Module 2: The 13 Principles of ICH GCP

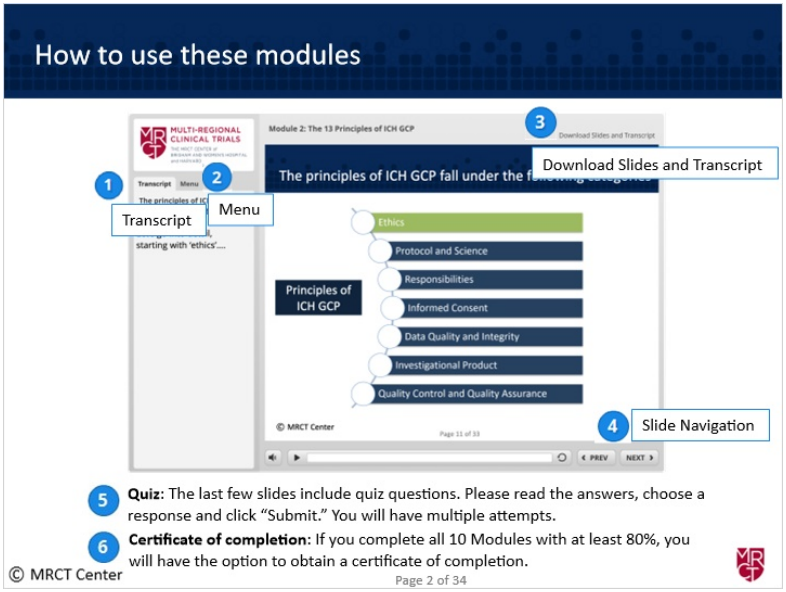
1. Module 2

1.1 Interpretation and application of ICH E6(R2)

Notes:

Welcome to Module 2 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

Notes:

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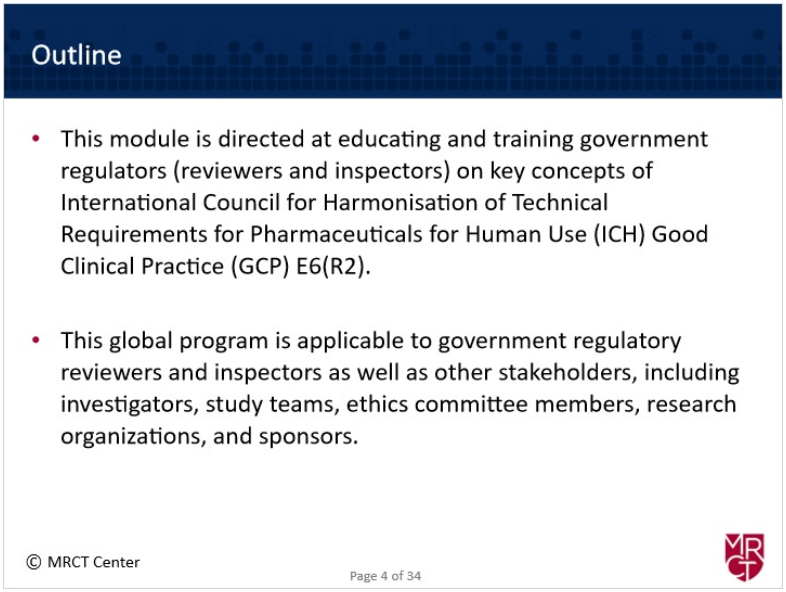
This presentation includes the author's views on "Interpretation and application of ICH E6(R2)" theory and practice. The presentation does not represent official guidance or policy of authorities or industry.

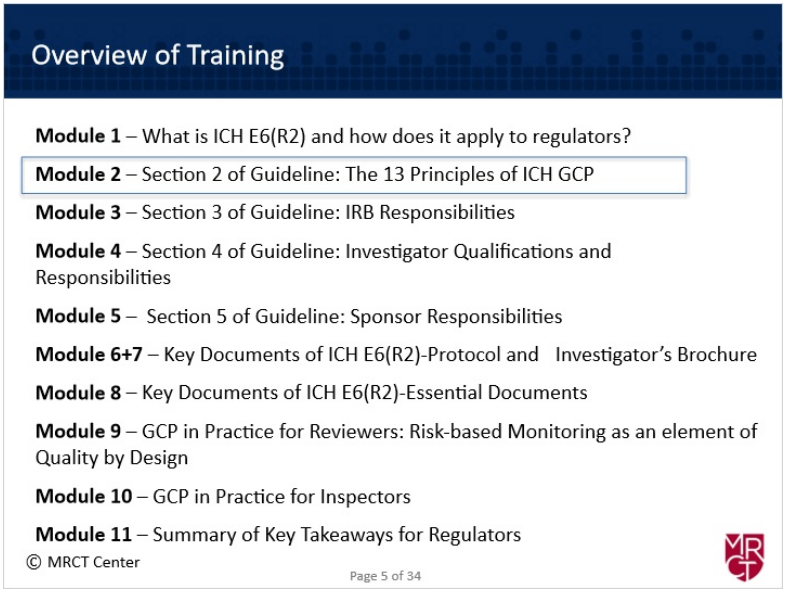
1.4 Outline



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).

