

# Module 4: Investigator Qualifications and Responsibilities

## 1. Module 4

### 1.1 Interpretation and application of ICH E6(R2)



**MULTI-REGIONAL CLINICAL TRIALS**  
THE MRCT CENTER of  
BRIGHAM AND WOMEN'S HOSPITAL  
and HARVARD

Interpretation and application of ICH E6(R2)

Module 4:  
Investigator Qualifications and Responsibilities

Lead developer of this module:  
Sarah A. White, MPH  
MRCT Center

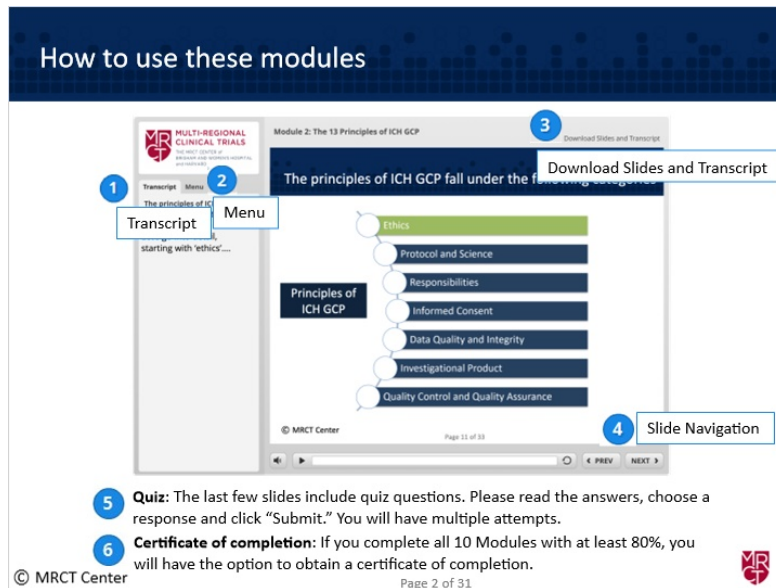
ICH  
Recognised Training Programme

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#### Notes:

Welcome to Module 4 of this training on the interpretation and application of ICH E6(R2)

## 1.2 How to use these modules



### Notes:

We want to familiarize you with how to use these modules. First, you can click on Transcript on the left side to read along with the audio. Second, if you click on Menu, next to Transcript, you can see where you are in this module. You can also go back to slides that you have previously viewed and listened to.

Third, you can click on the upper right on "Download Slides and Transcript" to view a printable PDF of the slides and transcript of the module. You can also click a link to the Guidelines for Good Clinical Practice.

Fourth, to move to the next slide, click "Next" after you listen to the audio. Click "Prev" to go to the previous slide.

Fifth, the last few slides include quiz questions. Please read the answers, choose a response and click "Submit." You will have multiple chances to answer correctly.

Sixth, if you complete all 10 Modules with at least 80%, you will have the option to obtain a certificate of completion.

### 1.3 Attribution and Disclaimer

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This presentation includes the author's views on "[Interpretation and application of ICH E6\(R2\)](#)" theory and practice. The presentation does not represent official guidance or policy of authorities or industry.

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## 1.4 Outline

### Outline

- This module is directed at educating and training government regulators (reviewers and inspectors) on key concepts of International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) [Good Clinical Practice \(GCP\) E6\(R2\)](#).
- This global program is applicable to government regulatory reviewers and inspectors as well as other stakeholders, including investigators, study teams, ethics committee members, research organizations, and sponsors.

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### Notes:

Overall this training is directed at educating and training government regulatory reviewers and inspectors (as well as other stakeholders including investigators, study teams, ethics committee members, research organizations, and sponsors) on key concepts of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) E6(R2).

