DEVIATION

Welcome everyone.

This time, we will discuss an important aspect of clinical trials: deviations.

Imagine baking a cake where every ingredient and step must be followed precisely to achieve the desired result. If you accidentally add too much sugar or forget to include eggs, those deviations from the recipe can lead to an undesired outcome. Just as a baker must document any changes made to the recipe to ensure consistency and reliability in future cakes, clinical trials must also report all deviations from established protocols. This documentation serves to uphold the integrity of the study, much like a baker strives for the perfect cake with each attempt.

This analogy illustrates the importance of adherence to protocols and highlights the necessity of reporting deviations to maintain quality and safety in clinical trials.

What is deviation?

- What is deviation (non-compliance)?
  - Failure to comply with GCP, protocols, or other regulatory requirements.

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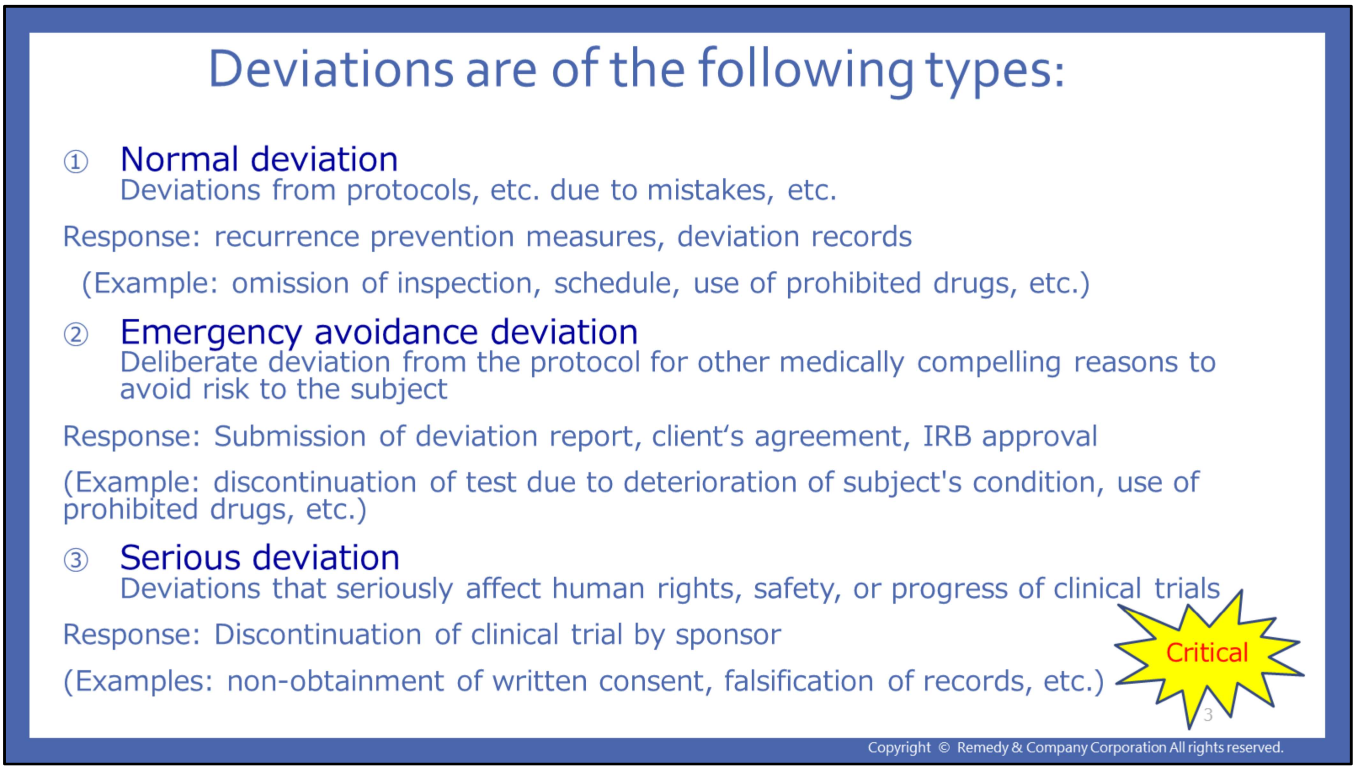
Deviations refer to instances when researchers do not comply with Good Clinical Practice (GCP) guidelines, the trial protocol, or regulatory requirements. Understanding these deviations is crucial because they can impact both subject safety and the integrity of the data we collect during clinical trials. A deviation from the clinical trial protocol refers to "any change, difference, or departure from the study design and procedures specified in the clinical trial protocol."

*For example, deviations from the temperature control of investigational drugs are also considered deviations from investigational drug management procedures.



The "use of prohibited drugs in combination" given as an example of a ① normal deviation is when a drug is used unknowingly, but it can become an emergency avoidance deviation depending on the situation.

→ For example, when steroids are prohibited in combination, but they are used unavoidably to avoid an emergency danger.

We will discuss the different types of deviations that can occur during a clinical trial, their implications, and the appropriate responses to each type. Understanding these deviations is crucial for ensuring the safety and integrity of the trial process.

