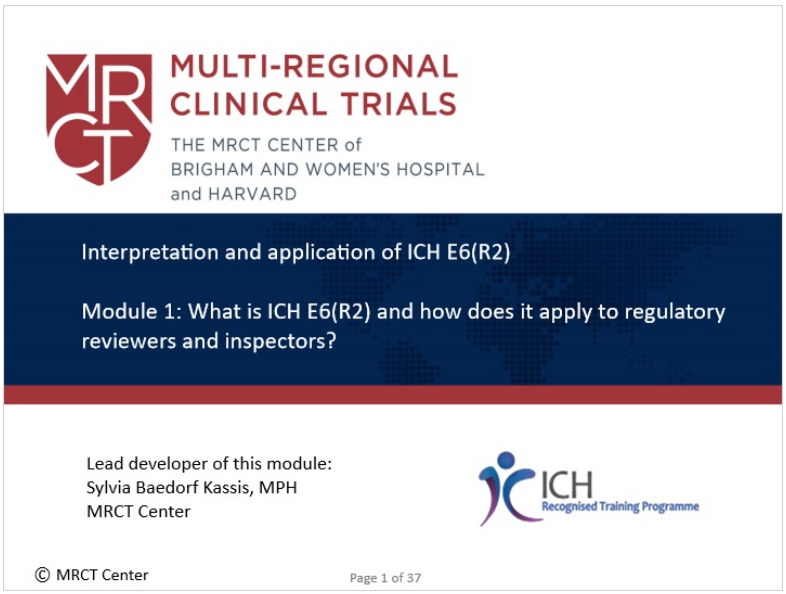
Module 1 - What is ICH E6(R2) and how does it apply to regulators?

1. Module 1

1.1 Interpretation and application of ICH E6(R2)

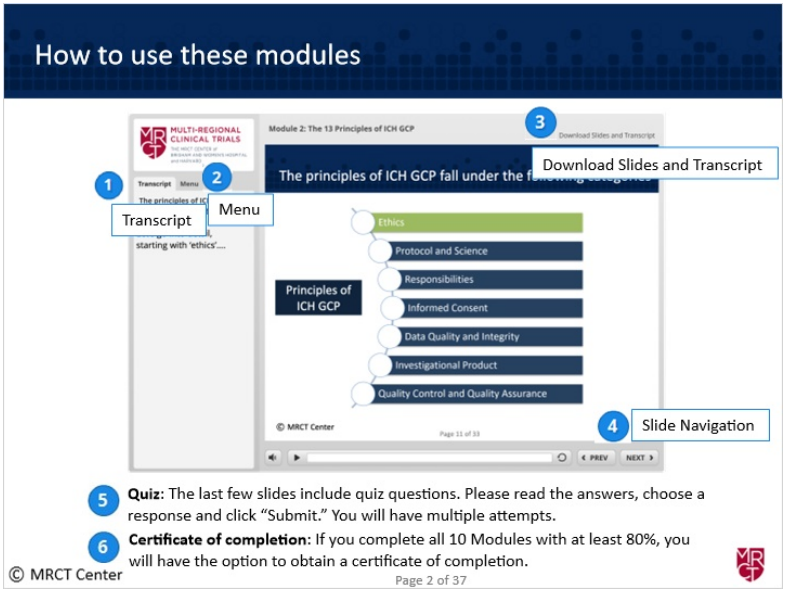


Notes:

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

The development of this training was lead by the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard. This group is a research and policy center that engages diverse stakeholders to define emerging issues in global clinical trials and implement ethical, actionable and practical solutions. You can learn more about us at www.mrctcenter.org

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 training programme is recognised by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

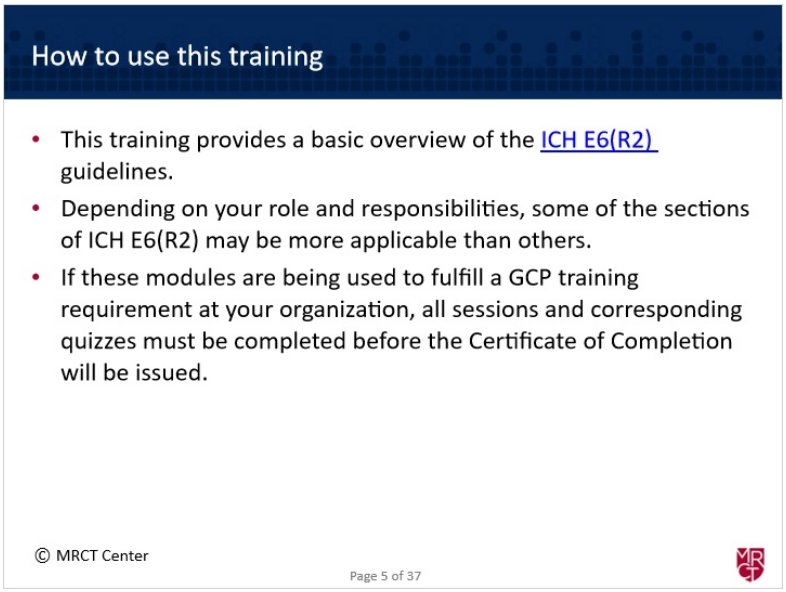
This presentation includes the author's views on "Interpretation and application of ICH E6(R2)" theory and practice. The presentation does not represent official guidance or policy of authorities or industry.

1.4 Team of Content Developers

Notes:

A special thank you must be given to the multi-stakeholder international team of experts who contributed to the development of this training.

1.5 How to use this training



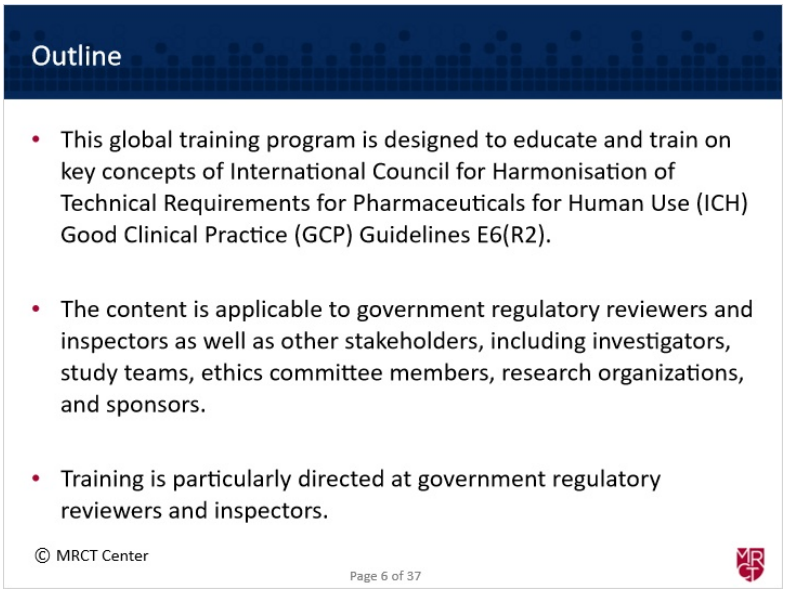
Notes:

This training provides a basic overview of the ICH E6(R2) guidelines

Depending on your role and responsibilities, some of the sections of ICH E6(R2) may be more applicable than others, and thus some of these modules may be more applicable than others.

