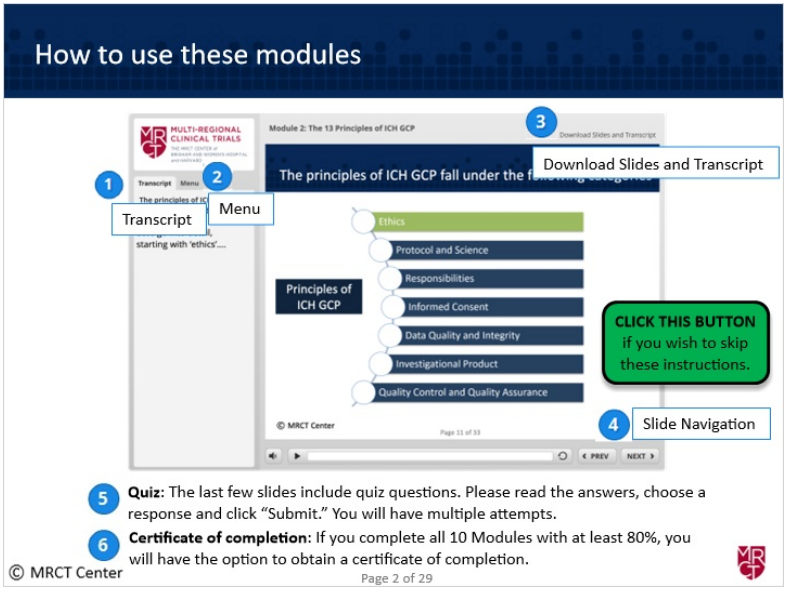
Module 6&7: Clinical Trial Protocol and Protocol Amendment(s)

1.1 Interpretation and application of ICH E6(R2)

Notes:

Welcome to Module 6+7 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.

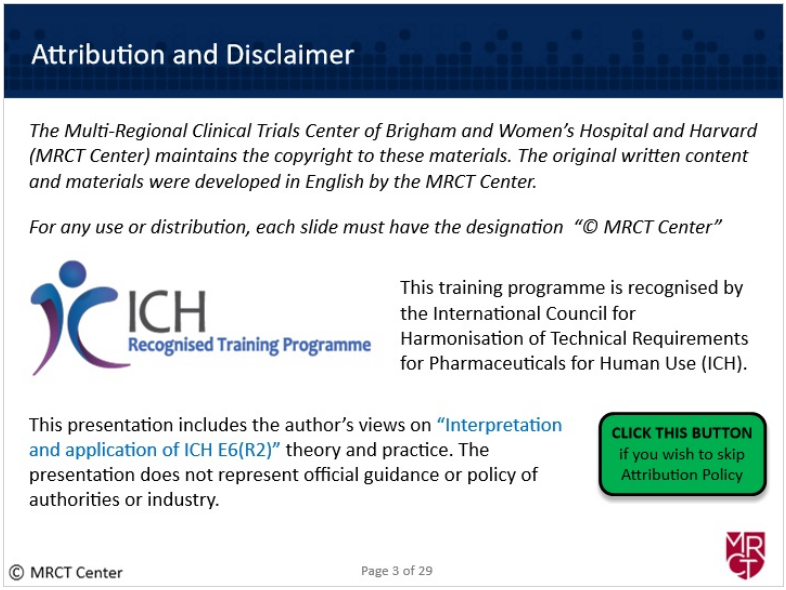
Third, you can click on the upper right on "Download Slides and Transcript" to view a printable PDF of the slides and transcript of the module. You can also click a link to the Guidelines for Good Clinical Practice.