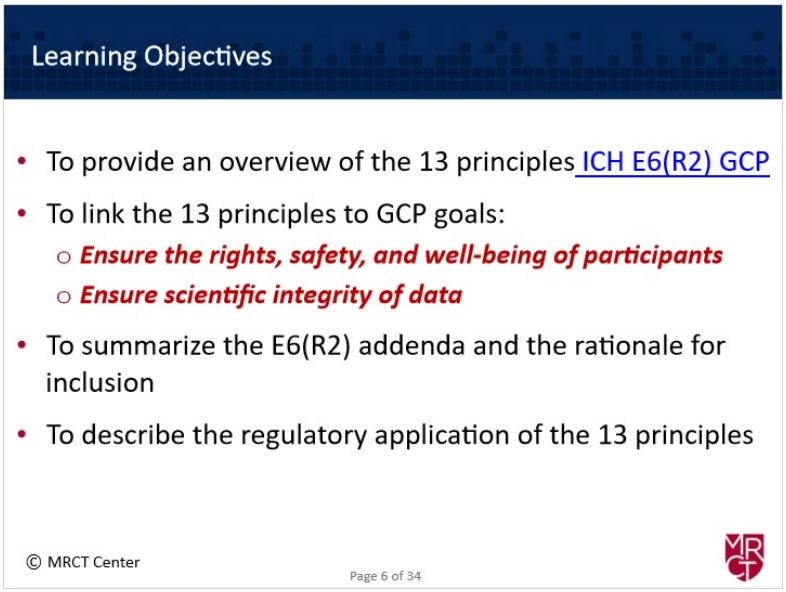
1.5 Overview of Training



Notes:

In Module 2 we will focus on describing the 13 principles of ICH GCP as outlined in the guideline

1.6 Learning Objectives



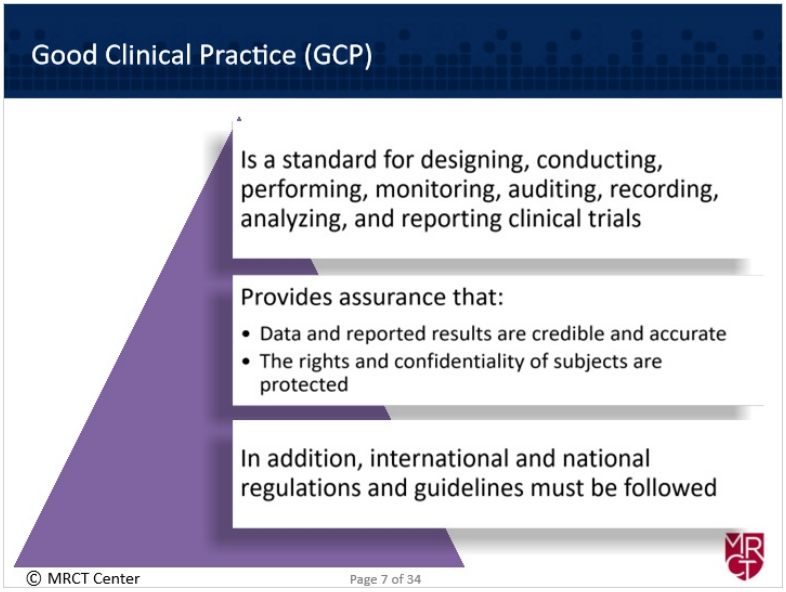
Notes:

By the end of this module you are expected to be able to link those 13 principles to the goals of GCP, which are:

- to ensure the rights, safety and well-being of participants,
- to ensure the scientific integrity of the study data.

By the end of this module you should have a more complete understanding of the addenda and their rationale, as well as an ability to describe the regulatory application of the 13 principles of GCP.

1.7 Good Clinical Practice (GCP)



Notes:

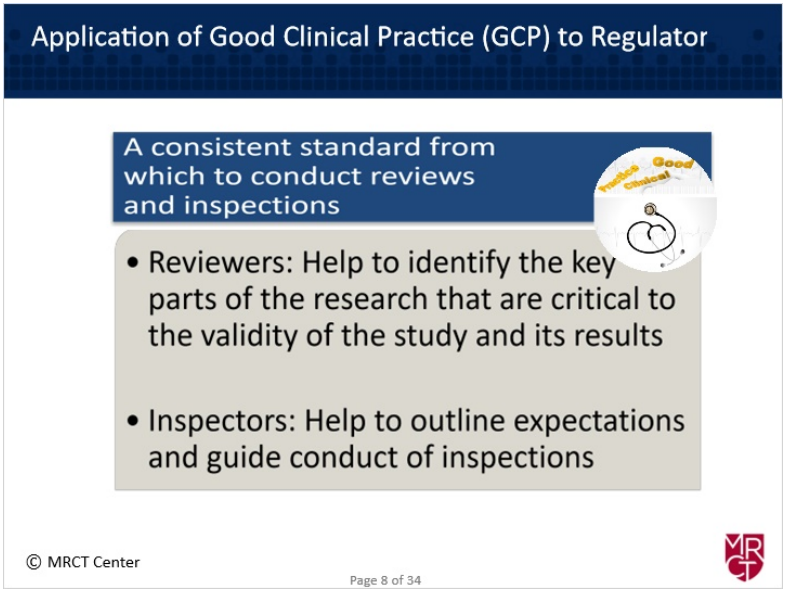
As you know, GCP is an international standard for designing, conducting, performing, monitoring, auditing, recording, analyzing, and reporting clinical trials.

It also provides public assurance that data and reported results are credible and accurate and that the rights and confidentiality of subjects are protected,

facilitating mutual acceptance of data across regions.

In addition to GCP, applicable international and national regulations and guidelines should be known and followed.

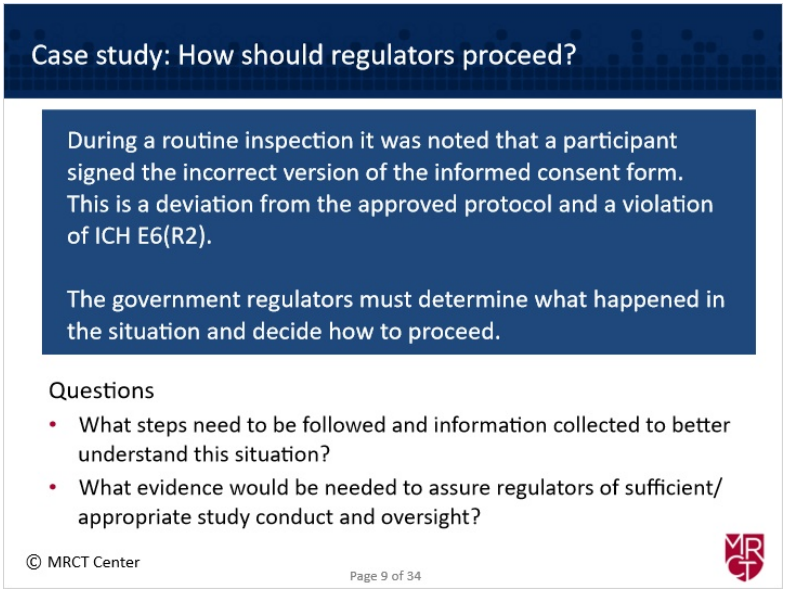
1.8 Application of Good Clinical Practice (GCP) to Regulators