If these modules are being used to fulfill a GCP training requirement at your organization, all sessions and corresponding quizzes must be completed before the Certificate of Completion will be issued.

1.6 Outline



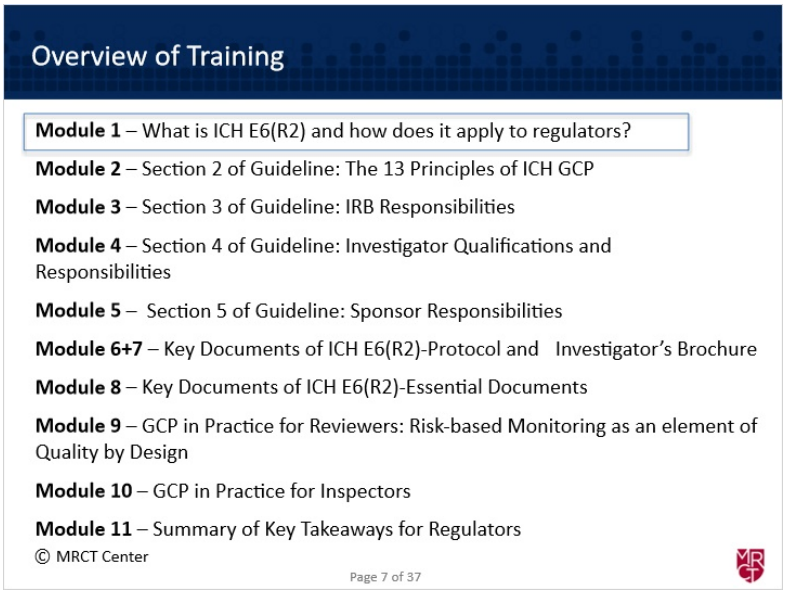
Notes:

The overall goal of this training is to provide an overview on how to apply the ICH E6 (R2) Good Clinical Practice guidelines.

These modules cover a basic introduction to GCP that is applicable to all stakeholders including investigators, study teams, ethics committee

members, research organizations, and sponsors but is particularly directed at educating and training government regulatory reviewers and inspectors on key concepts of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice Guidelines: ICH GCP E6(R2).

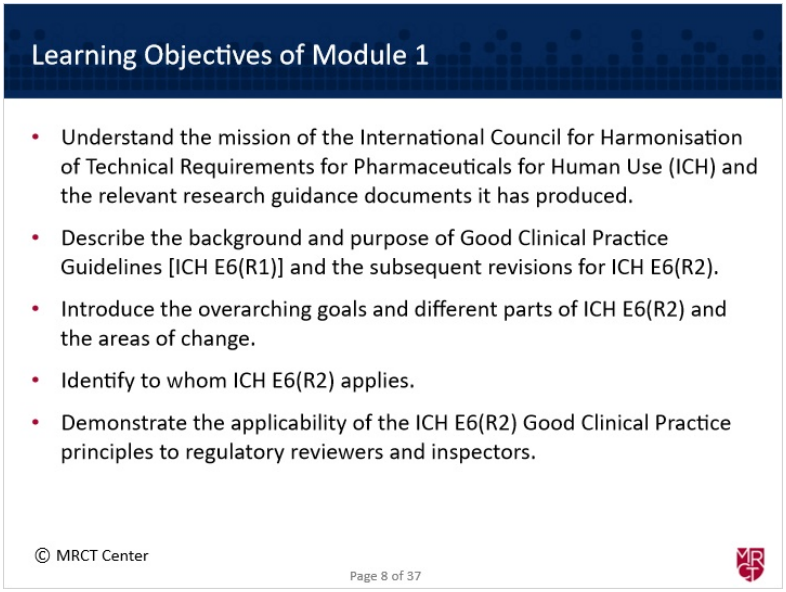
1.7 Overview of Training



Notes:

In Module 1 we will focus on describing ICH E6(R2), and introducing how it applies to regulatory roles of reviewers and inspectors.

1.8 Learning Objectives of Module 1

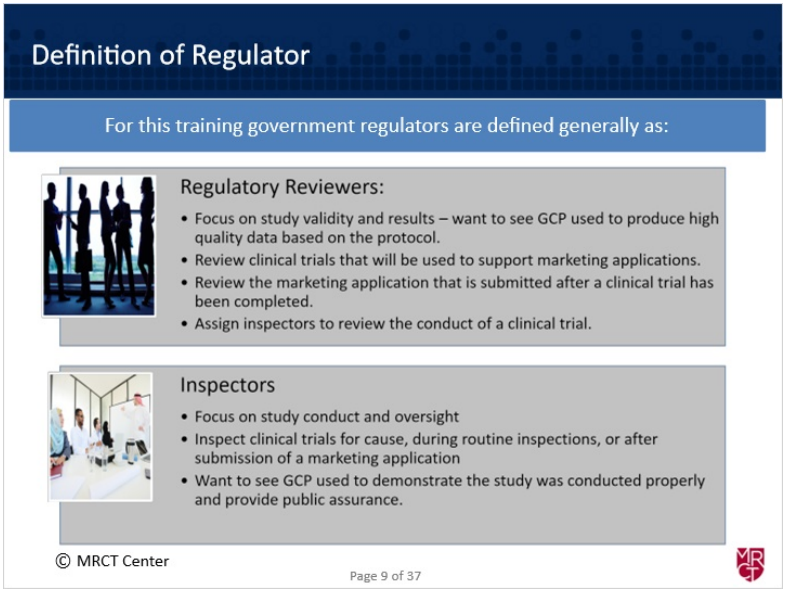


Notes:

As we proceed through the modules, you will be presented with the learning objectives and related content. In this module you will be introduced to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, abbreviated as ICH. By the end of this module you are expected to:

- Have developed an understanding of the ICH mission and research guidance documents it has produced
- Be able to describe the background and purpose of the Good Clinical Practice guidelines, referred to in the training as ICH E6(R2). The 'R2' refers to the fact that the guideline underwent a revision and is in its second version.
- Be aware of the overarching goals and different parts of ICH E6(R2), as well as the areas of change
- Be able to identify to whom these guidelines apply (and understand its relevance to regulatory reviewers and inspectors)

1.9 Definition of Regulator



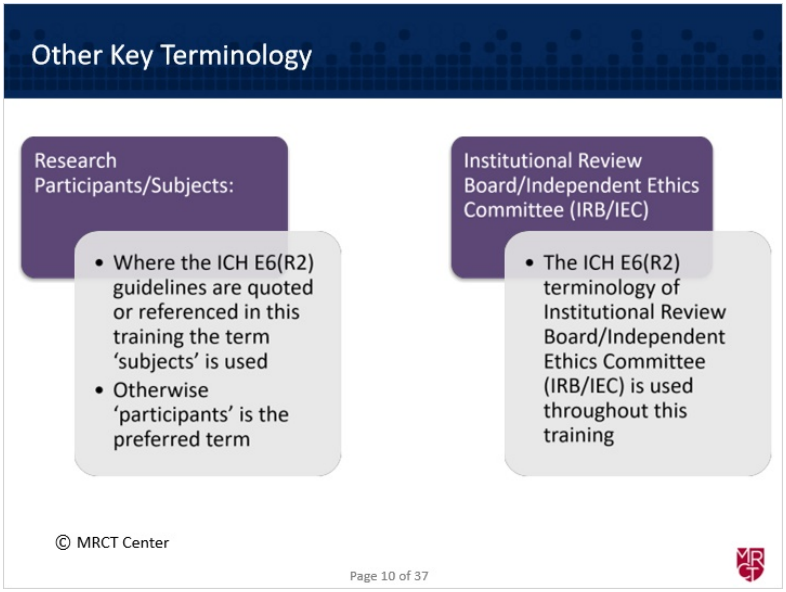
Notes:

For the purpose of this training, we have differentiated regulatory reviewers and inspectors, and applied ICH E6(R2) GCP to their respective roles, as follows:

Regulatory reviewers review clinical trials that will be used to support marketing applications, and the subsequent marketing applications once the trial has been completed, assigning inspectors as applicable to review the study's conduct. As a result, regulatory reviewers are most concerned with study validity and results, and want to see GCP used to produce high quality data based on the protocol

Inspectors, on the other hand, are mostly concerned with study conduct and oversight - they inspect clinical trials in three different scenarios: for cause, for a routine inspection or after submission of a marketing application. Inspectors want to see GCP used to demonstrate that the study was conducted properly so as to provide public assurance.

1.10 Other Key Terminology

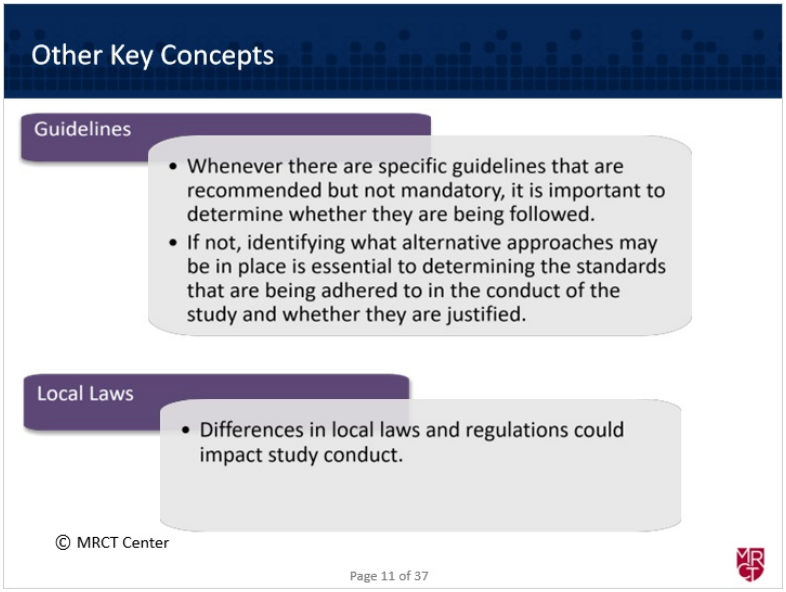


Notes:

It should also be noted that when we directly quote or reference ICH E6(R2) we will use the term "subjects" as is used in the guidelines. Otherwise, we use the preferred term of 'participants' throughout the training.

We also use the ICH E6(R2) terminology of Institutional Review Board/Independent Ethics Committee (IRB/IEC). Going forward we will just use the acronym IRB/IEC in this training

1.11 Other Key Concepts



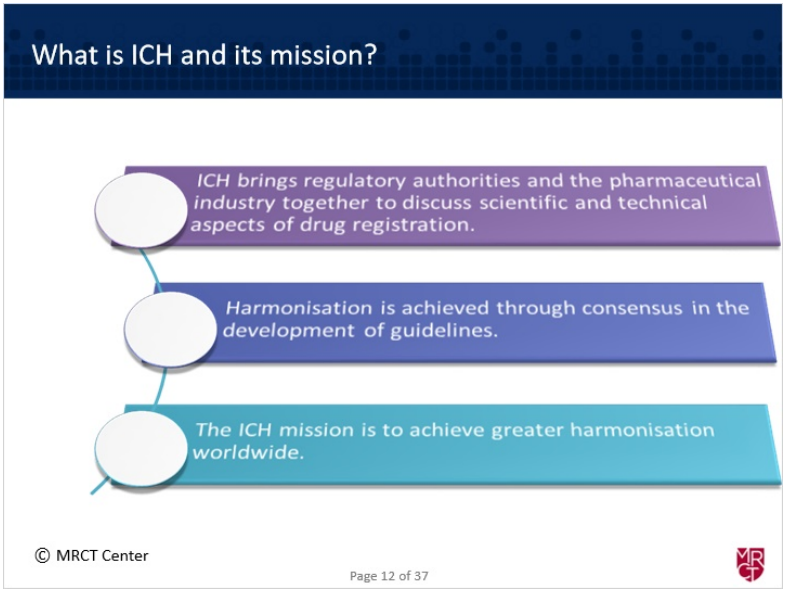
Notes:

A couple of other things to keep in mind relate to Guidelines and Local Laws.

For the first , 'guidelines' - Whenever there are specific guidelines that are recommended but not mandatory, it is important to determine whether they are being followed. If guidelines that are not legally binding are being followed this facilitates assessment of the product. However, alternative approaches may be in place and can be taken if appropriately documented and justified.

As for 'local laws,' there could be differences in local laws and regulations that could impact how a study is conducted. Knowing these can facilitate appropriate assessment of the product.

1.12 What is ICH and its mission?



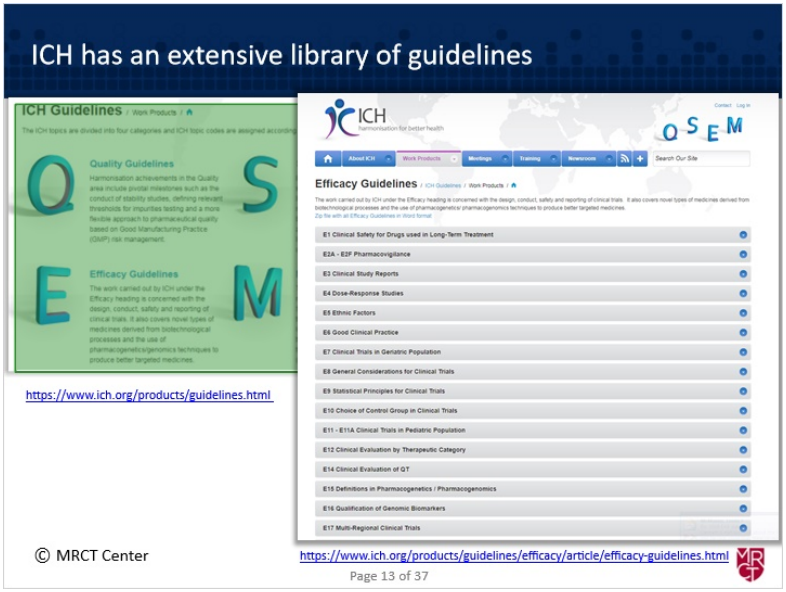
Notes:

Keeping those terms and definitions in mind, let us begin by defining ICH as a unique group that brings together regulatory and pharmaceutical industry stakeholders to discuss various aspects of the drug registration process….