Normal Deviation
Let's begin with the first type: Normal deviations. These are primarily caused by mistakes or lapses in following protocols. Examples of normal deviations include omissions, such as forgetting to conduct an inspection, falling behind on schedules, or using prohibited drugs. When a normal deviation occurs, it is essential to document it through a deviation record and implement recurrence prevention measures. This way, we can learn from these mistakes and avoid them in the future. The "use of prohibited drugs in combination" given as an example of a ① normal deviation is when a drug is used unknowingly, but it can become an emergency avoidance deviation depending on the situation.

→ For example, when steroids are prohibited in combination, but they are used unavoidably to avoid an emergency danger.

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Emergency Avoidance Deviation
Now, let's move on to the second type: Emergency avoidance deviations. These are deliberate deviations from the protocol that are made in response to medically compelling reasons to prevent any risk to the subject involved. For instance, this might mean discontinuing a test due to the deterioration of a subject's condition, or using a prohibited drug when absolutely necessary.

In cases of emergency avoidance deviations, it is critical to follow specific procedures: you must submit a deviation report, obtain the client's agreement, and secure IRB

(Institutional Review Board) approval. This ensures that all actions taken are in compliance with ethical standards and protect the subject's well-being.

Serious Deviation
Finally, we have serious deviations. These situations seriously impact human rights, safety, or the progress of the clinical trial. Examples include failing to obtain written consent from subjects involved or falsifying records.

When a serious deviation occurs, the response is significant. It may lead to the discontinuation of the clinical trial by the sponsor. This step is taken to protect participants and maintain the integrity of the research being conducted.

Japan GCP Guidance Article 46-1

The investigator or sub-investigator will not allow the investigator to obtain protocol deviations or Do not make any changes.

However, this does not apply if the change is medically unavoidable, such as to avoid an emergency danger to the subject, or if the change is only related to administrative matters of the clinical trial.

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We will discuss an important aspect of Clinical Trials, specifically focusing on protocol deviations.

We will cover the guidance provided in Japan Good Clinical Practice (GCP), particularly Article 46.

This article highlights the responsibilities of investigators and sub-investigators when it comes to adhering to the study protocol.

Understanding Protocol Deviations
Protocol deviations refer to instances where there are changes made to the study protocol. According to GCP guidelines, it is crucial that these deviations are not allowed unless certain criteria are met. The guidance clearly states, “the investigator or sub-investigator will not allow the investigator to obtain protocol deviations or make any changes”.

◆ Why is it prohibited to deviate from or change the clinical trial protocol?

→ The clinical trial protocol is a set of procedures designed to ensure ethical and scientific standards.
Conducting a clinical trial according to the protocol leads to the collection of reliable information regarding the efficacy and safety of the investigational drug.

Exceptions to Protocol Deviations
However, we must understand the exceptions to this rule. The article mentions that changes can be made in cases that are “medically unavoidable”.
This means that if there is an emergency situation threatening the subject’s health or safety, then deviations might be necessary to protect the participant.

Administrative Matters and Protocol Deviations
Additionally, changes that are solely related to administrative matters of the clinical trial are also exempt from this restriction. For instance, if there are updates to administrative processes that do not affect the subject’s safety or the scientific integrity of the trial, these modifications can be made.

◆ What does the agreement on the clinical trial protocol entail? (This is also mentioned in the protocol agreement training materials!)

→ Before the trial is initiated, the principal investigator and the sponsor agree to conduct the trial in accordance with the protocol.

Conclusion

In summary, while protocol deviations are generally not permitted, there are critical exceptions to consider. Understanding these guidelines ensures that patient safety is prioritized while maintaining the integrity of the clinical trial process. We must be vigilant in differentiating between necessary changes and those that could compromise the trial’s validity.

Japan GCP Guidance Article 46-2

The investigator or sub-investigator should document all protocol deviations for any reason.

The investigator shall prepare a document stating the reason only for deviant acts that did not comply with the protocol for avoidance of immediate danger to the subject or other medically unavoidable reasons, and immediately start the clinical trial. Submit to the requester and the director of the medical institution.

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A protocol deviation refers to any instance where the conduct of a clinical trial does not adhere to the approved study protocol.

These deviations can occur for various reasons, including emergencies, medical necessity, or other unforeseeable circumstances.

Importance of Documentation/The Role of Documentation
It is crucial for investigators to document all protocol deviations. This documentation provides transparency and accountability. For deviations that do not comply with the protocol but were necessary to avoid immediate danger to the subject, investigators must clearly state the reason for these actions.

Steps for Documenting Deviations

1. **Identify the Deviation**: Notice any action that diverges from the approved protocol.
2. **Prepare a Document**: Clearly outline the specific reasons for the deviation, focusing on issues of immediate safety or medically unavoidable causes.
3. **Submission**: Immediately submit this document to the requester and the director of the medical institution.

In conclusion, proper documentation of protocol deviations is not only a regulatory requirement but also a fundamental aspect of ensuring participant safety in clinical trials. Let’s open the floor for any questions regarding the documentation process or protocol deviations. Thank you for your attention!