## 1.5 Overview of Training

### Overview of Training

**Module 1** – What is ICH E6(R2) and how does it apply to regulators?

**Module 2** – Section 2 of Guideline: The 13 Principles of ICH GCP

**Module 3** – Section 3 of Guideline: IRB Responsibilities

**Module 4** – Section 4 of Guideline: Investigator Qualifications and Responsibilities

**Module 5** – Section 5 of Guideline: Sponsor Responsibilities

**Module 6+7** – Key Documents of ICH E6(R2)-Protocol and Investigator's Brochure

**Module 8** – Key Documents of ICH E6(R2)-Essential Documents


**Module 9** – GCP in Practice for Reviewers: Risk-based Monitoring as an element of Quality by Design

**Module 10** – GCP in Practice for Inspectors

**Module 11** – Summary of Key Takeaways for Regulators

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### Notes:

In Module 4 we will focus on describing investigator qualifications and responsibilities as outlined in the guideline.


## 1.6 Learning Objectives

### Learning Objectives

- Review Investigator qualifications
- Discuss Investigator responsibilities
- Apply the elements of Investigator responsibilities through case examples

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## Notes:

This module will focus on the Investigator. The learning objects are to:

1. Review Investigator qualifications, specifically the criteria that make an individual qualified to be an investigator
2. Discuss Investigator responsibilities, emphasizing new sections added with the E6(R2) revisions.
3. Apply elements of the Investigator responsibilities through case examples.

### 1.7 Investigator Qualifications & Agreements

#### Investigator Qualifications & Agreements

		
<b>Definition of the Investigator</b>	<b>The Investigator should be qualified to assume responsibility for the conduct of the trial</b>	<b>The Investigator should permit:</b>
<p>"A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator" (1.34).</p>	<p>A CV should provide evidence of the Investigator's education, training, and experience</p> <p>The Investigator should be familiar with applicable regulatory requirements and the appropriate use of the investigational product to be used in the trial</p>	<p>Monitoring/auditing by the sponsor</p> <p>Inspection by the appropriate regulatory authorities</p>

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Citation: ICH E6(R2) Section 4.1



## Notes:

ICH GCP E6(R2) defines an Investigator as "a person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the "principal investigator"

The Investigator should be qualified to assume responsibility for the conduct of the trial. The Investigators qualifications, including education, training, and experience should be documented and provided in a curriculum vitae, or CV, and/or other relevant documentation.

The Investigator should be familiar with applicable regulatory requirements including national regulations, institutional requirements and Good Clinical Practices, and be thoroughly familiar with the investigational product to be used in the trial.


During and after the clinical trial, the Investigator should permit the sponsor to monitor or audit and/or national regulatory authorities to conduct inspections of the study files.

### **1.8 Adequate Resources**

#### Adequate Resources


- The Investigator should have sufficient time and resources, including as necessary, qualified staff, facilities, and funding to conduct the trial.

Citation: ICH E6(R2) Section 4.2



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#### **Notes:**

In order to conduct a trial, the Investigator needs to have sufficient time and resources to conduct the trial within the agreed trial period. Adequate resources include:

- Sufficient time to properly conduct and complete the trial
- Available facilities and funding to support the trial
- The ability to recruit the required number of subjects
- And if needed, qualified staff that are adequately trained on the protocol, investigational products, and their trial-related duties and functions.

## 1.9 Investigator Responsibilities

### Investigator Responsibilities

<p>The Investigator can <b>delegate</b> significant trial-related duties to a study team:</p> <ul style="list-style-type: none"><li>• The Investigator can delegate <i>tasks</i> but cannot delegate <i>responsibilities</i></li><li>• Delegation is appropriate if the study staff is qualified by education, training, and experience</li><li>• Delegation should be documented on a delegation of responsibility log or signature sheet (Citation 8.3.24)</li></ul>	<p>If the Investigator delegates to a study team, <b>adequate training</b> must be provided.</p> <ul style="list-style-type: none"><li>• Training must be specific for the protocol, applicable regulatory requirements, and specific delegated tasks</li><li>• A training log can be used to document adequate training</li></ul>
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Citation: ICH E6(R2) Section 4.2.4



### Notes:

As stated in GCP section 4.2.4, the Investigator should ensure that all persons assisting with the trial are adequately informed of the protocol, the investigational product or products, and their trial-related duties. This is called Investigator delegation.

