Toward high-quality clinical trials and
implementation of genomic medicine

ATLAS Training Program

Course: Phase1 Trial Development Course

Lecture: Responsibilities of principal investigators and important personnel in Phase I clinical trial team

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Position/Title	Name and Location of Institution	Dates
Present Head of Physician / Dept of Experimental Therapeutics	National Cancer Center Hospital (Chuo-ku, Tokyo, Japan)	Apr/2022-Present
Previous Attending Physician / Dept of Experimental Therapeutics	National Cancer Center Hospital (Chuo-ku, Tokyo, Japan)	May/2018- Mar/2022
Previous Research fellow / Dept of Experimental Therapeutics	National Cancer Center Hospital (Chuo-ku, Tokyo, Japan)	Apr/2018
Previous Resident / Dept of Experimental Therapeutics	National Cancer Center Hospital (Chuo-ku, Tokyo, Japan)	Apr/2016- Mar/2016
Previous Attending Physician / Dept of Medical Oncology	Kameda Medical Center (Kamogawa-shi, Chiba, Japan)	Apr/2011- Mar/2016
Previous Resident / Dept of Medical Oncology	Kameda Medical Center (Kamogawa-shi, Chiba, Japan)	Apr/2008- Mar/2011
Previous Resident / Dept of General Internal Medicine	Kishiwada Tokushukai Hospital (Kishiwada, Osaka, Japan)	Apr/2006- Mar/2008

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Principal investigator requirements

1. Able to properly implement the clinical trial based on their education, training, and experience.

2. Familiar with the protocol, latest investigator's brochure, product information, and appropriate usage methods

3. Complies with monitoring, audits, and inspections by the institutional review board and regulatory authorities.

4. Has sufficient time to properly implement and complete clinical trials within the agreed timeframe.

5. Can demonstrate, through past performance, the ability to recruit the required number of eligible patients within the agreed recruitment period.

6. Can secure qualified staff, including sufficient numbers of sub-investigators and clinical trial collaborators, and ensure the availability of appropriate facilities for use during the scheduled clinical trial period to implement the clinical trial properly and safely.

Sub-investigators and clinical trial collaborators ①

1. When the principal investigator delegates some important tasks, related to the clinical trial, to sub-investigators or clinical trial collaborators, they must create a list of delegated work and the people performing the work and submit this information to the director of the clinical trial site in advance to obtain approval.

2. The work may be delegated after approval is granted by the director of the clinical trial site; however, sub-investigators require review by the institutional review board.

3. The director of the clinical trial site approves the list of sub-investigators and clinical trial collaborators submitted by the principal investigator and is required to submit the list of sub-investigators and clinical trial collaborators to the principal investigator.

4. The director of the clinical trial site or the principal investigator is required to submit the list of sub-investigators and clinical trial collaborators to the sponsor in clinical trials implemented by sponsors.

Sub-investigators and clinical trial collaborators ②

1. The principal investigator must provide sufficient information about guidance and supervision with respect to the protocol, study drug, and contribution of each individual to sub-investigators, clinical trial collaborators, and other personnel.

2. The principal investigator must provide sufficient information about guidance and supervision with respect to each individual's responsibilities to the sub-investigators and clinical trial collaborators. Information regarding the quality, efficacy, and safety of the study drug examined by sponsor-investigators, and other information required for proper implementation of the clinical trial must also be reported. Furthermore, matters corresponding to the onset of disease, disability, or death suspected to be attributed to an adverse reaction to the study drug should also be reported.

3. The provisions stated in (2) are also applicable to clinical trials implemented by sponsors.

Selection of prospective patients

1. The principal investigator team must carefully consider the suitability of requesting a person to participate in the clinical trial when selecting prospective patients. The selection must meet the following criteria: 1) It should be based on the inclusion and exclusion criteria stipulated in the protocol. 2) It should be performed with due consideration of the patient's health condition, symptoms, age, gender, ability to consent, dependency relationship with the principal investigator and other personnel, and whether the person has participated in other clinical trials, in view of protecting the human rights of patients.