Japan GCP Guidance Article 46-4

The investigator or sub-investigator shall obtain prior written consent from the sponsor and the prior written consent of the institutional review board for medically unavoidable circumstances, such as to avoid immediate danger to the subject. Protocol deviations or changes may be made without approval.

At that time, the investigator should inform the sponsor, the head of the clinical trial site, and the clinical practice as soon as possible about the details and reasons for the deviation or change, and, if appropriate, a draft revision of the protocol. Submit to and obtain approval from the institutional review board via the director of the institution, and obtain approval in writing from the director of the medical institution and consent from the sponsor via the director of the medical institution.

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We will discuss an important aspect of Good Clinical Practice (GCP), specifically Article 46-4. This article outlines the responsibilities of investigators when it comes to obtaining consent and managing protocol deviations. Understanding these principles is crucial for maintaining the integrity of clinical trials and ensuring the safety of subjects.

Importance of Prior Written Consent
Let’s begin with the requirement for prior written consent. According to Article 46-4, the investigator or sub-investigator must obtain prior written consent from the sponsor as well as the institutional review board (IRB) before making any changes due to medically unavoidable circumstances. These circumstances may include situations where there is an immediate danger to the subject. This ensures that any actions taken are ethically justified and in line with regulatory expectations.

Protocol Deviations and Changes
Next, let’s talk about protocol deviations. Sometimes, deviations or changes to the trial protocol might be necessary. Importantly, these changes can be implemented without prior approval in cases of immediate danger.

However, it is crucial to keep in mind that deviations should be promptly communicated. The investigator is responsible for informing the sponsor, the head of the clinical trial site, and the clinical practice about the details and reasons for the deviation as soon as possible.

Documentation and Approval Process
Following the notification, the investigator must submit documentation, including if necessary, a draft revision of the protocol. This is submitted to the IRB through the director of the institution.

It’s essential to obtain the needed approvals in writing: first from the medical institution’s director and then from the sponsor, also via the director of the medical institution. This process ensures that everyone involved is aware of the changes and that all actions comply with regulatory requirements.

In conclusion, adhering to the guidelines set in GCP Article 46 is not just a matter of regulatory compliance; it is about ensuring the safety and well-being of trial subjects.

By following the proper procedures for obtaining consent and documenting protocol deviations, we help uphold the ethical standards of clinical research. Thank you for your attention, and I hope this discussion has clarified the key points of GCP Guidance Article 46-4 for you.

Japan GCP Guidance Article 46-5

The investigator should follow the randomization procedure, if one is specified, and ensure that the investigational product allocation code is opened only in accordance with the protocol.

In a blinded clinical trial, if the opening is performed earlier than the predetermined time (accidental opening, opening due to a serious adverse event, etc.), the investigator should promptly inform the investigator of this along with the reason. In the case of a sponsor-initiated clinical trial, it shall be submitted to the sponsor, and in the case of a sponsor-investigated clinical trial, the sponsor-investigator shall retain the information.

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We are going to discuss an essential aspect of clinical trials, particularly focusing on the roles and responsibilities of an investigator in maintaining the integrity of randomized procedures. Specifically, we will explore the guidelines set forth in the GCP Guidance Article 46-5. Randomization is a key element in clinical trials as it helps prevent bias and ensures that the results are reliable. Following the randomization procedure outlined in the study protocol is crucial. This means that the allocation of investigational products must be managed strictly according to the predetermined randomization plan.

Investigational Product Allocation Code
Next, let's dive deeper into the investigational product allocation code. It is imperative that investigators only open the allocation code in accordance with the protocol specified at the outset of the trial. This strict adherence is vital; any deviations can affect the validity of the study outcomes. Remember, the allocation code represents a commitment to unbiased results—opening the code prematurely might compromise the trial's integrity.

Blinded Trials and Premature Opening of Codes (unblinding)
The key unblinding by the Principal Investigator (in emergency situations) is stipulated in the protocol.

In the context of blinded clinical trials, sometimes unforeseen circumstances may lead to premature code opening (break code). For example, if a serious adverse event occurs, this may necessitate an earlier opening than initially planned. If such an accidental opening happens, it is the responsibility of the investigator to promptly inform the relevant parties about this event and the reasons for it. This step is critical for maintaining transparency and accountability within the trial.