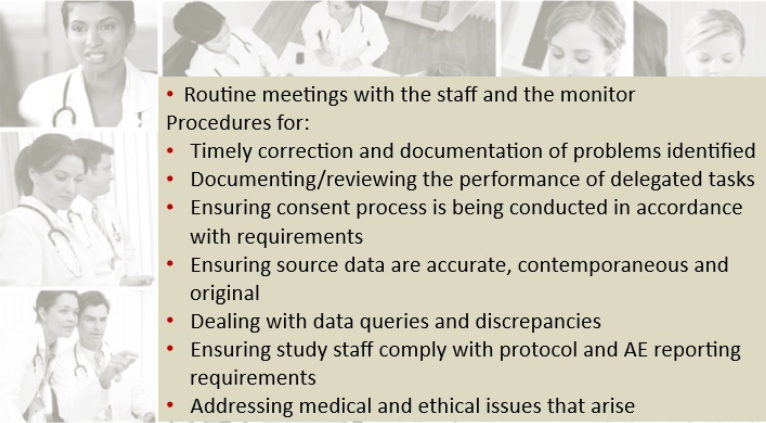
- Investigators can delegate significant trial-related tasks to a study team, but cannot delegate responsibilities.
- Delegation is appropriate if the study staff is qualified by education, training, and experience
- Delegation should be documented on a delegation of responsibility log or signature sheet as identified in section 8.3.24 of the GCP guidelines.

If the Investigator chooses to delegate tasks to study team, the Investigator must provide adequate training. The training must be specific for the protocol, regulatory requirements, and the specific delegated tasks. A training log can be used to document the protocol specific training.



## 1.10 Investigator Responsibilities

### Investigator Responsibilities



- Routine meetings with the staff and the monitor


Procedures for:

- Timely correction and documentation of problems identified
- Documenting/reviewing the performance of delegated tasks
- Ensuring consent process is being conducted in accordance with requirements
- Ensuring source data are accurate, contemporaneous and original
- Dealing with data queries and discrepancies
- Ensuring study staff comply with protocol and AE reporting requirements
- Addressing medical and ethical issues that arise

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Adequate supervision includes (Summary from [FDA Guidance for Industry: Investigator Responsibilities](#))

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### Notes:

The revised E6(R2) guidelines included new information about the investigator's responsibilities to provide adequate supervision to the study team.

As stated in section 4.2.5, supervision is required to any individual or party that is delegated study related tasks.

The extent of supervision will be appropriate to the staff, nature of the trial, and subject population.

Adequate supervision could include:

- Routine Meetings with the staff and monitor
- Procedures for:

Timely correction and documentation of problems identified

Documenting/reviewing the performance of delegated tasks

Ensuring consent process is being conducted in accordance with requirements

Ensuring source data are accurate, contemporaneous and original  
Dealing with data queries and discrepancies  
Ensuring study staff comply with protocol and AE reporting requirements  
Addressing medical and ethical issues that arise

### ***1.11 Investigator Responsibilities***

#### Investigator Responsibilities

- The Investigator must provide oversight of other parties
  - If the Investigator retains services of an individual or party to perform trial-related duties and functions, the Investigator should ensure this individual or party is qualified and should implement procedures to ensure the integrity of any duties, functions, or data generated during the trial.

Citation: ICH E6(R2) Section 4.2.6



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#### **Notes:**

In addition to the Investigator's own staff, he/she is responsible to provide oversight of other parties retained for trial services. Section 4.2.6 of the revised GCP guidelines states that oversight should be provided to any individual or party retained to perform trial specific duties and functions. The Investigator should ensure the individual or party is qualified to perform the delegated duties and functions and implement procedures to ensure integrity of the work performed and any data generated.