2. In principle, individuals who are unable to provide consent should not be selected as patients, unless it is unavoidable based on the purpose of the clinical trial.

3. When selecting individuals who "may be unfairly disadvantaged by not participating the clinical trial" [a)], it is essential to give due consideration to ensure that consent is provided voluntarily.

Footnote

a) Individuals who "may be unfairly disadvantaged by not participating in the clinical trial" typically refer to "people in a socially vulnerable position." "People in a socially vulnerable position" refer to individuals whose decision to voluntarily participate in the clinical trial may be unduly influenced by the benefits associated with participating in the trial or by retaliation from their superiors if they refuse to participate.

Responsibilities toward patients ①

1. The principal investigator must ensure that the study drug is used only in accordance with the methods stipulated in the approved protocol.

2. The principal investigator team must explain and provide guidance to each patient on the correct use of the study drug and must confirm whether each patient is correctly complying with the explained instructions at appropriate intervals for the clinical trial.

3. The principal investigator team will confirm with the patient whether they are being examined by another attending physician. The team is required to notify the attending physician of the person participating in the clinical trial, with the consent of the patient. The purpose of this action is to prevent damage to the health of the patient caused by interactions with pharmaceuticals administered with the current treatment.

Responsibilities toward patients ②

1. The principal investigator is responsible for all medical decisions related to the clinical trial.

2. The director of the clinical trial site and the principal investigator must ensure that patients are provided with adequate medical care for all clinically relevant adverse events related to the clinical trial, both during and after participation in the clinical trial.

3. The principal investigator is required to inform patients if they learn of adverse events that require medical treatment.

4. If the patient intends to or has withdrawn from the clinical trial partway through, they are not required to provide a reason; however, the principal investigator should make a reasonable effort to confirm the reason, while fully respecting the patient’s rights.

Deviation from the protocol ①

1. The principal investigator or sub-investigators may not deviate from or change the protocol without the principal investigator having secured prior written agreement from the sponsor and written approval based on prior review by the institutional review board.

2. The principal investigator or sub-investigators must record all deviations from the protocol, irrespective of the reason.

3. The principal investigator should create a document describing the reasons for deviation from the protocol, only for deviations from the protocol that were to performed to avoid immediate danger to the patient or for other medically unavoidable reasons, and should immediately submit the document to the sponsor and director of the clinical trial site.

Deviation from the protocol ②

1. The principal investigator or sub-investigators must record all deviations from the protocol, irrespective of the reason.

2. The principal investigator should create a document describing the reasons for deviation from the protocol, only for deviations from the protocol that were made to avoid immediate danger to the patient or for other medically unavoidable reasons, and should immediately submit the document to the director of the clinical trial site.

3. The principal investigator or sub-investigators may deviate from or make changes to the protocol without prior written agreement from the sponsor and without prior approval by the institutional review board for medically unavoidable circumstances, such as avoiding immediate danger to the patient.

Deviation from the protocol ③

1. The principal investigator must promptly submit a report to the sponsor, director of the clinical trial site, and the institutional review board via the director of the clinical trial site regarding all changes to the clinical trial that significantly affect the implementation of the clinical trial or increase the risk to the patients.

2. In clinical trials implemented by sponsor-investigators, when the principal investigator deviates from the protocol to avoid immediate danger to the patient or for other medically unavoidable reasons, they should immediately submit a document stating that they have deviated from the protocol and presenting the reason for the deviation to the director of the clinical trial site. The submitted content must also be promptly reported to the institutional review board via the director of the clinical trial site.

Case report forms ①

1. The principal investigator creates case report forms in accordance with the provisions of the protocol, inspects the contents, and applies their stamp or signature once they have confirmed that there is no problem with the case report forms. It is also necessary to keep a copy of case report forms submitted to the sponsor.