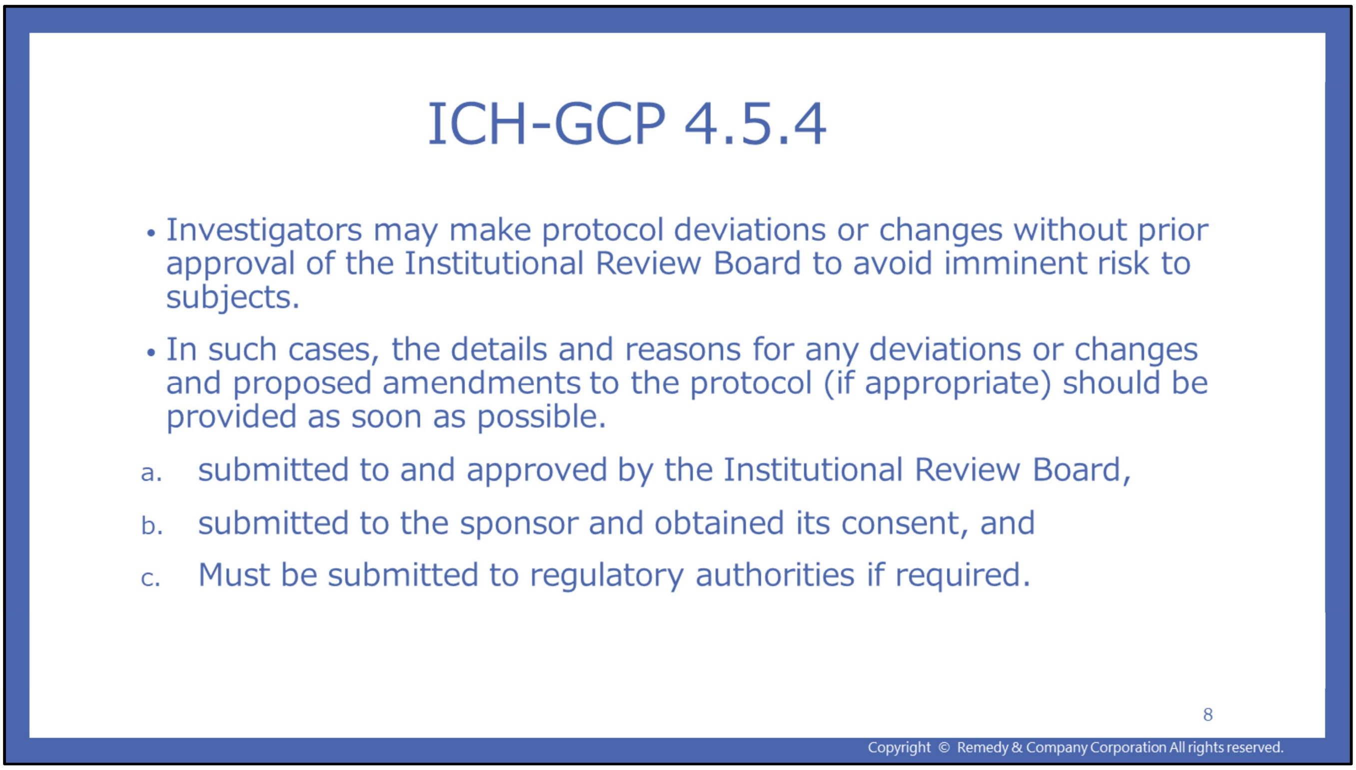
Reporting and Responsibilities in Sponsor-Initiated Trials
It is also important to distinguish between different types of clinical trials, particularly sponsor-initiated versus sponsor-investigated trials.

In a sponsor-initiated clinical trial, if there's a need to report a premature code opening, this information must be submitted to the sponsor. On the other hand, in a sponsor-investigated trial, the investigator takes on the dual role of both investigator and sponsor and must retain this information themselves. The term "document" here does not refer to a standardized format but is determined for each project. Some projects consider reporting by entering data into the EDC (Electronic Data Capture) system.

Overall, proper communication about any deviations from the protocol is essential in protecting the study’s integrity and ensuring the safety of participants.

Conclusion and Key Takeaways

In conclusion, adhering to the randomization procedures and managing investigational product allocation codes with care are vital components of conducting high-quality clinical trials. Always keep in mind the necessity of proper reporting protocols in case of any unforeseen events.



Understanding Protocol Deviations
In the realm of clinical research, there may be instances where investigators encounter situations that necessitate deviation from the approved study protocol. According to ICH-GCP 4.5.4, investigators have the authority to make such deviations or changes without prior approval from the Institutional Review Board (IRB) when the intent is to avoid imminent risk to subjects involved in the study.

This means that the safety and well-being of participants take precedence, and investigators can act swiftly to mitigate any potential harm.

Documentation of Deviations
However, it is crucial to document any protocol deviations or changes. The investigator must provide detailed accounts of the deviations, including:

1. **The details of the deviations or changes** – What exactly was altered or deviated from?
2. **The reasons for these actions** – Why was it necessary to take this step?
3. **Proposed amendments to the protocol** (if appropriate) – If changes to the existing protocol are warranted, these should also be outlined.

This documentation should be carried out as soon as possible, ensuring transparency and accountability in the research process.

Submission Requirements Post-Deviation
Now, let's discuss the next important aspect: after making these deviations, what needs to be done? The ICH-GCP guidelines specify that a few steps must be taken:

a. The details regarding the deviations must be **submitted to and approved by the Institutional Review Board**. Even though prior approval was not required for the immediate action, notifying the IRB is essential for ethical oversight.

b. The investigator must also **submit these details to the sponsor** and obtain its consent. This ensures that the sponsor is kept in the loop regarding any changes that may affect the study's integrity.

c. Lastly, if required, **submission to regulatory authorities** must be undertaken. Some jurisdictions may have specific requirements that necessitate this step.

In conclusion, while ICH-GCP 4.5.4 provides flexibility for investigators to ensure the safety of study participants through protocol deviations, it also emphasizes the importance of thorough documentation and appropriate communication with relevant stakeholders, including the IRB, the sponsor, and regulatory authorities.