…including how best to achieve greater worldwide harmonization in the drug development process to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner.

ICH achieves harmonization by developing guidelines via the scientific consensus of regulatory and industry experts

1.13 ICH has an extensive library of guidelines

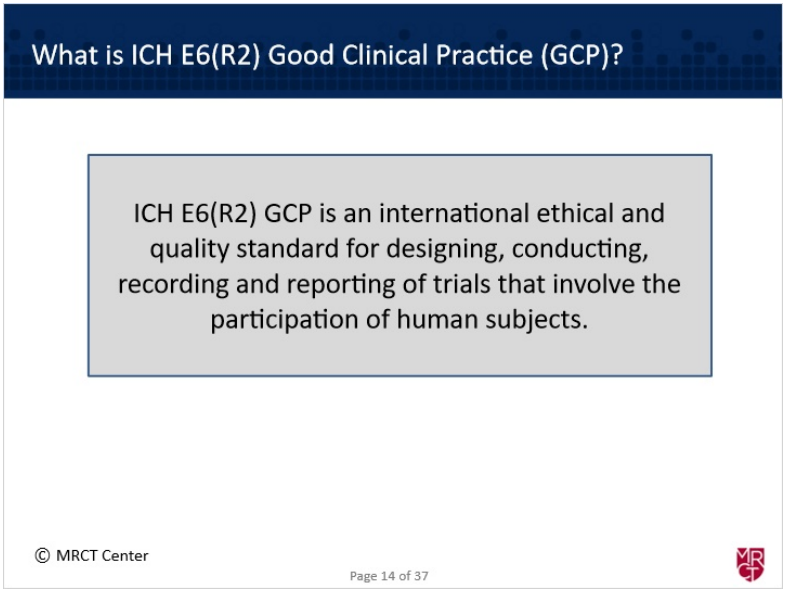


Notes:

ICH has an extensive library of guidelines. These guidelines span various thematic categories, including quality, safety, efficacy, and multidisciplinary subject areas,

Our current topic of ICH E6(R2) falls under the category of ‘efficacy’ - which is concerned mostly with the design, conduct, safety and reporting of clinical trials.

1.14 What is ICH E6(R2) Good Clinical Practice (GCP)?



Notes:

And ICH E6(R2) Good Clinical Practice is the international ethical and quality standard for designing, conducting, recording and reporting on trials that enroll human subjects

1.15 Why follow ICH E6(R2) Good Clinical Practice (GCP)?

Notes:

The reasons for following ICH E6(R2) GCP are multifold.

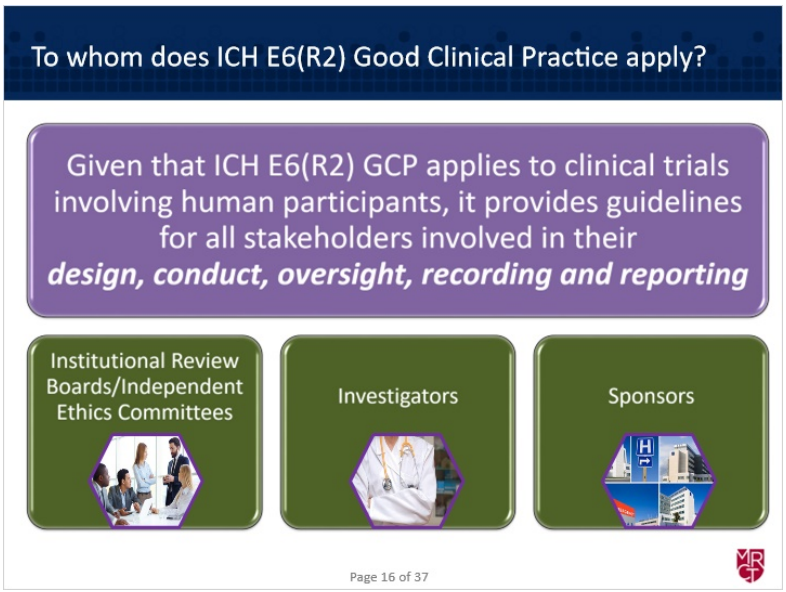
First, it provides a unified standard for ICH countries that promotes mutual acceptance of clinical trial data that is submitted to regulatory authorities.

Current ICH countries include the European Union, China, Japan, United States, Australia, Canada, and Nordic countries, though there are other countries that serve in an advisory or observational capacity and may join ICH in the future.

Another reason for complying with GCP is that it provides public assurance that the rights, safety, and wellbeing of trial subjects are protected and that the clinical trial data are credible.

Thus, ICH E6(R2) is relevant to all studies involving human participants and must be followed when generating clinical trial data that are intended to be submitted to regulatory authorities.

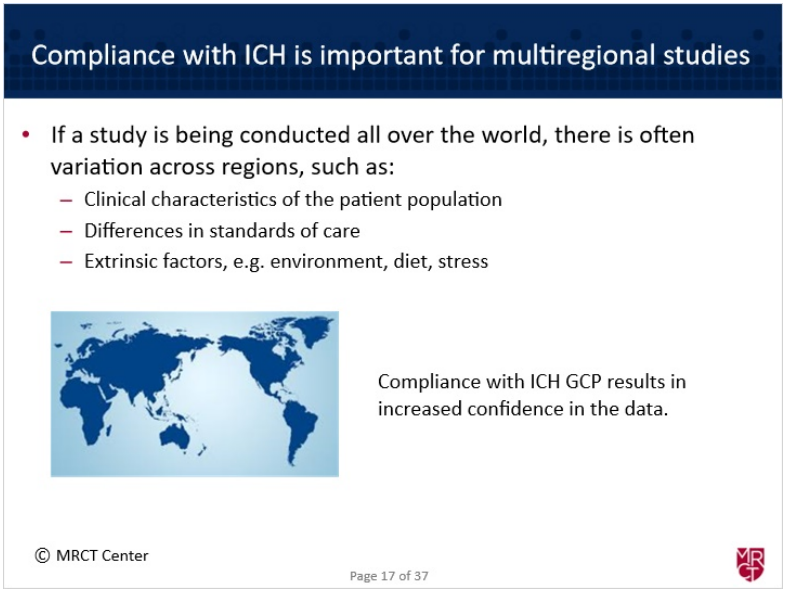
1.16 To whom does ICH E6(R2) Good Clinical Practice apply?



Notes:

Thus, given its applicability to all clinical trials involving human participants, it follows that the guidelines outline the role that all of the stakeholders involved in the design, conduct, oversight, recording, and reporting of clinical trials, play. The guideline highlights the collective responsibility that IRB/IECs, investigators, and sponsors all share.