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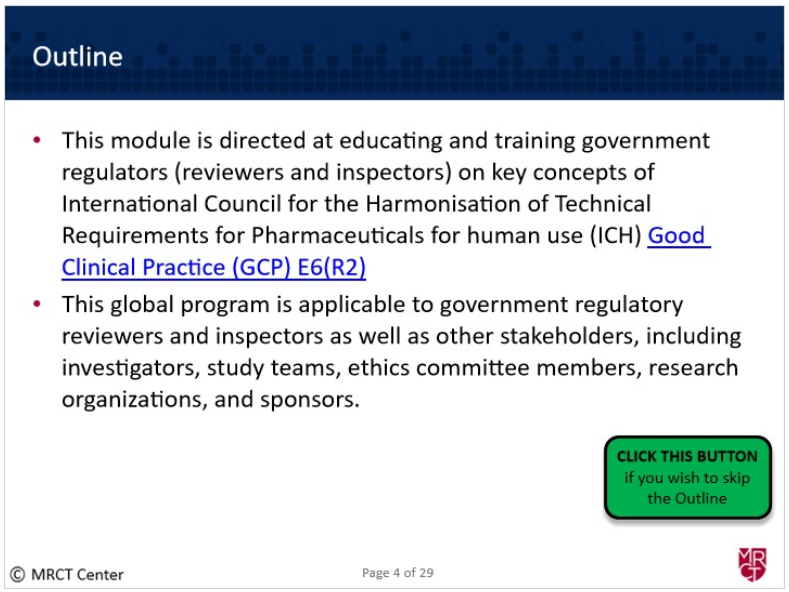
This presentation includes the author's views on "Interpretation and application of ICH E6(R2)" theory and practice. The presentation does not represent official guidance or policy of authorities or industry.

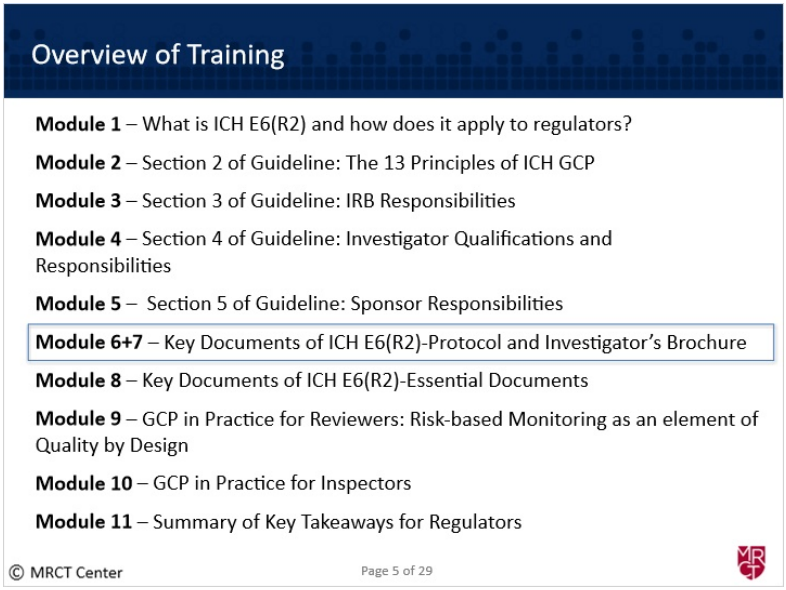
1.4 Outline



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).

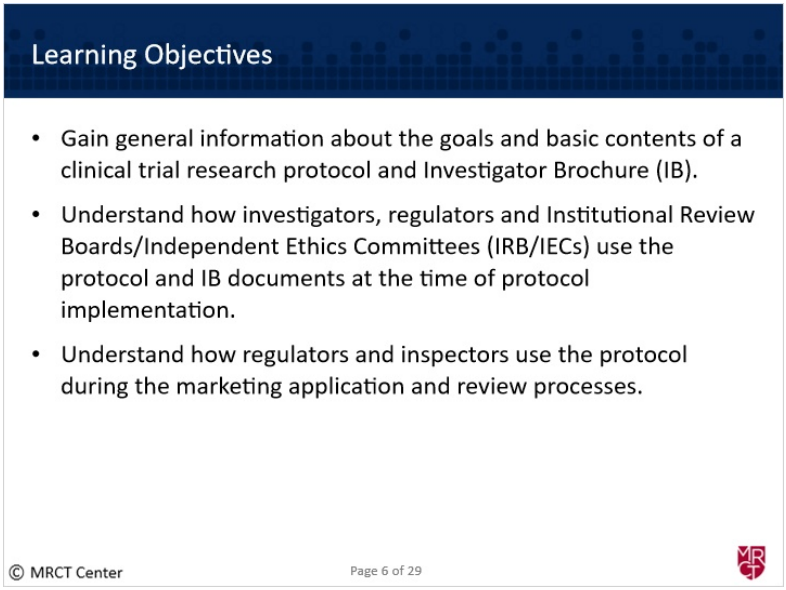
1.5 Overview of Training



Notes:

In this module we have combined the information in Sections 6 and 7 of the ICH E6(R2) guideline to provide an overview of two areas of key research documents, namely the clinical trial research protocol (and related amendments) and Investigator Brochure (IB).

1.6 Learning Objectives



Notes:

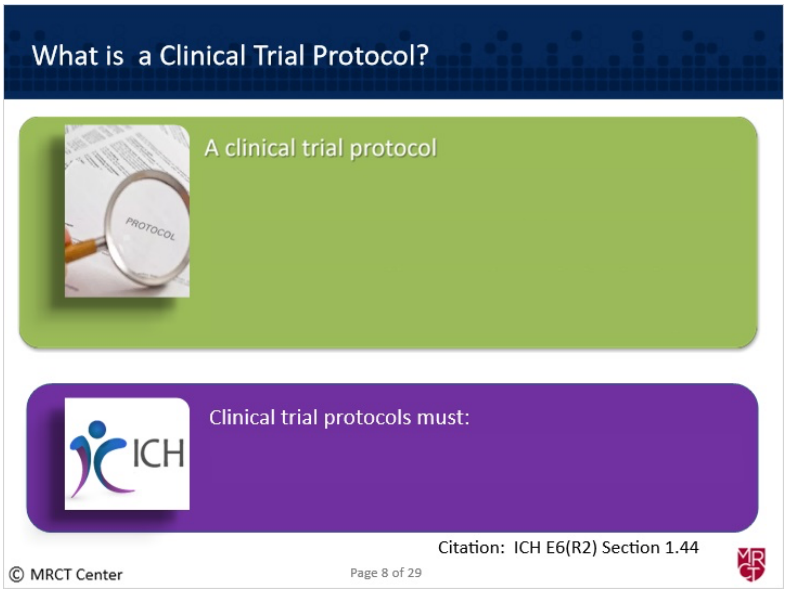
By the end of these modules you are expected to have gained more information about the goals and basic contents of a protocol and IB, a greater understanding of how clinical trial stakeholders use the protocol and IB documents at the time of protocol implementation, as well as during the marketing application and review processes.

1.7 Clinical Trial Protocol

Notes:

We will first look at the Clinical Trial Protocol.

1.8



Notes:

The protocol is both the roadmap and driver of a clinical trial.

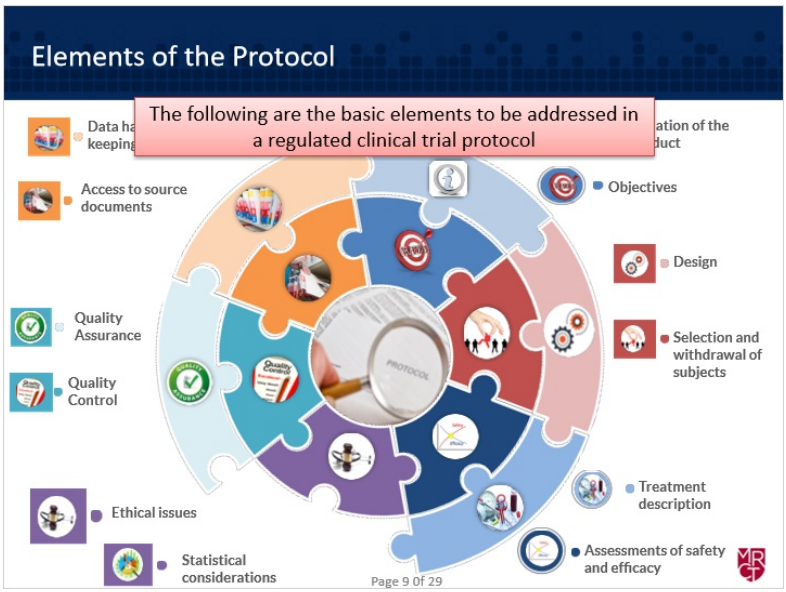
A clinical trial protocol

- is a regulated document that describes the goals and objectives, design, activities and statistical considerations.
- provides the background and rationale for conducting a study, highlighting specific research questions that are being addressed.
- contains sections addressing quality standards, ethical issues, publication policies, as well as protocol specific issues such as the use of specific devices, novel data collection methodologies, etc.