This proactive approach not only protects the subjects but also maintains the integrity of the research. Thank you for your attention, and I look forward to our next discussion on ethical considerations in clinical trials.

“Deviation” described in clinical study report

From Guidelines for the Structure and Content of Clinical Study Reports
Deviations from the clinical trial protocol should be follow as below

- Any significant deviations related to study inclusion or exclusion criteria, study conduct, patient management or patient evaluation should be described.
- In the text, protocol deviations should be appropriately summarized by site and grouped as follows:
  - -Patients enrolled in the trial despite not meeting the inclusion criteria
  - -Patients who met the discontinuation criteria during the trial period but were not discontinued
  - -Patients for whom the treatment method or dose was inappropriate
  - -Patients who received prohibited concomitant therapy

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We are going to discuss an essential aspect of clinical trials, particularly focusing on “Deviation” described in clinical study report.

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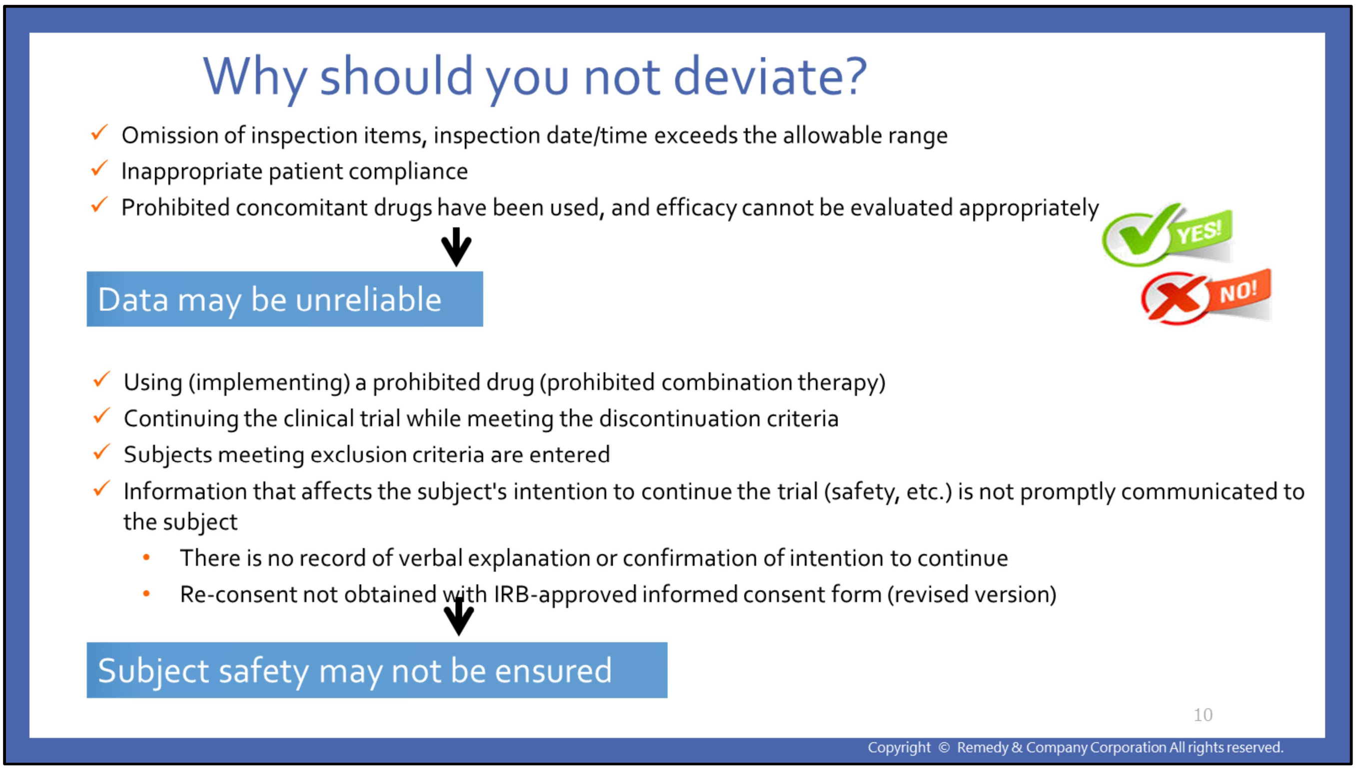


We are going to discuss the critical topic of why deviations in clinical trials should be avoided. Clinical trials are essential for ensuring the safety and efficacy of new treatments, and maintaining strict adherence to protocols is fundamental to their success. Any deviation can compromise the integrity of the trial, leading to unreliable data and potential harm to subjects. Let's explore some key reasons why deviations should not occur.