1.17 Compliance with ICH is important for multiregional studies

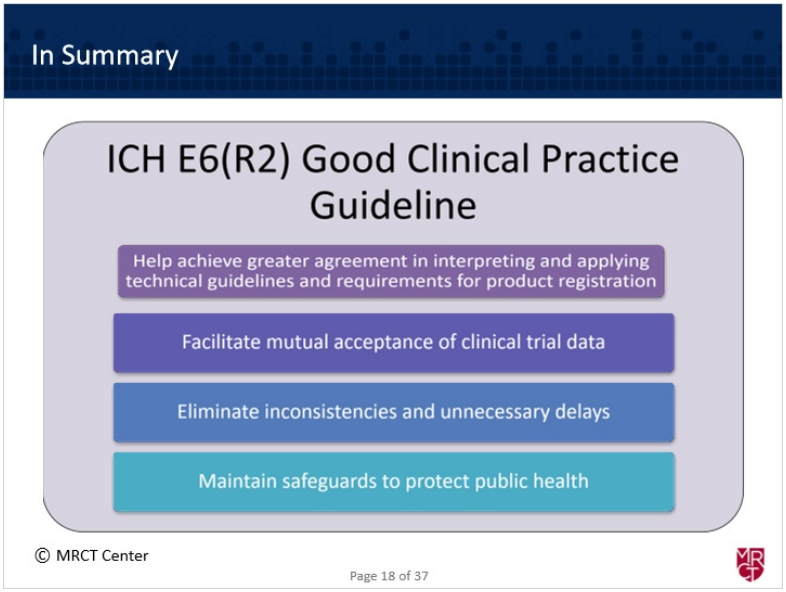


Notes:

Compliance with ICH is especially important for multiregional trials since there can be great variation across regions including differences in study population characteristics and standard of care, or extrinsic factors like the environment, diet and stress.

When all groups involved with a clinical trial comply with ICH E6(R2) there can be increased confidence that the protocol is being conducted in the same way around the world, and the data are collected in a uniform way, with the rights and welfare of participants being protected.

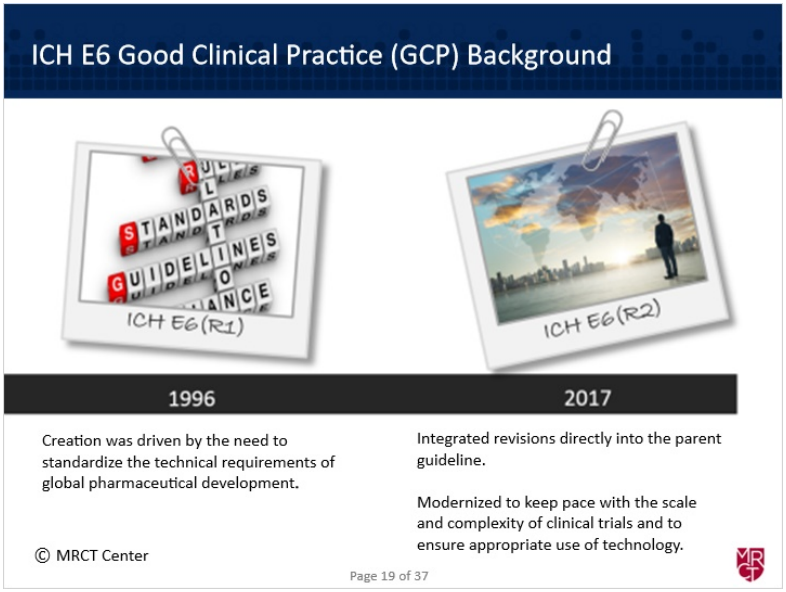
1.18 In Summary



Notes:

As a result - ICH E6(R2) Good Clinical Practice Guideline:
- Help achieve greater agreement in interpreting and applying technical guidelines and requirements for product registration
- Facilitate mutual acceptance of clinical trial data
- Eliminate inconsistencies and unnecessary delays
- Maintain safeguards to protect public health

1.19 ICH E6 Good Clinical Practice (GCP) Background



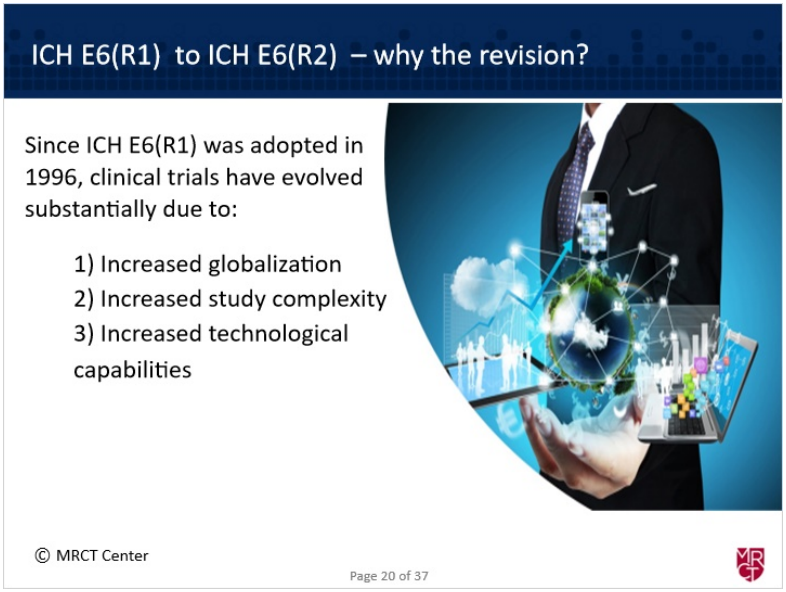
Notes:

Now that we've covered what ICH GCP is and why it is important, let's review how the guideline became what it is today.

The first revision [ICH E6(R1)] originated from a need to standardize the technical requirements of global pharmaceutical development, and was approved for adoption in 1996.

The second version [ICH E6(R2)], which was approved in 2017, modernized the original guideline to keep pace with the scale and complexity of clinical trials and ensure the appropriate use of technology. All revisions were integrated directly into the parent guideline via addenda.

1.20 ICH E6(R1) to ICH E6(R2) – why the revision?



Notes:

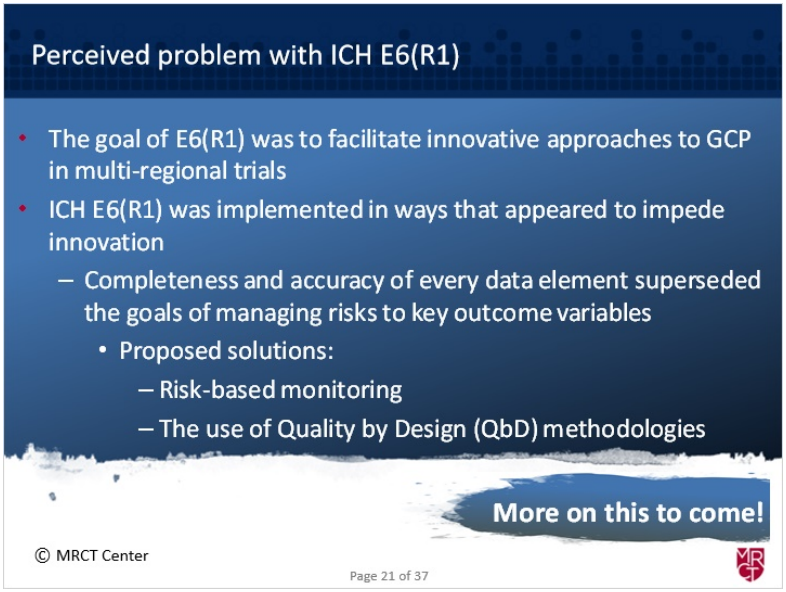
The guideline was modernized for 3 main reasons

1)Increased globalization moving from mostly single-site, randomized controlled trials to more multi-site, multi-country trials, which resulted in .....