And clinical trial protocols must:

- demonstrate compliance with ICH E6(R2) Good Clinical Practice (GCP)
- comply with local regulatory and IRB/IEC requirements.

1.9 Elements of the Protocol



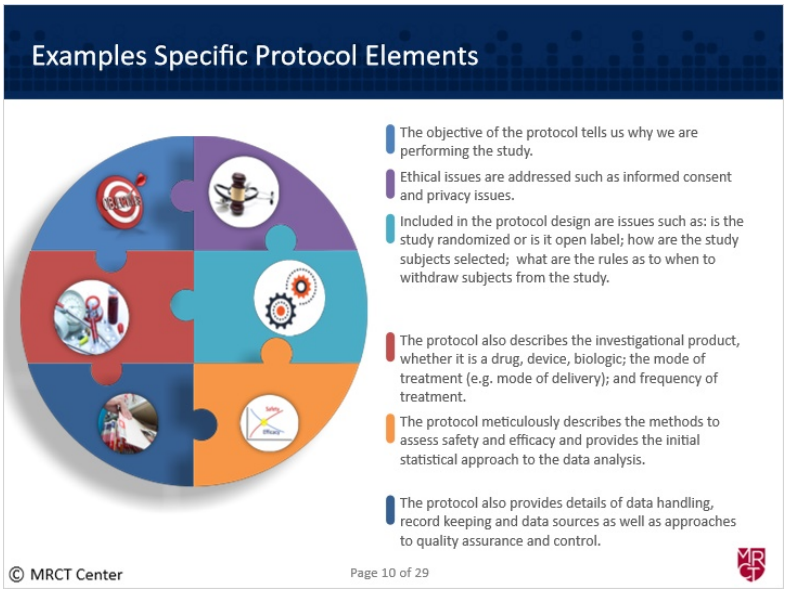
Notes:

The following are the basic elements set forth in ICH E6(R2) GCP to be addressed in a clinical trial protocol:

- Background information of the investigational product
- Objectives
- Design
- Selection and withdrawal of subjects
- Treatment description
- Assessments of safety and efficacy
- Statistical considerations
- Ethical issues
- Quality Assurance
- Quality Control
- Data handling and record keeping
- Access to source documents

Some of this information may be found in other protocol-referenced documents such as an Investigator's Brochure.

1.10 Examples Specific Protocol Elements



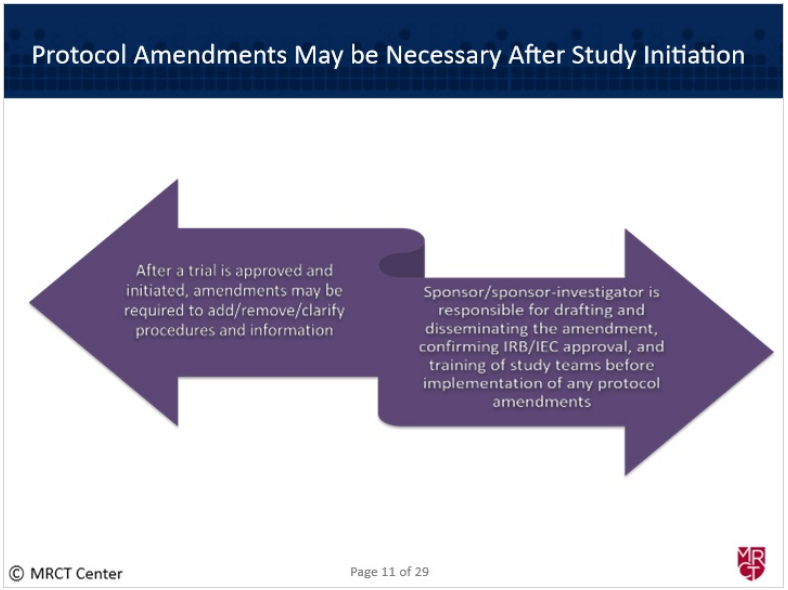
Notes:

This slide addresses the content to be described in specific protocol sections:

- The objective of the protocol tells us why we are performing the study.
- Ethical issues are addressed such as informed consent and privacy issues
- Included in the protocol design are issues such as: is the study randomized or is it open label; how are the study subjects selected; what are the rules as to when to withdraw subjects from the study.
- The protocol also describes the investigational product, whether it is a drug, device, biologic; the mode of treatment (e.g. mode of delivery); and frequency of treatment.
- The protocol meticulously describes the methods to assess safety and efficacy and provides the initial statistical approach to the data analysis.

- The protocol also provides details of data handling, record keeping and data sources as well as approaches to quality assurance and control.

1.11 Protocol Amendments May be Necessary After Study Initiation

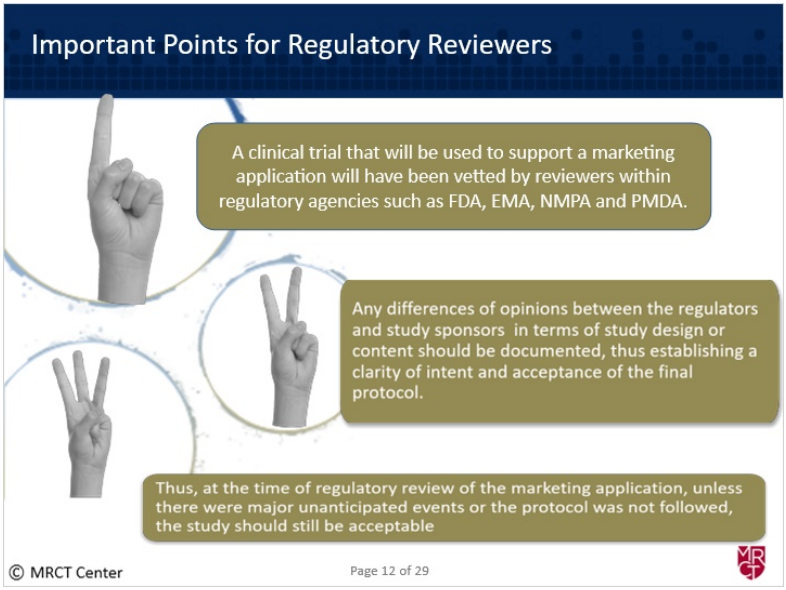


Notes:

It is common for protocols to be amended during a study in order to add, remove and/or clarify procedures and information. Protocol amendments may be needed due to unforeseen events, elimination or modification of inclusion or exclusion criteria, or to implement changes to make certain procedures, for example, easier to implement based on feedback from the clinical sites.

The sponsor/sponsor-investigator is responsible for drafting and disseminating the amendment, confirming IRB/IEC approval, and training study staff before implementation of any protocol amendments

1.12 Important Points for Regulatory Reviewers



Notes:

Regulatory Reviewers should consider that any protocol for a clinical trial that will be used to support a marketing application will have been vetted by reviewers within regulatory agencies …

…and any differences of opinion between the regulators and study sponsor should have been documented before acceptance of the final protocol.

If implemented and executed according to the agreed upon protocol, the clinical trial results should support regulatory decision-making about the marketing application. Unless there were major unanticipated events or the protocol was not followed, the study should still be acceptable.

1.13 Important Points for Regulatory Inspectors

Notes:

After a marketing application is initially assessed by the review divisions with the regulatory body, inspectors are directed to perform site, sponsor and CRO inspections to assure that the protocol was followed and compliant with GCP. These Inspections are called pre-approval inspections.

Trained Inspectors visit the study sites, sponsors, CROs, and critical vendors, to provide assurance that the protocol was followed.