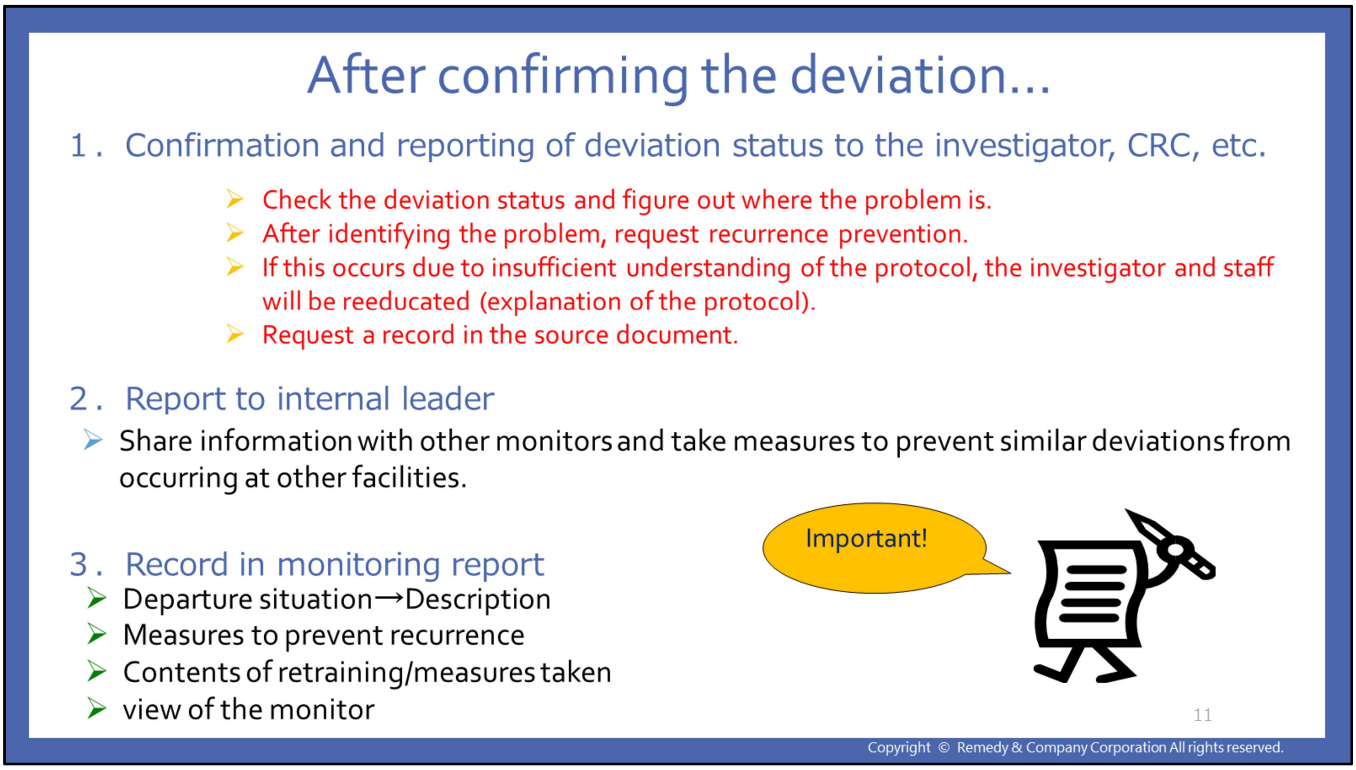
Omission and Timing of Inspections
To start with, one major concern is the omission of inspection items and inspection dates or times that exceed the allowable range. This can result in incomplete data and raise questions about the validity of the trial outcomes. In the clinical setting, timely inspections are crucial to ensure that every aspect of the trial is being conducted as intended, and skipping these can severely impact the trial's reliability.

Compliance and Concomitant Drugs
Another critical factor is inappropriate patient compliance. This refers to situations where patients do not follow the prescribed treatment regimen. When patients use prohibited concomitant drugs, it becomes challenging to evaluate the efficacy of the treatment under investigation properly. It may lead to unreliable data, as the effects of the primary drug could be obscured by these other medications .

Issues with Trial Continuation
Continuing a clinical trial despite meeting discontinuation criteria is an alarming issue. Trials are designed with specific guidelines that, if met, necessitate stopping the study to protect patient safety. Ignoring these criteria can put subjects at risk and may lead to ethical violations. It is imperative that we prioritize subject safety at all times.

Exclusion Criteria and Subject Communication
Furthermore, entering subjects who meet exclusion criteria—who should not be part of the trial due to various risks—can skew results and compromise safety. It is essential to have clear communication regarding any information impacting a subject's intention to continue participating in the trial. If subjects are not updated on safety concerns or have not been re-consented via the appropriate IRB-approved informed consent form, their safety cannot be assured.

In conclusion, adhering to protocol in clinical trials is non-negotiable. Deviations such as omission of inspections, inappropriate compliance, and failure to follow established criteria can lead to unreliable data and jeopardize subject safety. By maintaining strict adherence to trial protocols, we uphold the integrity of clinical research and ensure the safety and well-being of all participants. Thank you for your attention, and let's ensure we keep these principles at the forefront of our research efforts.



We will discuss the process of confirming and reporting deviations within clinical trials.

We'll break down the process into manageable steps. First, we will look at how to confirm and report the deviation status to the relevant personnel, such as the investigator and the Clinical Research Coordinator (CRC).

STEPS TO CONFIRM AND REPORT DEVIATION STATUS

The first step in handling a deviation is to confirm and communicate its status.