2)increased study complexity due to an increase in sites, participants, data elements and secondary objectives

3)And increased technological capabilities like electronic data capture and digital systems (vs paper collection), adoption of electronic medical records, direct data entry over the internet, and electronic management of clinical trial conduct.

1.21 Perceived problem with ICH E6(R1)

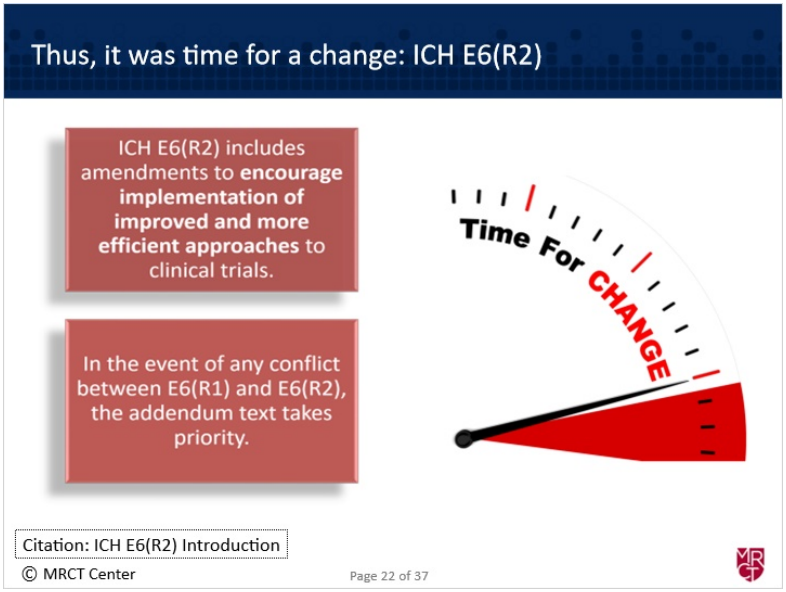


Notes:

And the revision was deemed necessary to better facilitate innovative approaches to GCP in highly complex multi-regional trials since the implementation of ICH E6(R1) frequently seemed to impede innovation

For example, the completeness and accuracy of every data element superseded the goals of managing risks to oversight to ensure the integrity of key outcome variables. In response, E6(R2) introduced risk-based monitoring and the use of Quality by Design methodologies to assure the absence of errors that matter and that the data are fit for purpose.

1.22 Thus, it was time for a change: ICH E6(R2)



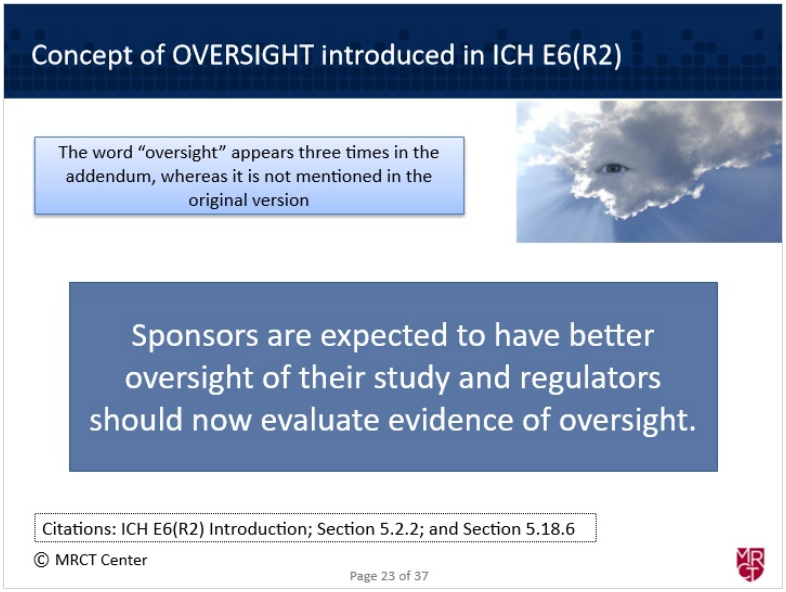
Notes:

So, ICH E6(R2) actually encourages the implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording, and reporting, while continuing to ensure human subject protection and the reliability of trial results.

And this applies to government regulators because review and inspection procedures must be adapted to keep up with this push for innovation.

It should be noted that in the event of any conflict between E6(R1) and E6(R2), the addendum takes precedence.

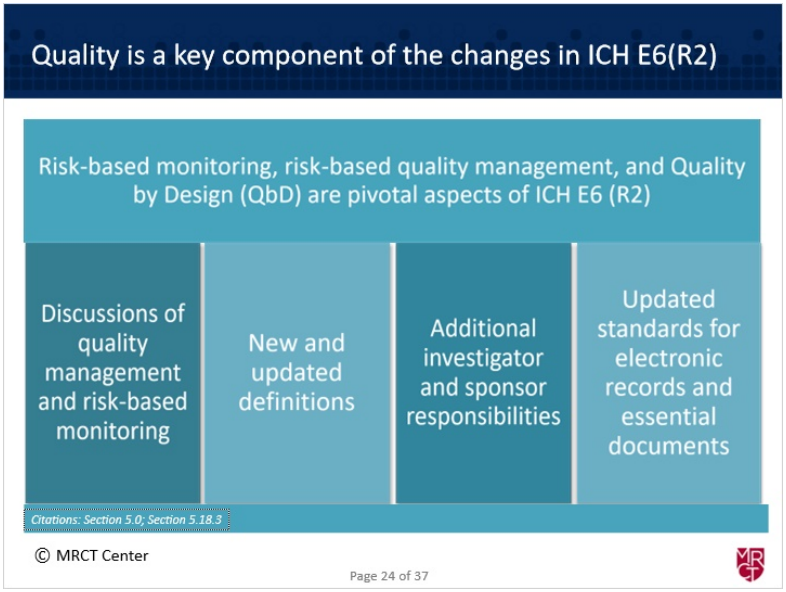
1.23 Concept of OVERSIGHT introduced in ICH E6(R2)



Notes:

Another change which is notable in ICH E6(R2) is that the concept of "oversight" is introduced and mentioned three times - pointing to the need for sponsors to strengthen their oversight activities, and for regulators to evaluate clinical trials for evidence of said oversight.