2. Data in case report forms based on source material must be consistent with the source material.

3. The principal investigator must ensure that case report forms and all other report data are accurate, complete, and legible and submitted in a timely manner and that patient identification codes are used to identify patients.

Case report forms ②

1. The principal investigator must follow the instructions provided by the sponsor or created by the sponsor-investigator when changing or modifying case report forms. Any changes or modifications to case report forms must be dated and signed or stamped, and significant changes or modifications also require an explanation. The changes or modifications must not obscure the original content.

2. The principal investigator must create records of the changes and modification to the case report forms, submit the documents to the sponsor in clinical trials implemented by sponsors, and keep a copy. In clinical trials implemented by sponsor-investigators, the sponsor-investigator must keep a copy of the documents.

3. The principal investigator must inspect the contents of case report forms created by sub-investigators and apply their stamp or signature once they have confirmed that there is no problem with the case report forms.

Adverse drug reactions during clinical trials ①

1. The principal investigator is required to submit a summary of the clinical trial implementation status in writing to the director of the clinical trial site once a year or more frequently depending on the requirements of the institutional review board for continued review.

2. The principal investigator is required to immediately report all serious adverse events in writing to the director of the clinical trial site. In these cases, the principal investigator must also identify serious and unexpected adverse drug reactions of the reported serious adverse events.

3. The principal investigator is required to immediately report all serious adverse events to the sponsor, unless it is stipulated in documents, such as the protocol and investigator's brochure that an immediate report is not required. After submitting an immediate report, it is also necessary to promptly submit a detailed written report.

4. The principal investigator is required to report any adverse events stipulated in the protocol, as important for evaluation of the safety of the study drug to the sponsor, in accordance with the reporting requirements and deadlines stipulated in the protocol.

Adverse drug reactions during clinical trials ②

1. The principal investigator is required to submit any additional information on serious adverse events or adverse drug reactions, including reported deaths, as requested by the sponsor, director of the clinical trial site, and institutional review board. Examples include autopsy reports, end-of-life medical records, and other required information.

2. When sponsor-investigators implement clinical trials, and the principal investigator becomes aware of a death or other serious adverse events suspected to be due to adverse reactions to the study drug, they must immediately report this to the director of the clinical trial site. When the clinical trial is implemented jointly as a multicenter clinical trial, the principal investigator must also notify principal investigators at other clinical trial sites and the study drug supplier. If the study drug supplier, director of the clinical trial site, or institutional review board requires further information, the principal investigator must respond to that request and provide the information.

Discontinuation of clinical trials

1. If a clinical trial is discontinued or suspended for any reason, the principal investigator must promptly notify patients regarding the same and ensure that the patients are provided with appropriate treatment and follow-up.

2. If the sponsor decides to discontinue or suspend a clinical trial or to terminate the development of the study drug, the principal investigator is notified of this decision via the director of the clinical trial site.

3. If the principal investigator discontinues or suspends a clinical trial, they must promptly notify the director of the clinical trial site in writing and provide a detailed written explanation of the discontinuation or suspension.

4. When a clinical trial is completed, the principal investigator must notify the director of the clinical trial site in writing and submit a written report of the summary of the clinical trial results.

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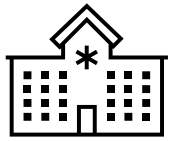
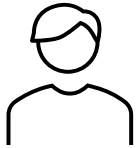
Organization of personnel who appeared in the first half

①

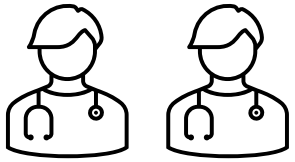


Clinical trial site

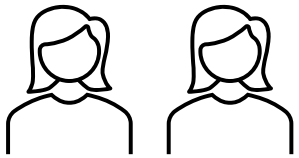


Director of the clinical trial site

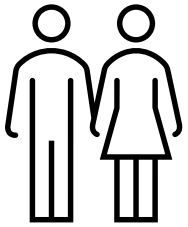
Principal investigator



Sub-investigators



Clinical trial collaborators



patients

IRB

Institutional review board: IRB

Regulatory authorities

Sponsor

Organization of personnel discussed in the first half ②

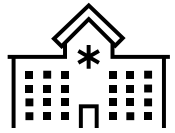
Principal investigator:
Refers to doctors or dentists who supervise operations related to the clinical trial at the clinical trial site.