Notes:

So when we think of the regulator role and how GCP applies, consider that GCP is a consistent standard from which to conduct reviews and inspection, allowing reviewers to identify the key parts of the research that are critical to the validity of the study and its results [For example: Risks/safety concerns, data collection details, scientific/statistics plan, qualifications of study team], and providing inspectors with the expectations that guide the conduct of inspections [For example: ensure appropriate delegation/assignment of responsibilities, Identify deficiencies in following the protocol].

1.9 Case study: How should regulators proceed?

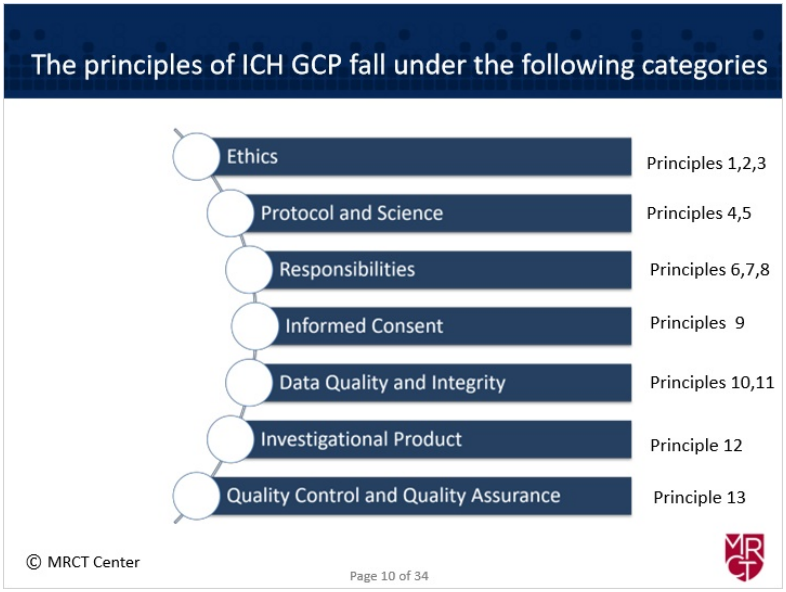


Notes:

Here is a case study. How should the regulator proceed?
In this case, during a routine inspection it was noted that a participant signed the incorrect version of the informed consent form. This is a deviation from the approved protocol and a violation of ICH E6(R2). The government regulators must determine what happened in the situation and decide how to proceed.
For this case, consider these questions:
- What steps need to be followed and information collected to better understand this situation?
- What evidence would be needed to assure regulators of sufficient/appropriate study conduct and oversight?

We will return to this case later on in this module, but in the meantime, consider those questions.

1.10 The principles of ICH GCP fall under the following categories



Notes:

The 13 principles of GCP generally fall under the following categories

Ethics

Protocol and science

Responsibilities

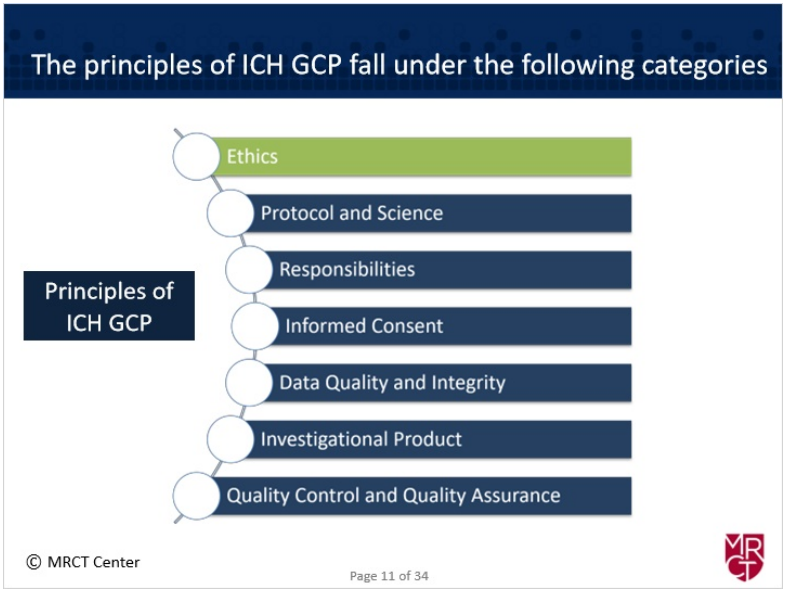
Informed Consent

Data Quality and Integrity

Investigational Product

Quality Control and Quality Assurance

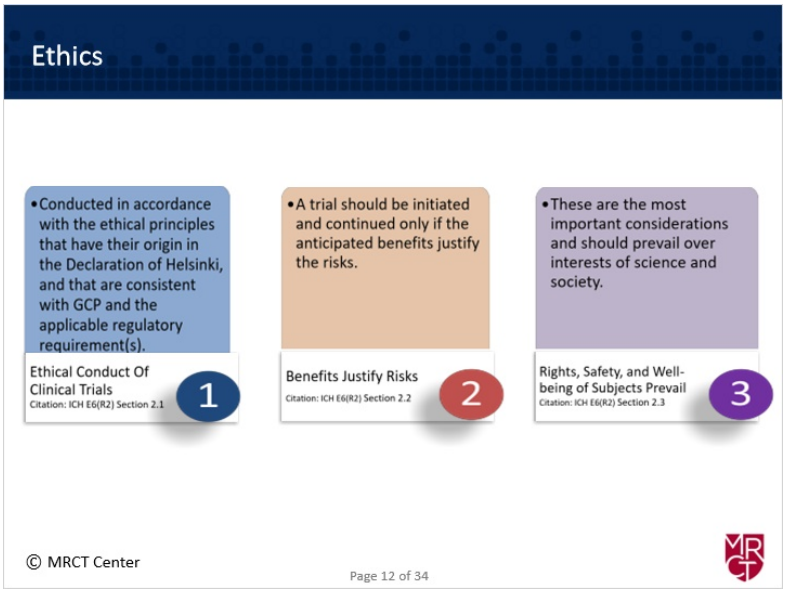
1.11 The principles of ICH GCP fall under the following categories



Notes:

Let's go into detail, starting with 'ethics'….