Inspectors also assess compliance with GCP and ensure the study is of high quality (for example, the absence of errors that matter) and that the data will be fit for purpose.

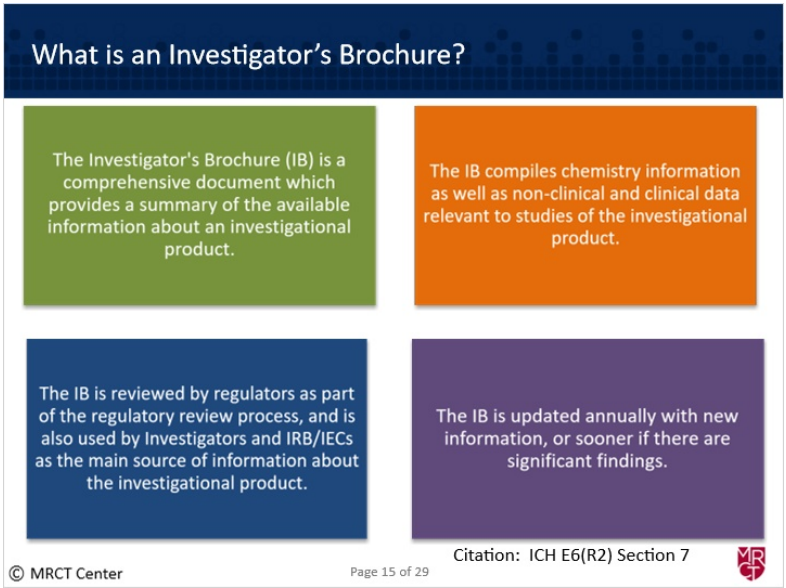
This overall study conduct, including, for example, protocol study procedures, data collection techniques, and the way the CRFs are signed electronically should be considered acceptable by the Inspectors if the approved study protocol was followed.

1.14 Investigator's Brochure

Notes:

We will now look at the Investigator's Brochure.

1.15 What is an Investigator Brochure?



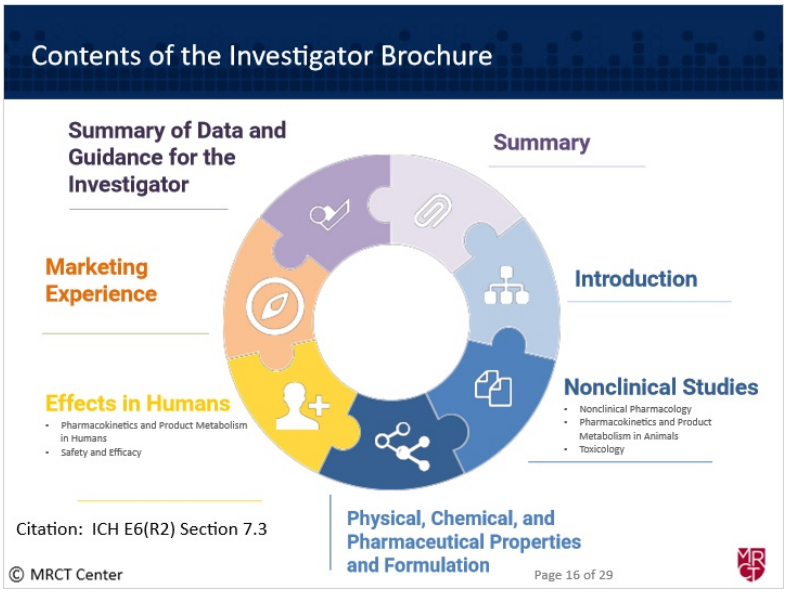
Notes:

The Investigator Brochure is a summary of what is currently known about the investigational project, including chemistry information, as well as relevant non-clinical and clinical data.

The IB is reviewed by regulators as part of the regulatory review process as well as by investigators and IRB/IECs as the main source of information about the investigational product.