## 1.12 Case study: Investigator delegation and training


### Case study: Investigator delegation and training

- During an inspection the Investigator site revealed that trial participants who did not meet specific eligibility procedures were enrolled in the trial.
- The Investigator indicated that day-to-day trial activities were delegated to an Independent Research Company (IRC) but the Investigator held regular meetings with the IRC. At these meetings, the Investigator received updates on recruitment and follow-ups, signed required documents, and reviewed tests.
- The IRC did not bring any of the above-mentioned violations to the Investigator's attention during these regular encounters.

- Question
  - Who is responsible for ensuring protocol adherence? Why?

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### Notes:

To emphasize the Investigator's responsibility, let's review a brief case study. Here is a situation where the Investigator delegated trial related activities to an Independent Research Company. Let's see what happens:

- During an inspection the Investigator site revealed that trial participants who did not meet specific eligibility procedures were enrolled in the trial.
- In response to the finding, the Investigator indicated that day-to-day trial activities were delegated to an Independent Research Company (IRC) but the Investigator held regular meetings with the IRC. At these meetings, the Investigator received updates on recruitment and follow-ups, signed required documents, and reviewed tests.
- The IRC did not bring any of the above-mentioned violations to the Investigator's attention during these regular encounters.

### 1.13 Case study: Investigator delegation and training

#### Case study: Investigator delegation and training

Who is responsible for ensuring protocol adherence? Why?

- The PI is responsible for supervising *any* individual or party whom has been delegated trial-related duties. (Citation: ICH E6(R2) Section 4.2.5)
- A lack of supervision of trial related activities can raise concern about the adequacy of the protection of the trial subjects enrolled, and about the integrity of the data generated by the site



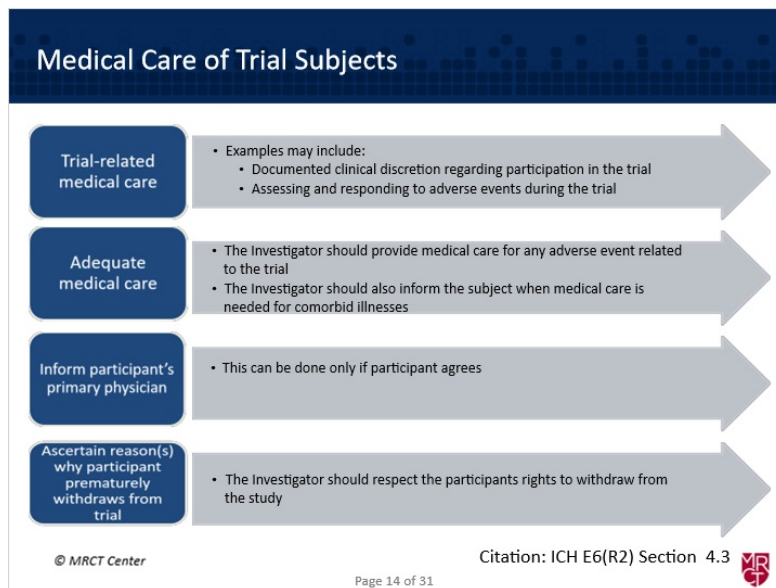
#### Notes:

In this situation, who is responsible for ensuring protocol adherence. And why?

The PI is responsible for supervising any individual or party whom has been delegated trial related duties.

Beyond the statements in ICH GCP, a lack of supervision of trial related activities can raise concern about the adequacy of the protection of the trial participants enrolled, and about the integrity of the data generated by the site.