1.12 Ethics



Notes:

Under this category, the three principles stipulate that the clinical trial conduct be ethical. The ethical principles have their origin in the Declaration of Helsinki and the Belmont Report that we will discuss later. These principles are consistent with GCP and the applicable regulatory requirement(s).

Second the benefits should justify the risks of the trial, so that before a trial is initiated, foreseeable risks and inconveniences are weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

And third, the rights, safety and well-being of participants prevail as the most important considerations, over the interests of science and society.

1.13 Ethical Principles

Notes:

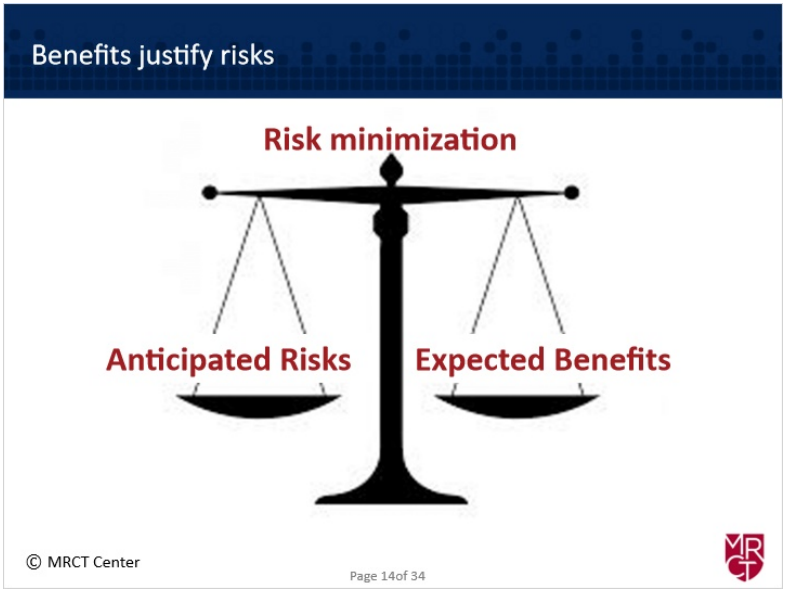
These GCP principles reflect those outlined in the Belmont Report - that research be designed and conducted with respect for persons, beneficence, and justice in mind.

First, research should have respect for persons (i.e. research participants). This means that participants should maintain their inalienable rights - autonomy and the right to make decisions for themselves and have complete information about participation and whether they want to participate. Participation should always be voluntary. Respect for persons is enacted by safeguarding these rights through adequate informed consent and ensuring that the circumstances of the trial do not force or unduly influence an individual to participate (for example, if participants with a serious disease are told the trial is their only option for care). Participants should not give up any legal rights through trial participation. And, if a trial is to involve a **vulnerable population**, additional action to safeguard rights may be needed. (For example, in the case of enrolling children or decisionally-impaired individuals, requiring certain additions to the consent process such as having a guardian execute the informed consent or having an impartial witness during the process would be ideal.)

Second, research should satisfy the concept of beneficence. This means participants should only be subject to a clinical trial if such trial has an acceptable risk to benefit ratio, all risks have been minimized, and the trial is scientifically well-designed such that valid results will be derived. Of course, the scientific question should also be important.

Third, research should take into account justice. This means the burdens and benefits of research should be equally distributed to research participants. Justice is upheld by safeguarding participant well-being through study recruitment that makes sense. For example, there should be rationale for why certain populations are targeted and why other populations may be excluded. Also, one may have to consider issues like participant compensation to determine if such payment may cause an individual (or groups of individuals - like those who are economically disadvantaged) to act against their own best health interest.

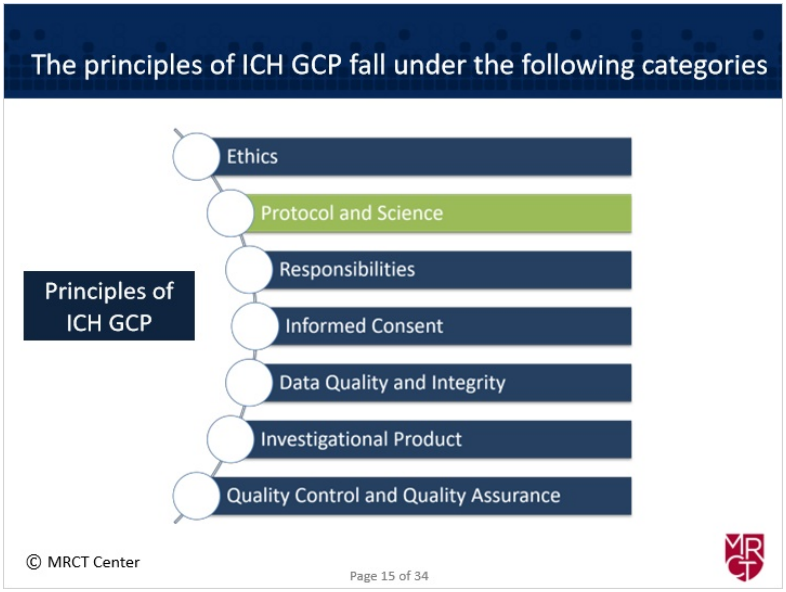
1.14 Benefits justify risks



Notes:

The IRB/IEC must review the protocol to determine that risks have been minimized and that the anticipated benefits equal or exceed the anticipated risks. These determinations are dependent on the specifics of the study itself, and why each protocol must be reviewed individually by the IRB/IEC.