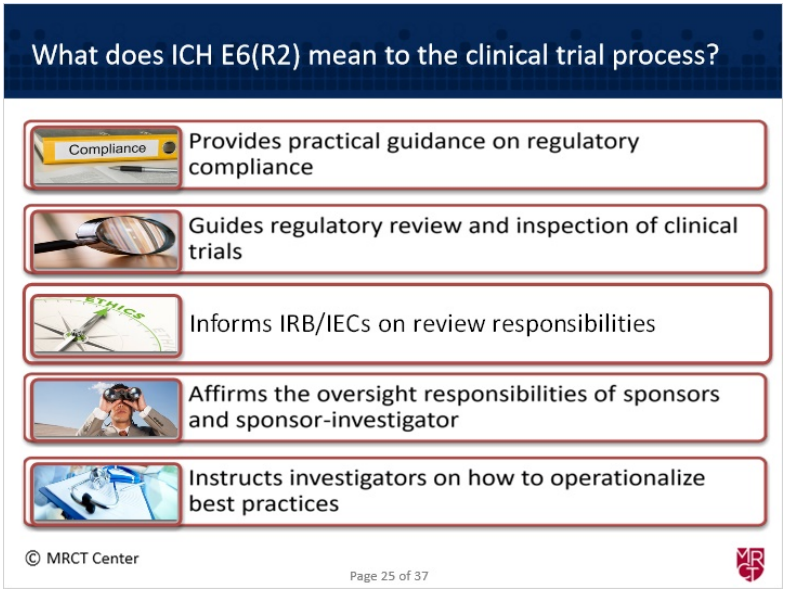
1.24 Quality is a key component of the changes in ICH E6(R2)



Notes:

As we review the summary of changes within ICH E6(R2) we return to the topics of risk based monitoring and Quality by Design, mentioned earlier in the module, and introduce risk-based quality management, all of which are pivotal aspects of this updated guideline. In addition to increased discussion of quality management and risk-based monitoring, there are new definitions of terms such as 'certified copy' and "validation of computerized systems." There are also additional investigator and sponsor responsibilities described, and updated standards for electronic records and essential documents. These will be described in subsequent modules.

1.25 What does ICH E6(R2) mean to the clinical trial process?



Notes:

What does ICH E6(R2) actually mean to the clinical trial process?

Practically speaking, then, ICH E6(R2) affects the clinical trial process in that it

-provides practical guidance on compliance with the regulations that pertain to research

-guides regulatory review and inspection of clinical trials

-informs institutional review boards/ethics committees on their review responsibilities

- affirms the oversight responsibility of sponsors (and sponsor-investigators)

- instructs investigators on how to operationalize best practices

1.26

Notes:

Although some principles of GCP may not apply to all types of research on human participants, consideration of these principles is strongly encouraged wherever possible as a means of ensuring the ethical, methodologically sound and accurate research conduct.

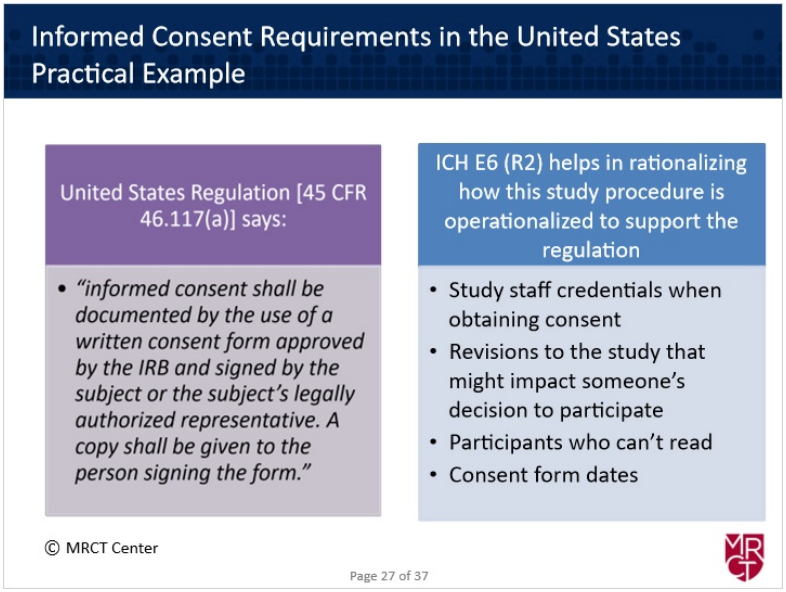
And as a government regulator, you can use ICH E6(R2) GCP to better understand

- Who the stakeholders in the research are
- What their responsibilities are
- What the study protocol should include given the study questions

And

- What sort of documentation is the principal investigator/IRB/IEC/sponsor required to keep?

1.27 Informed Consent Requirements in the United States



Notes:

So for example, in the federal regulations of the United States of America it states that:

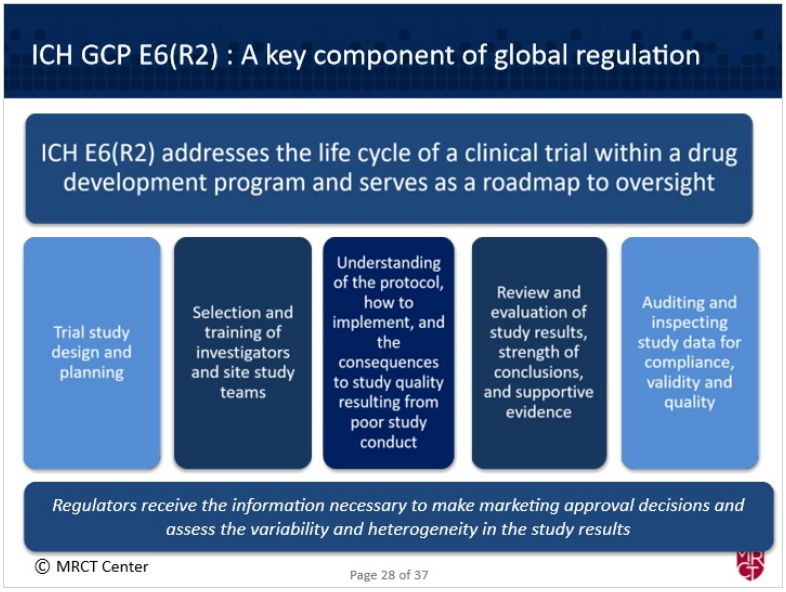
"*informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form*."

But in the context of a regulatory review or inspection, it is important to go beyond those few words to think about how this regulation is applied and operationalized, and ICH E6(R2) can help with that.

- You might have to consider whether there is an 'e-consent' that is being 'signed' or need to confirm that staff obtaining consent were appropriately qualified.
- You may have to determine whether there have there been other revisions to the study that would require reconsent in order to confirm a desire for continued participation.
- Or you might have to evaluate whether there was an acceptable process followed for participants who cannot read. Or are visually impaired.

- Or you might have to look critically at how the documents are dated

1.28 ICH GCP E6(R2) : A key component of global regulation



Notes:

Thus ICH E6(R2) is a key component of global regulation. It aids in the interpretation and application of the regulations and addresses the entire life cycle of a clinical trial within a drug development program by serving as a roadmap to oversight.