Sub-investigators:
Refers to doctors or dentists who are allocated work related to the clinical trial under the supervision of the principal investigator at the clinical trial site.

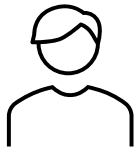
Clinical trial collaborators:
Refers to pharmacists, nurses, and other medical personnel who collaborate with these personnel regarding work related to the clinical trial under the supervision of the principal investigator or sub-investigators at the clinical trial site.

Patients:
Refers to persons administered the study drug or post-marketing clinical study drugs or those administered the control drug.

Organization of personnel discussed so far

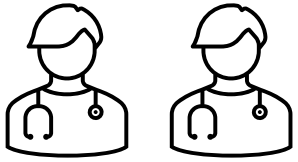


Clinical trial site

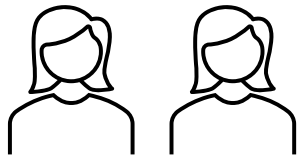


Director of the clinical trial site

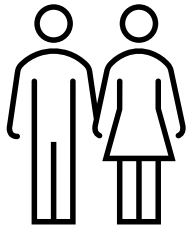
[Principal investigator]
Doctors or dentists who supervise operations related to the clinical trial at the clinical trial site.



[Sub-investigators]
Doctors or dentists who are allocated work related to the clinical trial under the supervision of the principal investigator at the clinical trial site.



[Clinical trial collaborators]
Pharmacists, nurses, and other medical personnel who collaborate with these personnel regarding work related to the clinical trial under the supervision of the principal investigator or sub-investigators at the clinical trial site.

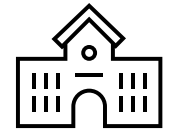


[Patients]
Persons administered the study drug or post-marketing clinical study drugs or persons administered the control drug.