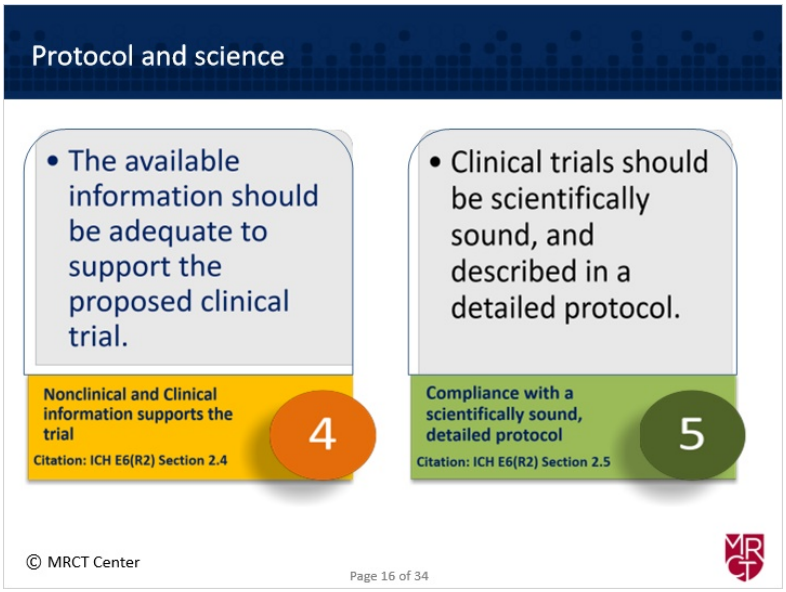
1.15 The principles of ICH GCP fall under the following categories



Notes:

The next of the 13 GCP principles fall under the category of protocol and science.

1.16 Protocol and science

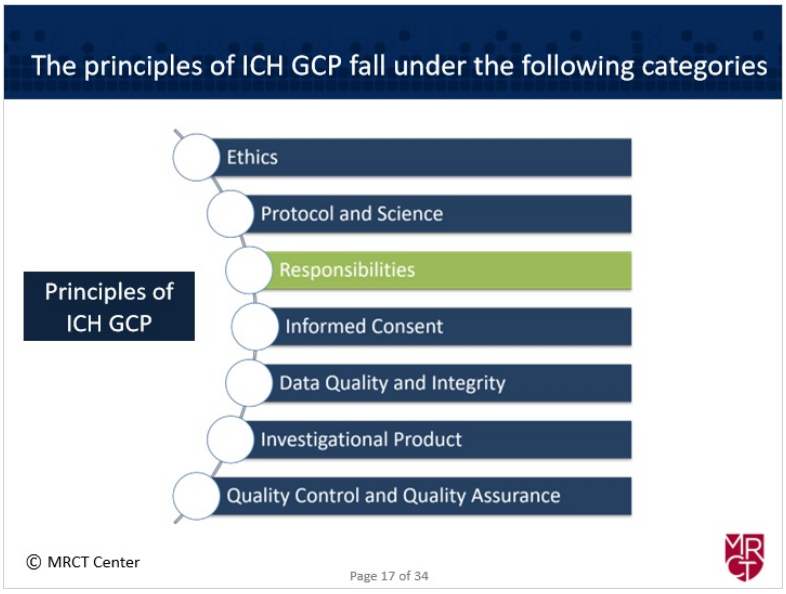


Notes:

The 4th principle stipulates that the available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

And the 5th principle requires that clinical trials be scientifically sound and described in a clear, detailed protocol.

1.17 The principles of ICH GCP fall under the following categories



Notes:

Under the next category of “responsibilities’ stakeholder roles are described.

1.18 Responsibilities

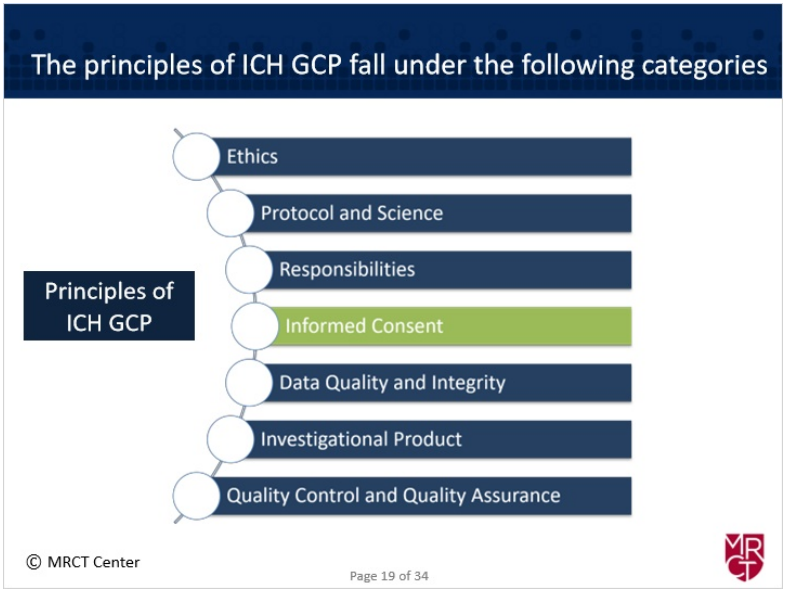
Notes:

Principle 6 states that the IRB/IEC must approve the protocol prior to the initiation of the trial and that it be conducted as it has been approved. This principle implies that any changes to the protocol must also be reviewed and approved by the IRB/IEC prior to initiating the change, unless the change is for the immediate protection of participants.

Principle 7 requires that medical decisions be made by appropriately qualified physicians or, as applicable, dentists.

While principle 8 refers to the investigators and their study teams requiring them to be qualified by education, training, and experience to perform their respective task(s).