## 1.14 Medical Care of Trial Subjects



### Notes:

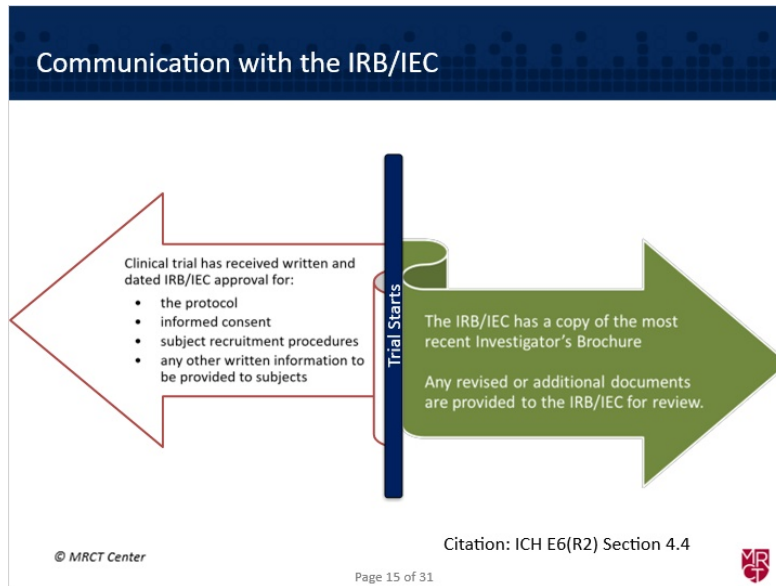
According to GCP section 4.3.1, a qualified physician, or dentist when appropriate, who is the Investigator or Sub-Investigator for the trial should be responsible for all trial-related medical or dental decisions. If medical care is given during the trial the Investigator should ensure that there is documented clinical discretion regarding the care and the participants' participation in the trial. When needed, the Investigator should ensure a participant receives trial-related medical care including assessing and responding to adverse events during the trial.

If the participant experiences an adverse event related to the trial, the Investigator should provide medical care. The investigator should also inform the subject when medical care is needed for a comorbid illness.

ICH GCP E6(R2) recommends that investigators inform the participant's primary physician about their patient's participation in the trial, however this can only be done if the participant agrees.

If a participant withdraws prematurely from the trial, the Investigator should make a reasonable effort to ascertain the reason why the participant is withdrawing. However, the subject is not obliged to do so and the Investigator should respect the participants rights to withdraw from the study.

## 1.15 Communication with the IRB/IEC

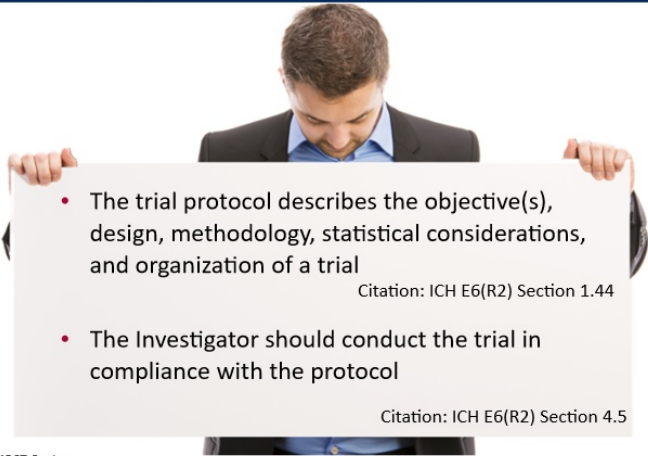


### Notes:

The Investigator must ensure good communication with the IRB/IEC. Prior to beginning the trial, the Investigator should ensure that the clinical trial has received written and dated IRB/IEC approval for the protocol, informed consent, subject recruitment procedures, and any other written information to be provided to subjects. The Investigator should also ensure the IRB/IEC has a copy of the most recent Investigator's Brochure. As the trial continues, the Investigator must provide the IRB/IEC with any revised or new document for review and approval.