1. **Check Deviation Status**: Begin by reviewing the details of the deviation to understand the extent of the issue and identify where the problem lies.
2. **Identify the Problem**: Once you have checked the status, pinpoint the root cause of the deviation.
3. **Request Recurrence Prevention**: After identifying the issue, it's essential to suggest measures to prevent the same deviation from happening again.
4. **Reeducation of Staff**: If the deviation stems from a lack of understanding of the protocol, we must reeducate the investigator and the staff. This means providing a thorough explanation of the protocol to ensure that all team members are well-informed.
5. **Documentation**: Finally, it's crucial to request a record of the deviation in the source document to ensure all occurrences are documented for future reference.

REPORTING TO THE INTERNAL LEADER

Next, after confirming the status of the deviation and taking initial steps to address it, we need to report to our internal leaders.

1. **Share Information**: It is important to disseminate information regarding the deviation with other monitors. Not only does this help in maintaining transparency, but it also aids in implementing measures that can prevent similar deviations from occurring at other facilities.

Once information is shared, the leadership team can strategize on a wider scale to address potential issues across various monitoring sites.

DOCUMENTING IN MONITORING REPORTS

Finally, detailed documentation is critical in maintaining oversight in our processes.

- **Record in Monitoring Report**:

1. **Departure Situation: Describe the situation that led to the deviation.**
2. **Measures to Prevent Recurrence: Outline the steps that will be taken to ensure this does not happen again.**
3. **Contents of Retraining/Measures Taken: Document what retraining took place and any other measures that were implemented.**
4. **View of the Monitor: Provide your perspective on the situation and the efficacy of the responses initiated.**

In conclusion, [Confirmation of Records Related to Deviations] the principal investigator or sub-investigator is required to record all deviations from the clinical trial protocol, regardless of the reason (GCP Guidance Article 46, Section 2).

If this information cannot be derived from the source documents, they are required to leave a record. In such cases, there are no prescribed formats or layouts, and they should be instructed to record the deviations promptly in accordance with the procedures established by the medical institution conducting the trial.

Cause of Deviation and Measures to Prevent Recurrence

	Cause of deviation	Recurrence prevention measures (example)
Sponsor	• Insufficient explanation of CRA to related parties • Lack of understanding of CRA • Difficult-to-understand descriptions in clinical trial documents (protocols, etc.)	• Appropriate explanation to relevant parties • Sufficient understanding of clinical trial content • Clear/detailed description in materials • Creation of auxiliary materials (tools), etc.
Medical institution	• Inadvertent mistakes • Insufficient understanding of clinical trial content • Insufficient explanation to subjects • Insufficient information sharing with related departments	• Use of check sheet • Double check, etc. • Creation of auxiliary materials (tools), etc. • Re-explanation/holding of re-explanatory meeting
subject	• Self-convenience • Insufficient understanding of clinical trial content	• Re-explanation • Ingenuity of tools, etc.

Point

If deviations occur, why did they occur?

Investigation of the cause and measures to prevent recurrence are important (PDCA cycle)

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Now, we are going to discuss an important aspect of clinical trials: understanding the causes of deviations and how to prevent them from recurring, using the PDCA (Plan-Do-Check-Act) cycle.

CAUSES OF DEVIATION
Sponsor:
Insufficient explanation of the Clinical Research Associate (CRA) to related parties
Lack of understanding of CRA
Difficult-to-understand descriptions in clinical trial documents, such as protocols
Medical Institution:
Inadvertent mistakes
Insufficient understanding of clinical trial content
Insufficient explanation to subjects
Insufficient information sharing with related departments
Subjects:
Self-convenience
Insufficient understanding of clinical trial content

MEASURES TO PREVENT RECURRENCE
For the Sponsor:
Provide appropriate explanations to relevant parties
Ensure a sufficient understanding of the clinical trial content
Use clear and detailed descriptions in materials
Create auxiliary materials and tools for better understanding
For Medical Institutions:
Use check sheets and double-check to prevent errors
Create and utilize auxiliary materials and tools
Conduct re-explanations or hold re-explanatory meetings to ensure clarity
For Subjects:
Offer re-explanations to ensure understanding
Innovate tools to aid comprehension

CONCLUSION
It’s crucial to investigate deviations thoroughly to understand their causes and apply effective measures for prevention. By implementing these strategies, and using the PDCA cycle, we

can enhance the efficiency and reliability of clinical trials.

Please always consider about Pursuing the Cause and Preventing Recurrence!!