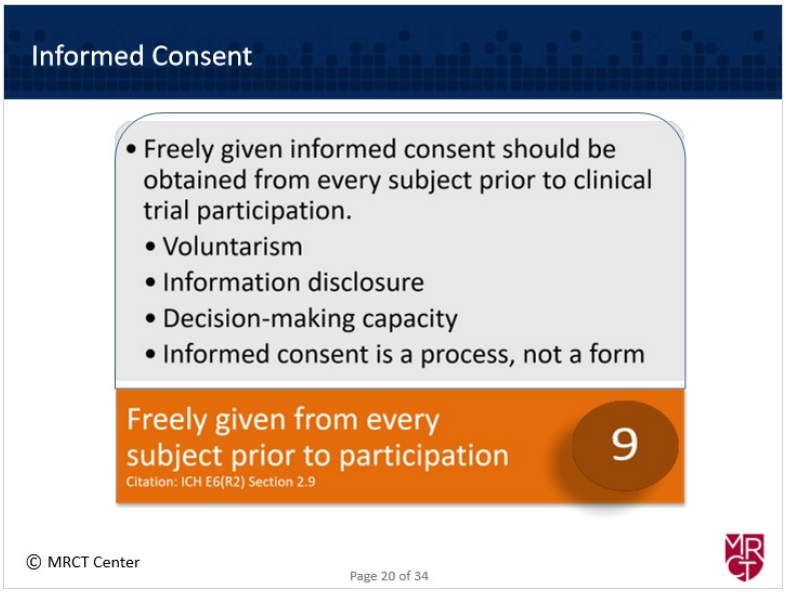
1.19 The principles of ICH GCP fall under the following categories



Notes:

Next, Principle 9 addresses the important category of informed consent.

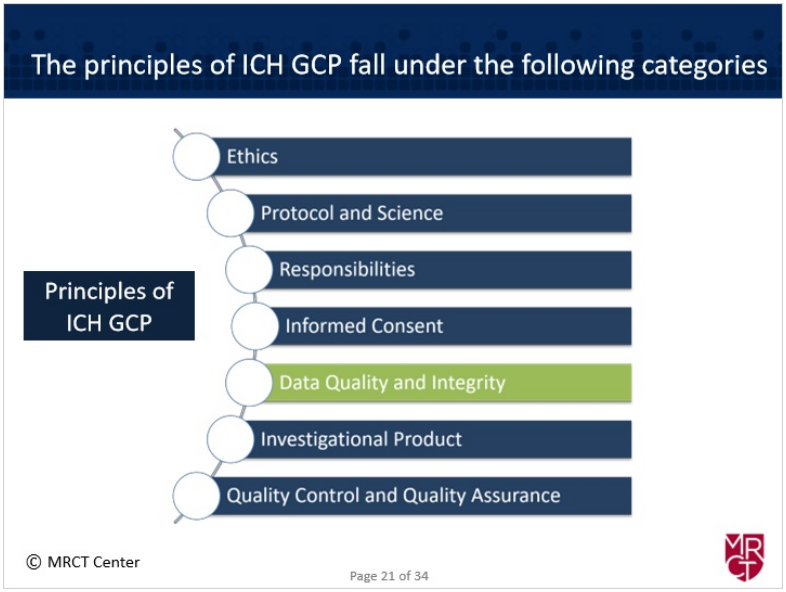
1.20 Informed Consent



Notes:

The concept of freely given informed consent describes the necessity that consent is voluntary, that all necessary information is disclosed appropriately and in a language understandable to the potential participant, and that the potential participants are able to make an informed decision, in other words, that they are capable of rendering a independent decision. That every subject provide freely given informed consent prior to clinical trial participation goes beyond the signing of the form, and speaks to the process of engaging with potential participants about the study and their willingness to join.

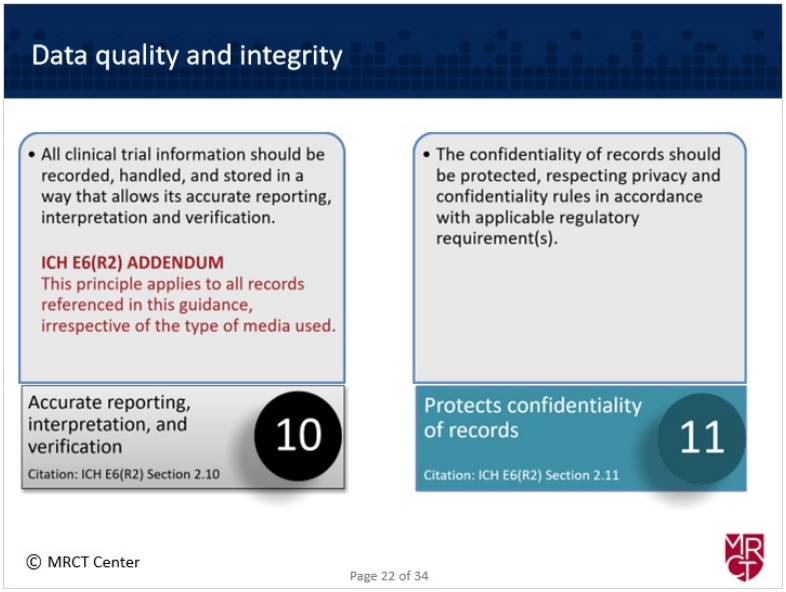
1.21 The principles of ICH GCP fall under the following categories



Notes:

Under the next category of ‘data quality and integrity’, we find two additional principles.

