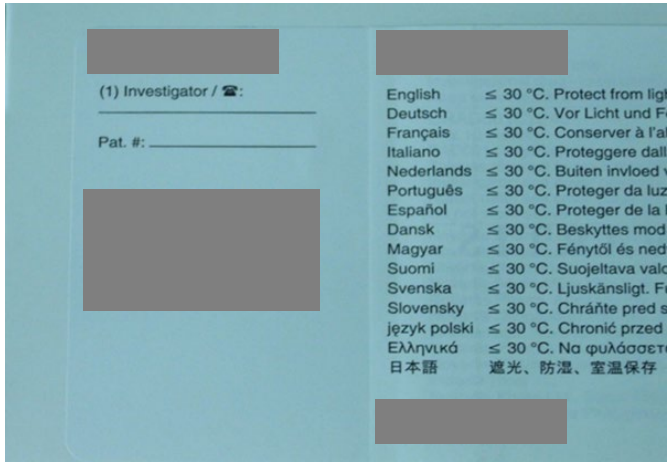
Points To Note During Clinical Trials

- Drugs
- Patient guidance

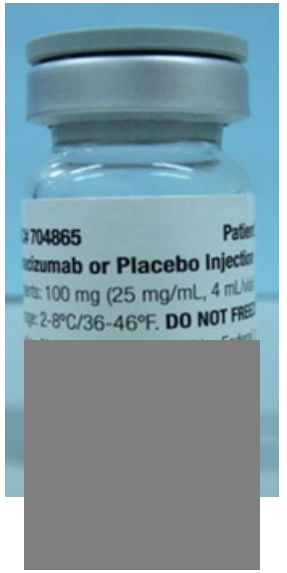
Oral medication (bottle)

Oral medication (box)





Injection



Cited from: CRC Textbook. Multi-regional clinical trials - Operating in medical institutions - Kaori Watanabe

Cited from Pharmacy Department student training materials

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Points To Note During Clinical Trials

- Subject recruitment, progress management, and safety information management

◎ Phase 1 (early phase)

- There are few subjects, and thus communication with study sponsor and each participating country is essential
- Prompt data input in EDC is mandatory
- Participate in regular meetings with sponsor and update study progress

◎ Phase 3

- Confirm the number of subjects required in each country
- Confirm the state of progress with the sponsor and respond accordingly

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Response After The Trial Is Complete

- Document management
- Preparation for supporting FDA inspections, EMA inspections

  FDA inspections website

  https: //www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations

  EMA inspections website

  https: //www.ema.europa.eu/en

- Participate in meeting

Cited from: CRC Textbook. Multi-regional clinical trials - Operating in medical institutions - Kaori Watanabe

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Summary

- More clinical trials are now being performed on a multi-regional scale to eliminate drug lag
- Preparations in your own institution are essential for conducting MRCT
- CRCs are required to understand and respond to regulations in other countries, the GCP, and the regulations in their own country

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