## 1.16 Protocol Adherence


Protocol Adherence



- The trial protocol describes the objective(s), design, methodology, statistical considerations, and organization of a trial  
Citation: ICH E6(R2) Section 1.44
- The Investigator should conduct the trial in compliance with the protocol  
Citation: ICH E6(R2) Section 4.5

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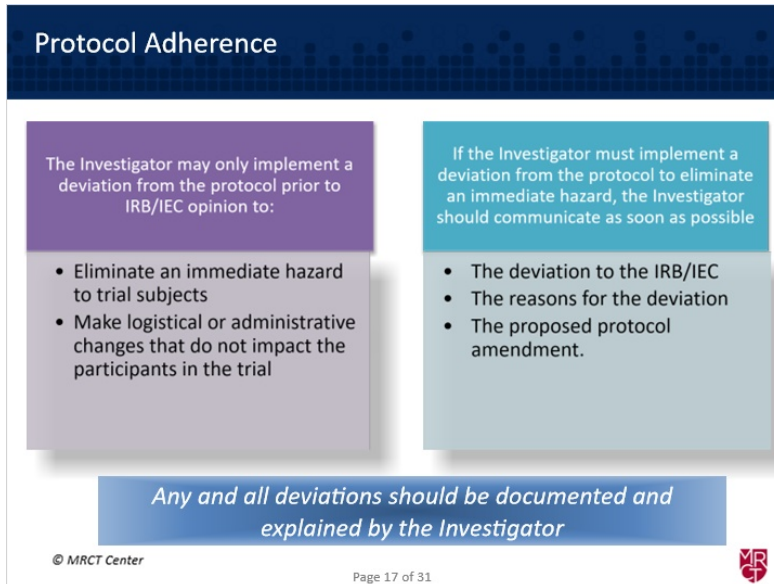


### Notes:

The GCP ICH definition of protocol states that it describes the objectives, design, methodology, statistical considerations, and organization of a trial. The Investigator should conduct the trial in compliance with the protocol at all times.

Any and all deviations should be documented and explained by the Investigator. See next slide for more details.

## 1.17 Protocol Adherence



The slide is titled "Protocol Adherence" in white text on a dark blue background. Below the title, there are two main colored boxes: a purple box on the left and a teal box on the right. The purple box contains text about implementing deviations prior to IRB/IEC opinion and a bulleted list of two items. The teal box contains text about implementing deviations to eliminate immediate hazards and a bulleted list of three items. Below these two boxes is a blue box with italicized text stating that all deviations should be documented and explained by the investigator. At the bottom left is the "© MRCT Center" copyright notice, and at the bottom right is the MRCT logo. The page number "Page 17 of 31" is centered at the bottom.

**Protocol Adherence**

The Investigator may only implement a deviation from the protocol prior to IRB/IEC opinion to:

- Eliminate an immediate hazard to trial subjects
- Make logistical or administrative changes that do not impact the participants in the trial

If the Investigator must implement a deviation from the protocol to eliminate an immediate hazard, the Investigator should communicate as soon as possible

- The deviation to the IRB/IEC
- The reasons for the deviation
- The proposed protocol amendment.

*Any and all deviations should be documented and explained by the Investigator*

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### Notes:

Deviations, or changes to the protocol, may be implemented, without IRB/IEC opinion in limited situations. Specifically, a deviation should be implemented only to eliminate an immediate hazard to trial subjects without prior IRB/IEC opinion or to make logistical or administrative changes (change of telephone numbers)

If the Investigator must implement a deviation from the protocol to eliminate an immediate hazard, the Investigator should communicate, as soon as possible, the deviation to the IRB/IEC, and provide details regarding the reasons for the deviation and the proposed protocol amendment. If required, the sponsor and the regulatory authorities should be notified and/or consulted as well.



## 1.18 Case study: Protocol Adherence

### Case study: Protocol Adherence

During a routine inspection, the Regulatory Inspector reviewed study files to confirm an accurate drug dose was given to the participant. The drug was to be administered according to the participants current body weight (mg/kg).

- In review of the participant files, the Inspector could not find a participant weight documented for the date of dose administration
- The Investigator said they did not have a scale on the hospital floor and asked the participant to state their weight at the time of visit

The Regulatory Inspector also questioned the Investigator regarding protocol-required 21 day, 3 month, 6 month follow up visits to capture/document adverse events.


- Instead of systematically following up with the participants, the Investigator relied on the hospital electronic medical record 'alert system' to notify of an adverse event.