1.22 Data quality and integrity

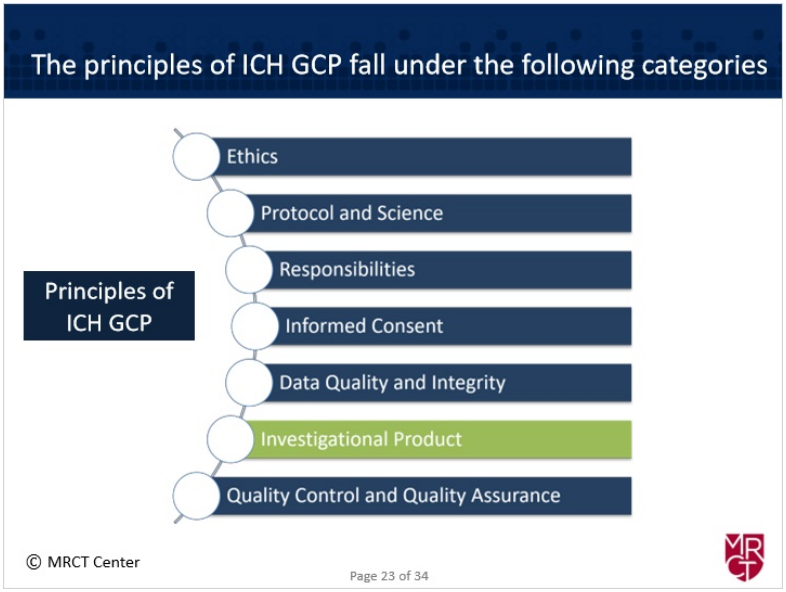


Notes:

Principle 10 describes the necessity of accurate reporting, documentation, interpretation, and validation of the data. We also see the first addendum of the section under Principle 10- expanding the Principle to all records regardless which type of media is used to record study data. This addendum was added specifically to call attention to the increasing use of digital data.

Principle 11 refers to the privacy and confidentiality of all records that could potentially identify subjects, and calls attention to applicable regulatory requirement(s) that may differ country to country.

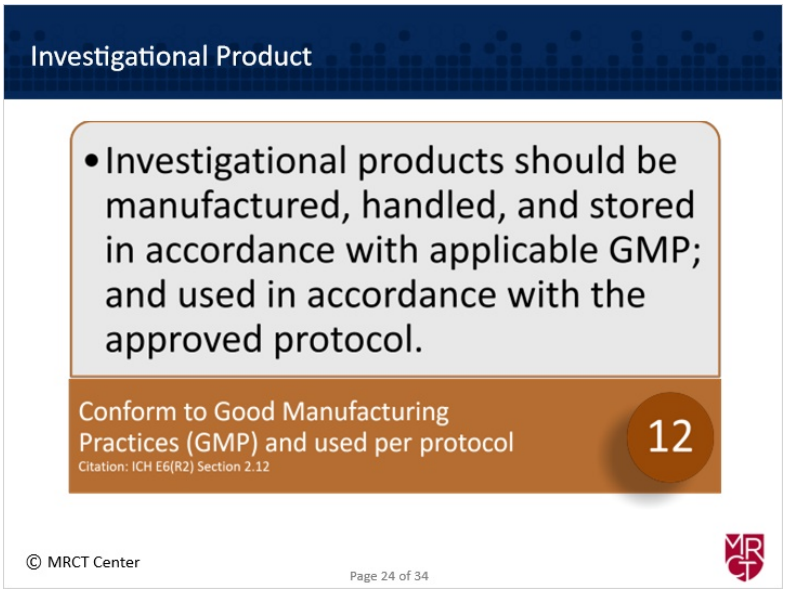
1.23 The principles of ICH GCP fall under the following categories



Notes:

The next category refers to the investigational product.

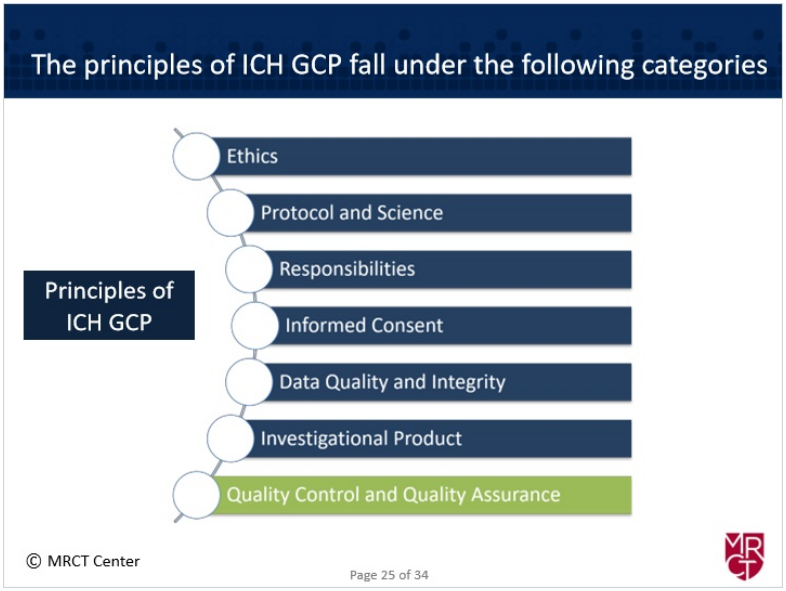
1.24 Investigational Product



Notes:

It stipulates that all investigational products should be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practices or GMP. Further, all investigational products should be used in accordance with the approved protocol.

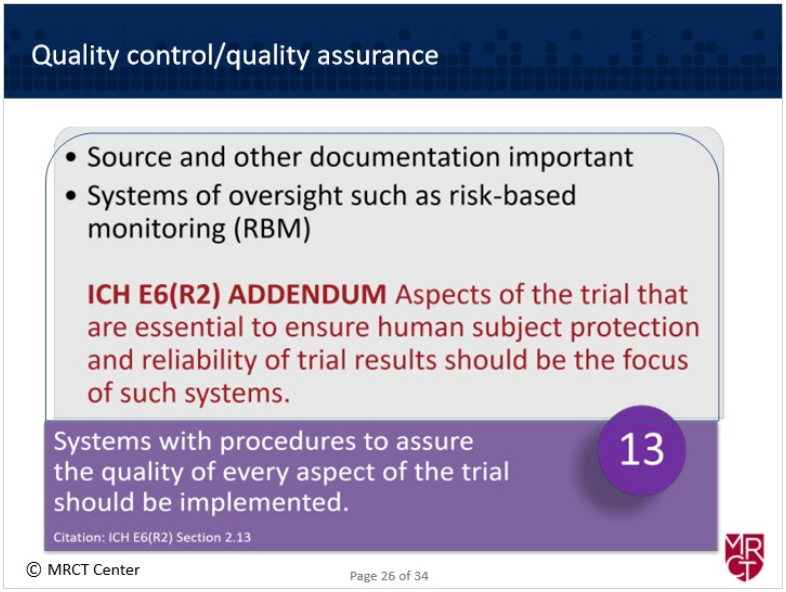
1.25 The principles of ICH GCP fall under the following categories



Notes:

Lastly, Principle 13 addresses quality control and quality assurance.