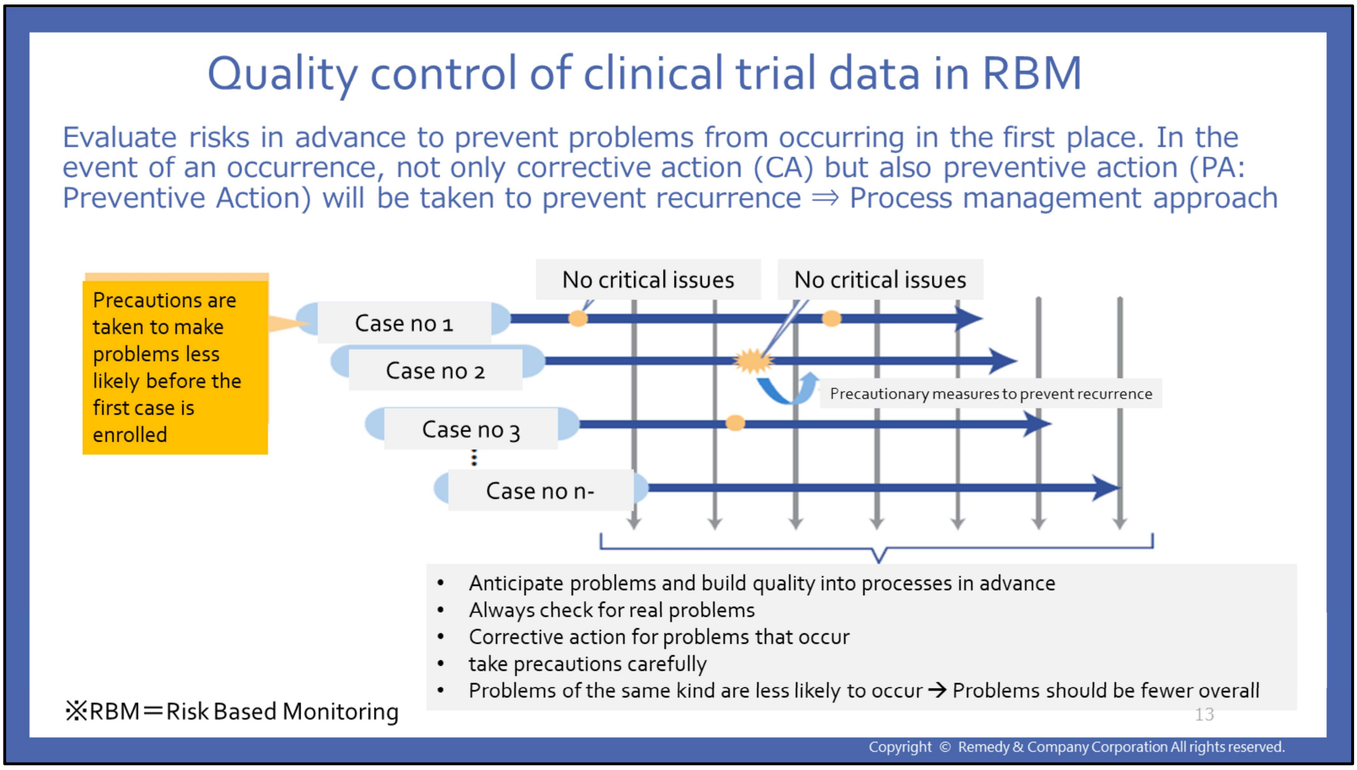
- The Importance of Applying the PDCA Cycle

Plan: Based on past performance and future projections, create a work plan.

Do: Carry out tasks according to the plan.

Check: Evaluate whether the tasks are being performed according to the plan. Assess and analyze the collected information, and analyze any problems identified to trace their root causes.

Act: Investigate areas that do not align with the plan and make improvements. Solutions should include corrective and preventive actions. Review the plan as necessary.



For the last slides We will talk about Quality Control in Clinical Trial Data with a focus on Risk-Based Monitoring (RBM).

Our goal is to understand how anticipating and managing potential risks can help prevent problems in clinical trials.

Firstly, it is essential to evaluate risks in advance. By identifying potential issues before they arise, we can take proactive measures to mitigate them. This is achieved through a process management approach, which includes both corrective actions (CA)/Addressing the problem that occurred, for issues that do occur and preventive actions (PA)/Preventing future occurrences of the problem, to stop the recurrence of these issues. The aim is to build quality into our processes from the start.

In our clinical trial framework, no critical issues should arise if precautions are taken. This starts well before the first case is enrolled. We need to anticipate possible problems and integrate quality measures early on. This ensures that real problems are always checked and addressed promptly.

When issues do arise despite our best precautions, they should be fewer overall due to our preemptive efforts. Corrective actions need to be taken for any problems that occur, ensuring they are less likely to happen again.

By doing so, similar problems become less likely in the future, thereby enhancing the quality and reliability of our clinical trial data.

This approach of Risk-Based Monitoring ensures that we are not only reacting to issues but are strategically preventing them, leading to a smoother and more efficient clinical trial process.

Risk-Based Quality Management is Fundamentally Based on the Concept of the PDCA Cycle (Plan-Do-Check-Act)
By continuously applying this cycle, quality can be improved. When issues arise during the trial, the cycle is driven by repeatedly evaluating the problems and adjusting methods accordingly.

Conduct a root cause analysis of the identified problems. For example, if a problem is discovered during the monitoring of a clinical site, it is important to determine whether it is a site-specific issue or a broader issue, such as insufficient descriptions in the trial protocol, that could affect all sites. Based on the analysis, consider solutions for the problem. Additionally, evaluate whether corrective actions for the issue itself and preventive measures (e.g., providing training, improving processes) are necessary.

These corrective and preventive measures are generally referred to as **CAPA** (Corrective Action and Preventive Action).

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Thank you