The IB is updated at least annually, and sooner if there are significant findings

1.16 Contents of the Investigator Brochure



Notes:

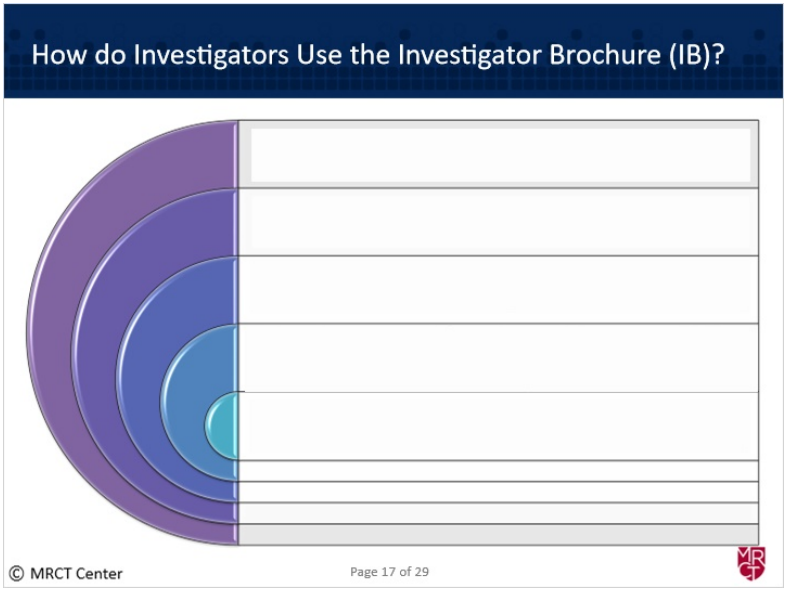
The contents of the Investigator Brochure include:

- A general summary
- Introduction
- Information on nonclinical studies, including specific results from animal

toxicology studies

- Physical, chemical and pharmaceutic properties and formulation – including shelf-life
- A section on the effects in humans including specific results from relevant clinical trials and other human experience with the investigational medicinal product
- Marketing experience
- And a summary of data and guidance for the investigator

1.17 How do Investigators Use the Investigator Brochure (IB)?



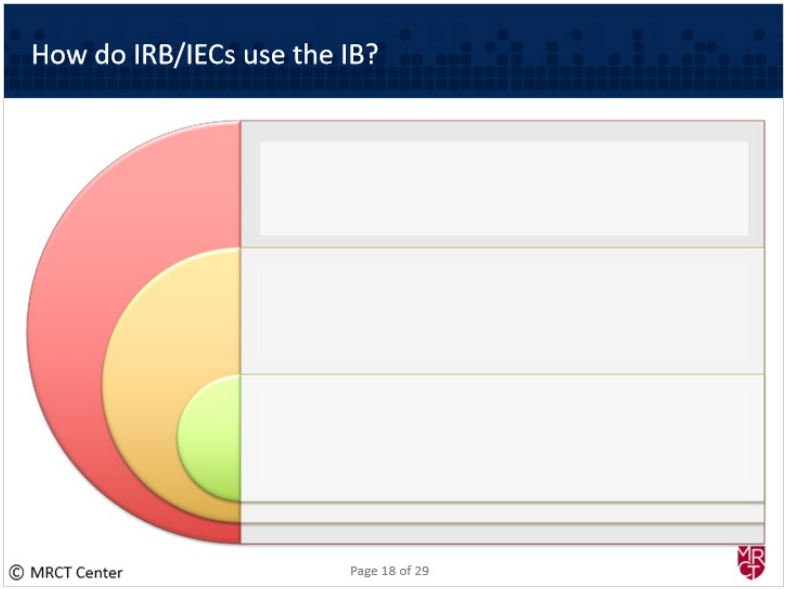
Notes:

Clinical investigators should review the IB to assess risk to benefit ratio of an investigational product and ensure they have sufficient information about the safety of the dosing regimen.

The investigator submits the IB to the IRB/IEC as part of the protocol review process and reviews any new information as it becomes available (usually annually, unless significant information is released sooner).

The investigator should update IRB/IEC about relevant patient safety data from ongoing clinical trials or non-clinical studies, derived from new information from ongoing clinical trials or non-clinical studies.