By following the guidelines set out in ICH E6(R2) one can more completely consider

- What needs to go into trial study design and planning, and the selection and training of investigators and site study teams
- The needs of the protocol and how to implement, as well as the consequences to study quality from poor study conduct
- How to review and evaluate the study results, the strength of conclusions and the supportive evidence
- And from an auditing and inspection perspective, ICH E6(R2) helps guide what should be reviewed for compliance, validity and quality

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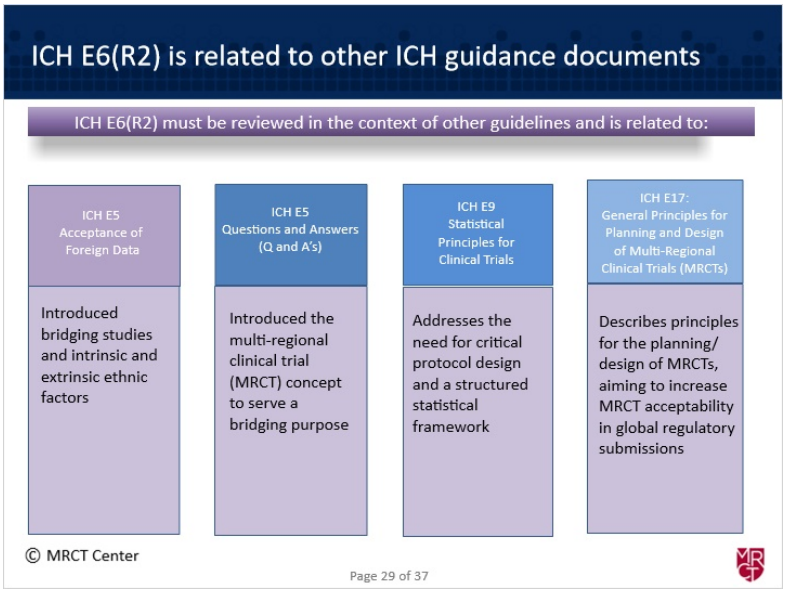
The last two points are especially relevant to the government regulators, as they receive the protocol, amendments, raw data, analyses, and the interpretation of data in order to make marketing approval decisions.

And they will frequently have to assess variability, heterogeneity, and other factors (like missing data and the consistency of data) in the study results, in order to make decisions that are not necessarily straightforward, and may even require evaluation of the submitted study in comparison to other studies.

1.29 ICH E6(R2) is related to other ICH guidance documents



Notes:

Before we end this module, we will spend a few minutes on the relationship ICH E6(R2) has to four other ICH guidance documents, namely:

ICH E5

And the related ICH E5 questions and answers document

ICH E9

ICH E17

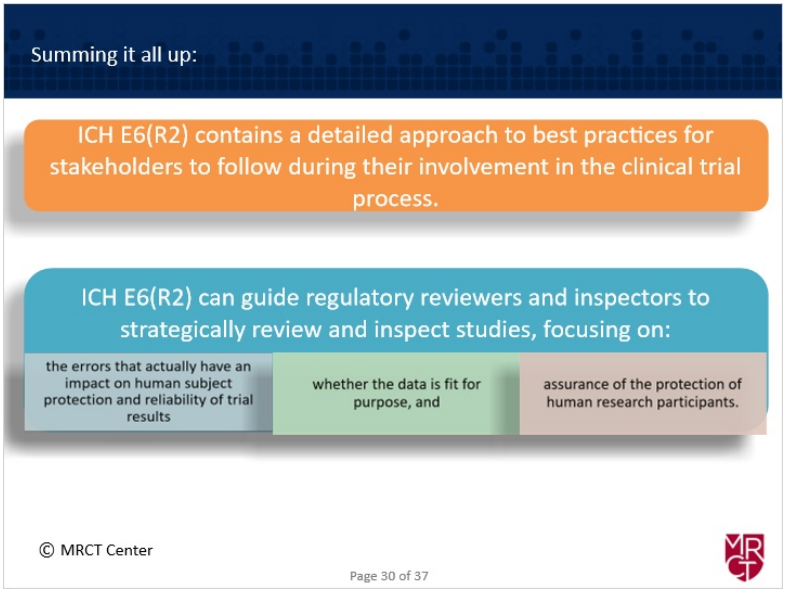
ICH E5 is the guideline on the acceptance of foreign data which Introduced the concept of the bridging study which is defined as a supplemental study performed in a new region to avoid unnecessary duplication and provide pharmacodynamic or clinical data on efficacy, safety, dosage, and dose regimen in the new region that will allow extrapolation from foreign data. ICH E5 also included information on assessing foreign data, via introduction of intrinsic and extrinsic ethnic factors.

The ICH E5 Question and Answer guideline clarified ambiguous issues and stimulated new thinking about using multi-regional clinical trials, which are now quite prevalent in the global research arena, for bridging because an MRCT can have one common protocol, and enroll a sufficient number of participants from each of the regions to reach conclusion about the effect of an investigational product in all regions.

ICH E9 is the guideline on statistical principles for clinical trials which specifically addresses the need for critical protocol design and providing a structured statistical framework to analyze and develop overall clinical development plans, trial design, trial conduct, data analysis, evaluation of safety/tolerability and reporting.

The last, and most recent ICH guideline, is E17 General Principles for Planning and Design of Multi-Regional Clinical Trials (MRCTs) which aims to increase MRCT acceptability in global regulatory submissions so that they satisfy regional and global post-marketing requirements through a valid design that gathers data that can be submitted to multiple regulatory authorities for approval of an investigational product concurrently, including approval of additional indications, new formulations and new dosing regimens. Also by applying the same quality standard for trial conduct across all regions there is strengthened scientific validity of trial results and the impact of intrinsic/extrinsic factors can be better evaluated.

1.30 Summing it all up:



Notes:

So as we approach the end of this module, and considering its review and application to the other previously mentioned guidances, ICH E6(R2) contains a detailed approach to best practices that IRB/IECs, sponsors, and investigators should follow during their involvement in the clinical trial process.

And that means that regulatory reviewers and inspectors, can use ICH E6(R2) as a guide for strategic review and inspection that prioritizes the quality of the data produced and focuses on

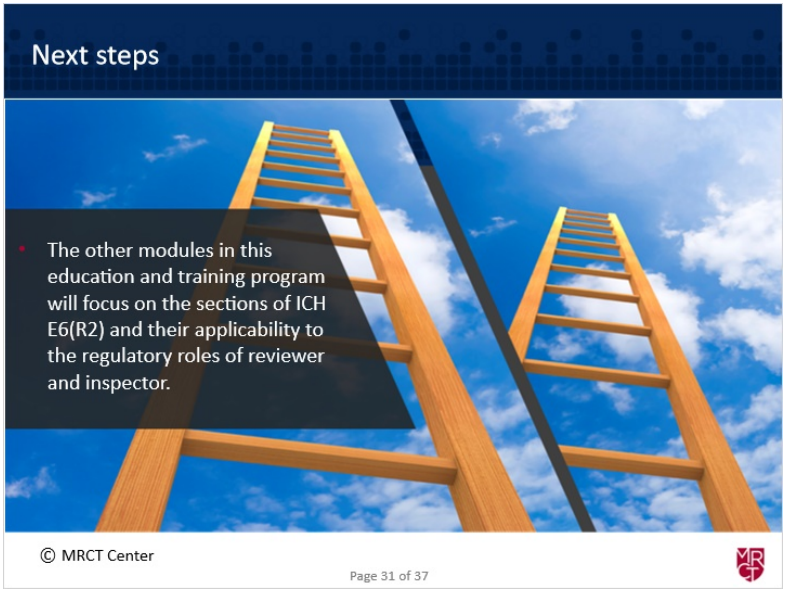
- the absence of errors that matter

- namely that any errors found actually are expected to impact human subject protection and reliability of trial results

-whether the data is fit for purpose, and

-assurance of the protection of human research participants.

1.31 Next steps



Notes:

In the following modules you will learn more about the specific details of ICH E6(R2), how they apply to reviewers and inspectors, and how to implement in your regulatory role.