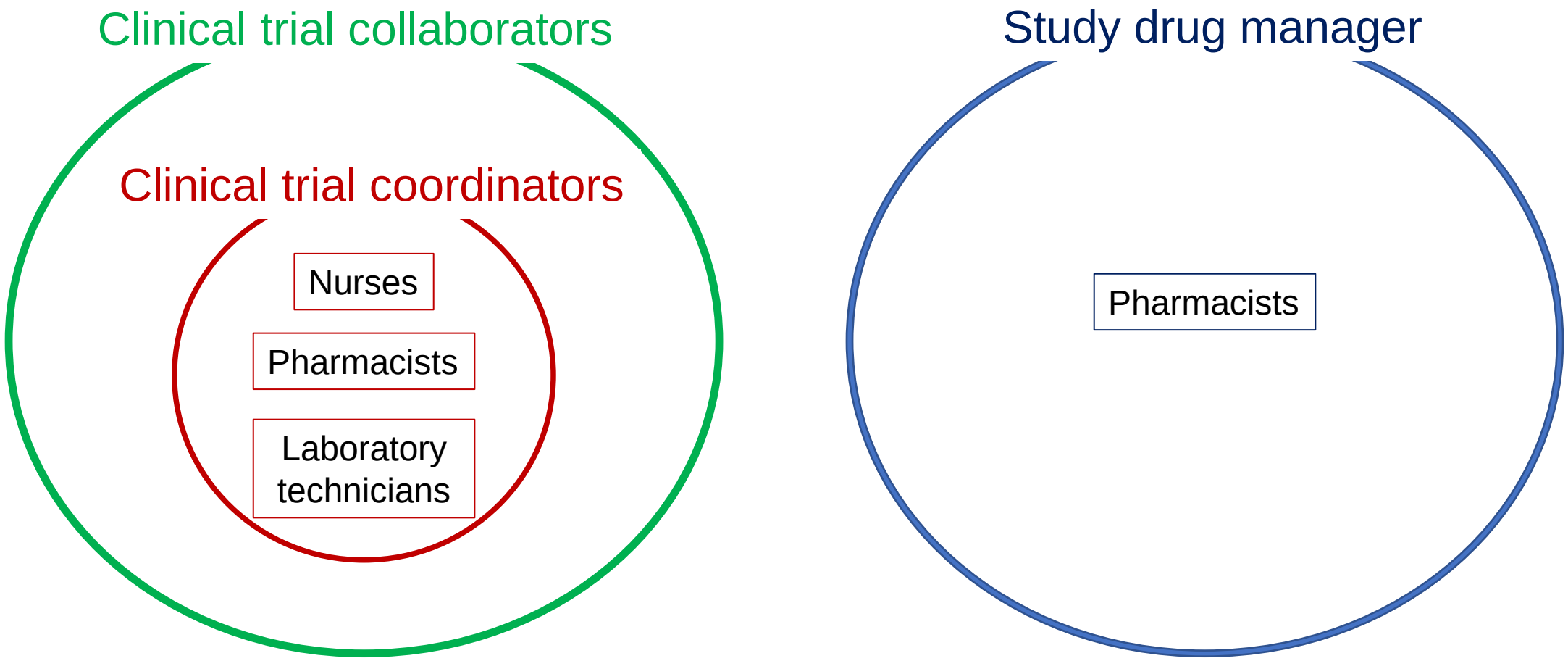
Regulatory authorities

Sponsor

IRB

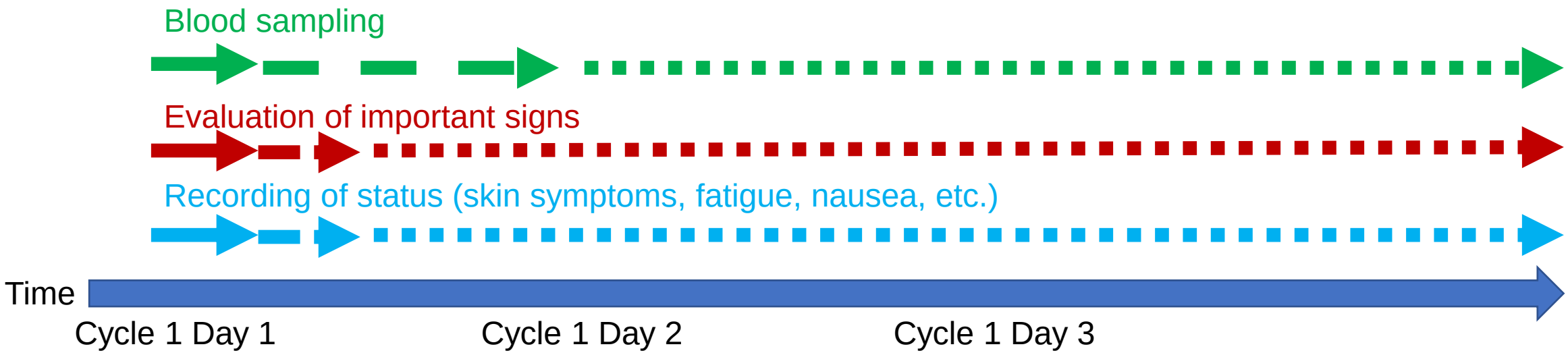


Clinical trial coordinators



Nurses and laboratory technicians

Role of nurses in Phase I clinical trials



Initial response to infusion reaction

Initial response to symptoms, such as nausea, vomiting, and diarrhea

Initial response to fever (particularly infection)

Thank you