1.18 How do IRB/IECs use the IB?

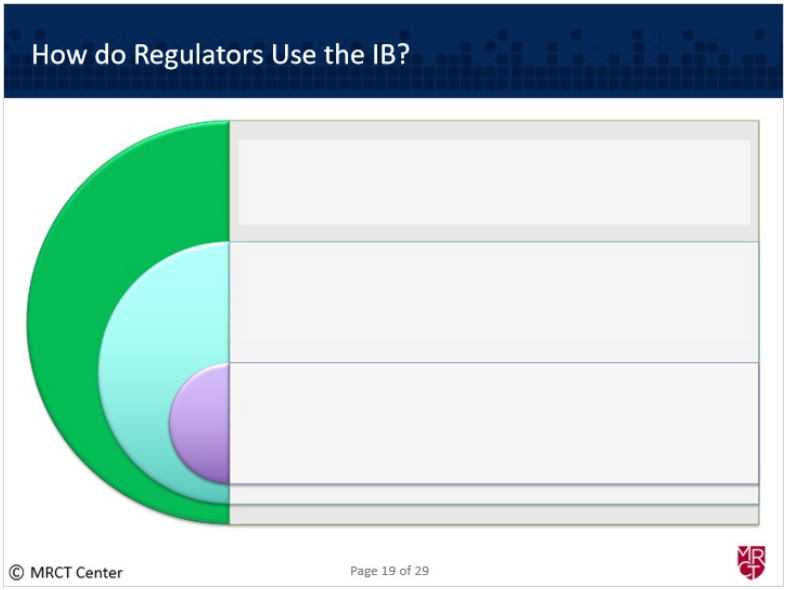


Notes:

The Investigator Brochure allows the IRB/IEC to assess the risk to benefit ratio of an investigational product during their protocol review process to ensure that there are sufficient data to support the safety of the dosing regimen.

The IB is also used to assess new information about reported safety signals during ongoing clinical trials.

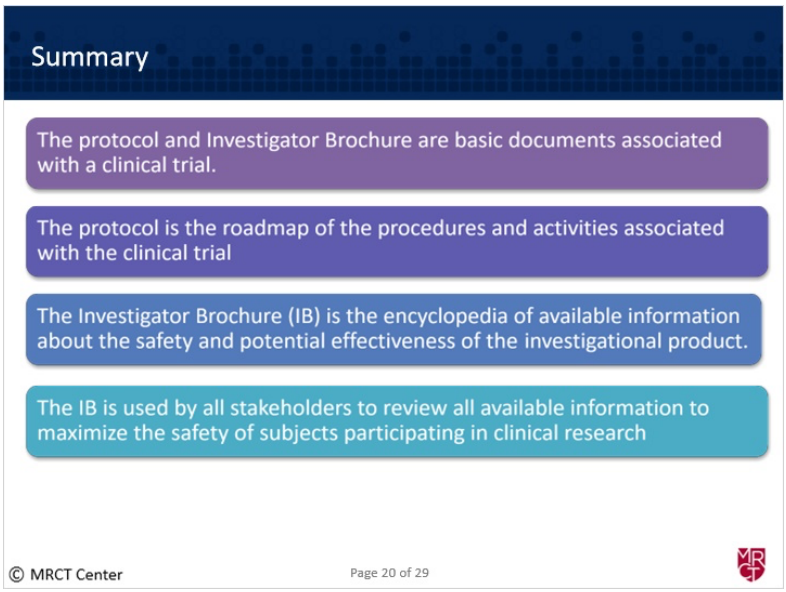
1.19 How do Regulators Use the IB?



Notes:

Regulators can use the IB to better understand the safety and effectiveness of the investigational medicinal product, search for information without having to delve into the Sponsor's regulatory submission, and assess conflicting information based on previous information provided by the sponsor.

1.20 Summary



Notes:

In summary:

- The protocol and Investigator Brochure are basic documents associated with a clinical trial
- The protocol is the roadmap of the procedures and activities associated with the clinical trial
- The Investigator Brochure (IB) is the encyclopedia of available information about the safety and potential effectiveness of the investigational product.
- The IB is used by all stakeholders to review all available information to maximize the safety of subjects participating in clinical research