• Question

— How did the Investigator fail to meet his/her responsibilities?

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### Notes:

Let's look at another case study - this time about protocol adherence:

During a routine inspection at a clinical site, the Regulatory Inspector reviewed study files to confirm an accurate drug dose was given to the participant. The drug was to be administered according to the participants current body weight (mg/kg).

- In review of the participant files, the Inspector could not find a participant weight documented for the date of dose administration
- The Investigator said they did not have a scale on the hospital floor and asked the participant to state their weight at the time of visit

The Regulatory Inspector also questioned the Investigator regarding protocol-required 21 day, 3 month, 6 month follow up visits to capture/document adverse events.

- Instead of systematically following up with the participants, the Investigator relied on the hospital electronic medical record 'alert system' to notify of an adverse event

How did the Investigator fail to meet his/her responsibilities?

### 1.19 Case study: Protocol Adherence


Case study: Protocol Adherence

How did the Investigator fail to meet his/her responsibilities?

- The Investigator failed to maintain compliance with the protocol (Citation: ICH E6(R2) Section 4.5). Self reported weight recorded instead of accurate weight determined by a scale. Failure could have resulted in over or under dosing the participant.
- The Investigator failed to maintain compliance with patient safety follow up visits. This could have affected participant safety if the participant experienced an adverse event that was not captured by the hospital alert system.

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#### Notes:

The Investigator failed to maintain compliance with the protocol. The drug was to be administered according to the participant's current body weight (mg/kg). Instead of getting an accurate participant weight prior to drug administration, the Investigator relied on participant self-report. The self-report may not be accurate and could have led to over or under dosing the participant.

The Investigator failed to maintain compliance with patient safety follow up visits. In turn, this could have affected participant safety if the participant experienced an adverse event that was not captured by the hospital alert system.


## 1.20 Informed Consent

### Informed Consent

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form

Prior to a participant's participation in the trial, the written informed consent form should be signed and personally dated by


- The participant/legally acceptable representative
- The person who conducted the informed consent discussion.



Citation: ICH E6(R2) Section 4.8

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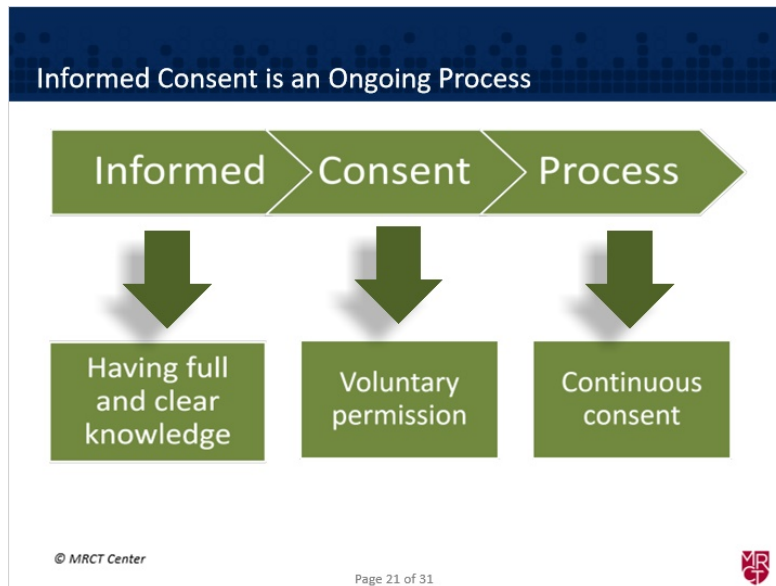


### Notes:

Informed consent is defined in ICH GCP Section 1.28 as a “process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate.” Informed consent is documented by means of a written, signed and dated informed consent form.

Prior to a participant starting trial related procedures, the written informed consent form should be signed and personally dated by the participant or legally acceptable representative and the person who conducted the informed consent discussion.