1.26 Quality control/quality assurance



Notes:

It dictates that systems should be implemented that support and assure the quality of every aspect of the trial, factoring in source and other study documentation, and putting appropriate systems of oversight into place. A second GCP addendum is added to this section, clarifying that oversight systems should focus on those aspects of a clinical trial that are essential to ensure human subject protection and reliability of trial results. This addendum addresses the concept of risk-based monitoring (or RBM) that suggests that the level of oversight may be apportioned to the level of risk either to participant safety or to data integrity. We will discuss RBM extensively later in this course.

1.27 Distributed Responsibilities: Understand their Roles

Notes:

There are many different stakeholders involved in designing, conducting, and reporting a trial. Each are responsible for the clinical trial, although their roles and responsibilities differ. Regulators should know and understand the many roles, including

- Sponsors
- Clinical investigators and the study team which can include
  - Research nurses
  - Clinical research coordinators
  - Clinical research associates

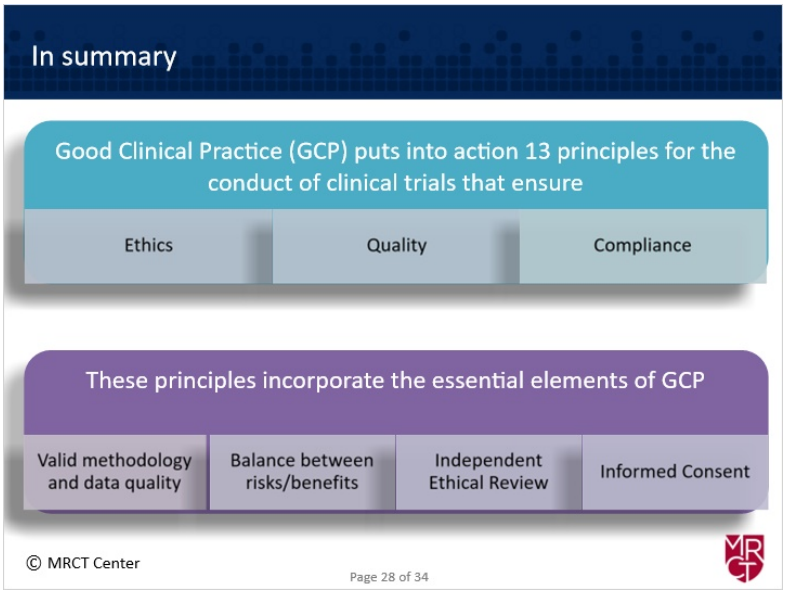
There are also the roles of

- Study pharmacists
- IRB/IEC
- Contract Research Organizations
- Medical monitors
- Data entry personnel and data managers
- Regulatory authorities

- Research participants
- And others, as applicable

We will discuss the roles and activities of many of these different stakeholders throughout this GCP course.

1.28 In summary

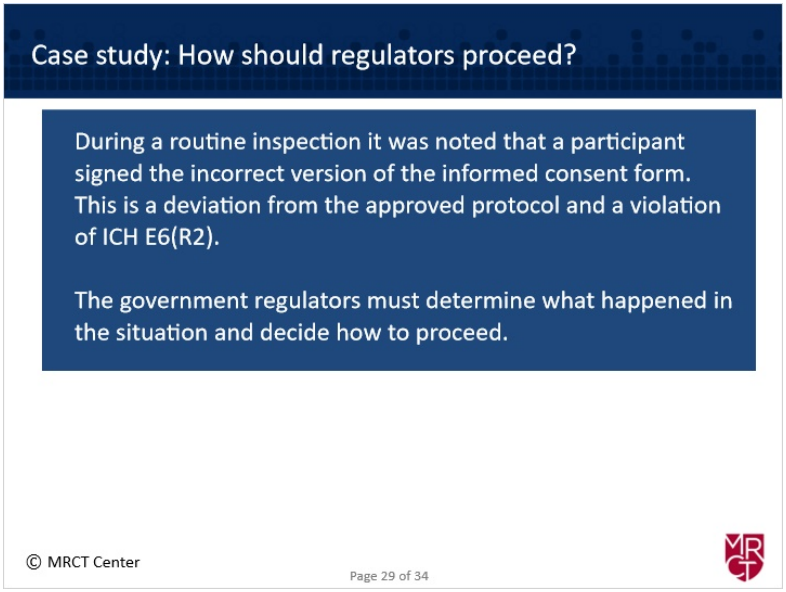


Notes:

In summary, good clinical practice puts into action 13 principles that ensure ethics, quality and compliance in the conduct of clinical trials, incorporating the essential elements of GCP:

- Valid methodology and data quality
- Balance between risks/benefits
- Independent ethical review
- Informed consent

1.29 Case study: How should regulators proceed?



Notes:

Returning to the case study presented earlier in the module, let us consider how we might investigate this issue given the principles of GCP just presented.

In Section 2.3 it is noted that the rights, safety, and well-being of the trial subjects are the most important considerations.

And in Section 2.9 it states that freely given informed consent must be obtained from every subject - but in order to give informed consent, the individual considering participation must be presented with the correct information. Signing the incorrect version of a consent form raises questions about the protection of subjects and the validity of the consent.

So let's review how you might respond to the following questions.