## 1.21 Informed Consent is an Ongoing Process



### Notes:

The Investigator must ensure the subject has provided and documented informed consent

Every point of contact with the participant is an opportunity to verify their understanding of the research and reiterate their willingness to continue participating

The Informed consent should be revised whenever important new information becomes available that may be relevant to the subject's consent

Any changes to the written informed consent should receive IRB/IEC approval in advance of use

## 1.22 Records and Reports

### Records and Reports



 Documentation	 Retention	 Accuracy
Essential documents Informed consent documents Subject Data	The Investigator should always check with the Sponsor before destroying documents  Local regulatory authorities or IRB/IECs may have different requirements	ALCOA-C: Attributable, legible, contemporaneous, original, accurate, and complete  Monitors and Inspectors should be able to identify and trace changes via an audit trail

Citation: ICH E6(R2) Section 4.9

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### Notes:

A clinical trial generates a tremendous amount of information about the participants in the trial. This information, is frequently referred to as source documents. As presented in section 4.9 of the GCP guidelines, the Investigator should maintain source documents and trial records of all trial participants. These documents should be accurate and include all pertinent and relevant observations.

Records include

- Essential documents
- Informed consent documents
- Subject Data

(For more detailed information about source data and trial records, see module 8 of this course):

Documents should be retained until at least 2-years after the last approval of a marketing application in an ICH region or at least 2 years after formal discontinuation of clinical development.

The Investigator should always check with the Sponsor before destroying documents

Local regulatory authorities or IRB/IECs may have different requirements

The Investigator is responsible for maintaining adequate and accurate source documents and trial records

the revisions to ICH GCP E6(R2) stated that the investigator or institution should maintain adequate and accurate source documents that include all pertinent observations related to the participant. The guidelines describe the ALCOA-C principles.


ALCOA-C stands for: Attributable, legible, contemporaneous, original, accurate, and complete

Monitors and Inspectors should be able to identify and trace changes via an audit trail

### 1.23 Safety Reporting

#### Safety Reporting

- Serious Adverse Event (SAE) reporting
  - immediately to the sponsor except for those SAEs identified as not needing immediate reporting
  - immediate reports should be followed promptly by detailed, written reports.
- Investigators should comply with the applicable regulatory requirement(s) and local IRB/IEC requirements related to the reporting of unexpected serious adverse drug reactions
- Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.
- For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports)

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#### Notes:

Safety reporting by the Investigator is described in section 4.11 of the GCP guidance.

All SAEs should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure)

identifies as not needing immediate reporting.

The immediate reports should be followed promptly by detailed, written reports.

The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.


Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

### ***1.24 Premature Termination or Suspension of a Trial***

#### Premature Termination or Suspension of a Trial


- If the trial is prematurely terminated or suspended for any reason, the investigator/institution should :
  - promptly inform the trial subjects
  - assure appropriate therapy and follow-up for the subjects
  - inform the regulatory authority(ies) and/or the IRB/IEC, if applicable



Citation: ICH E6(R2) Section 4.12

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#### **Notes:**

There is a chance that any trial could be prematurely terminated or suspended. Unexpected and serious adverse events are one reason why this might happen. The Investigator, sponsor, or IRB/IEC may terminate or

suspend the study. If the trial is prematurely terminated or suspended for any reason, the investigator/institution should :

- promptly inform the trial subjects
- assure appropriate therapy and follow-up for the subjects
- inform the regulatory authority(ies) and/or the IRB/IEC, if applicable

### 1.25 Summary



#### Notes:

This module reviewed the Investigator's Responsibilities. In summary:

The Investigator's role in conducting clinical trials requires adequate:

- qualifications as can be found in a CV
- resources, including adequately trained study staff
- oversight of all individuals or parties performing trial-related duties.

The Investigator is responsible for ensuring compliance with the protocol, patient safety, and informed consent of trial participants.



Records and reports provide evidence that the Investigator has: adequately trained the staff, maintained compliance with the protocol, and collected all pertinent data from the subjects.