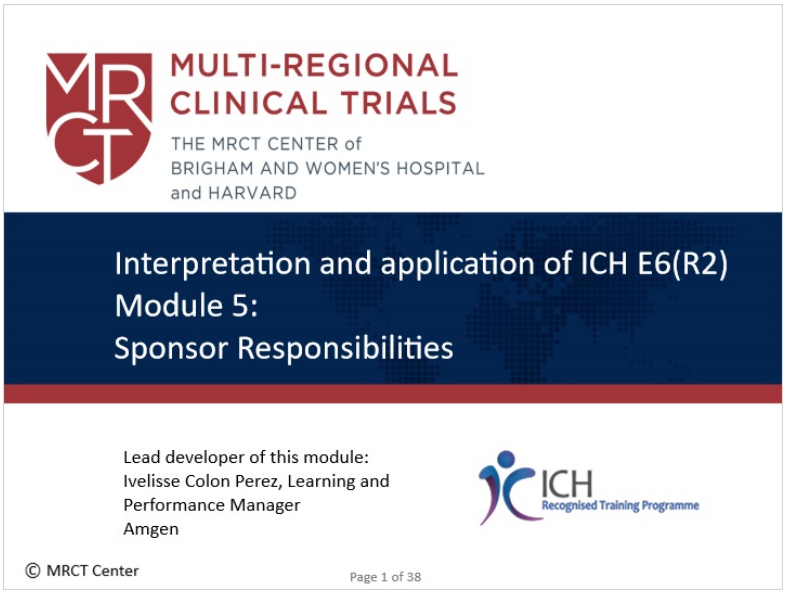
Module 5: Sponsor Responsibilities

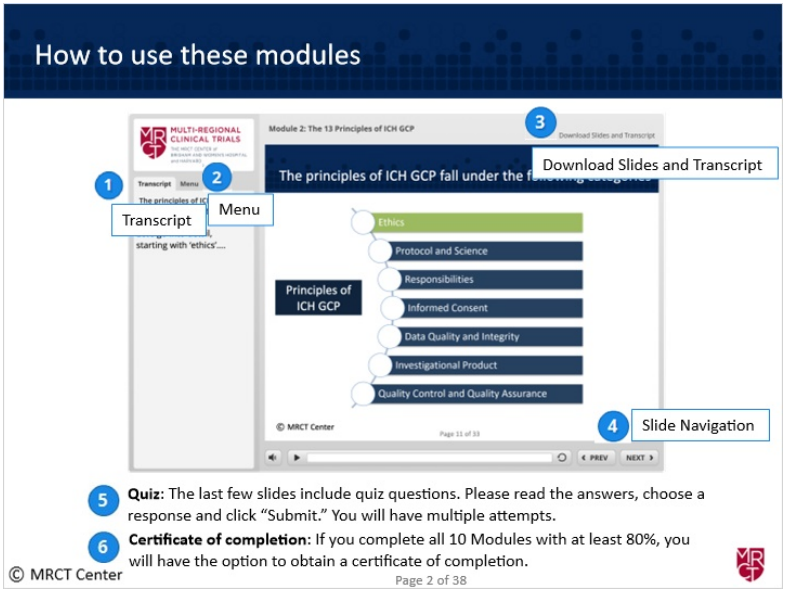
1.1 Interpretation and application of ICH E6(R2)



Notes:

Welcome to Module 5 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:

Please note that our attribution policy stipulates The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center) maintains the copyright to these training materials which were originally developed in English.

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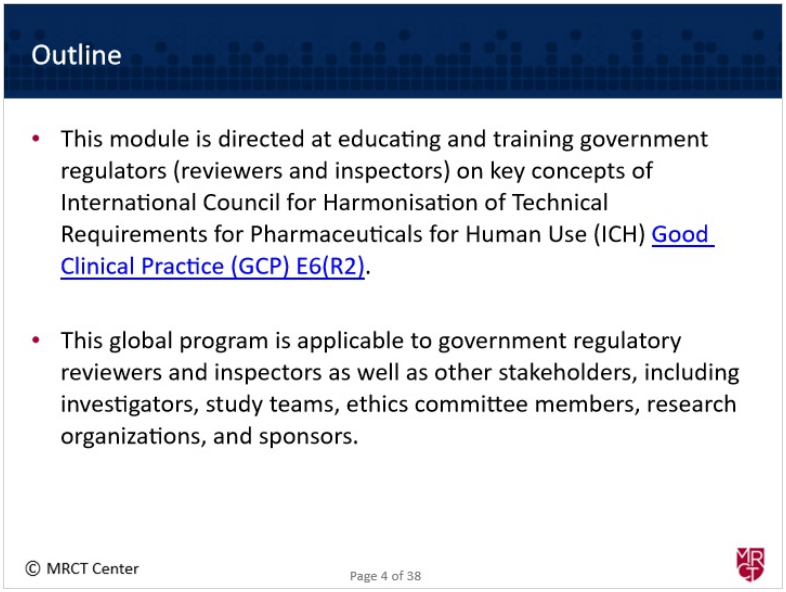
This training programme is recognised by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

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.

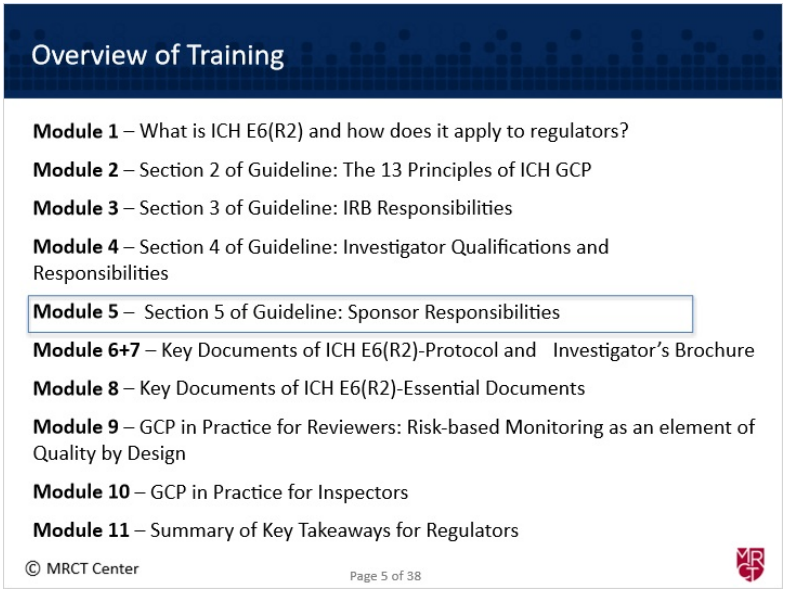
1.4 Outline



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).

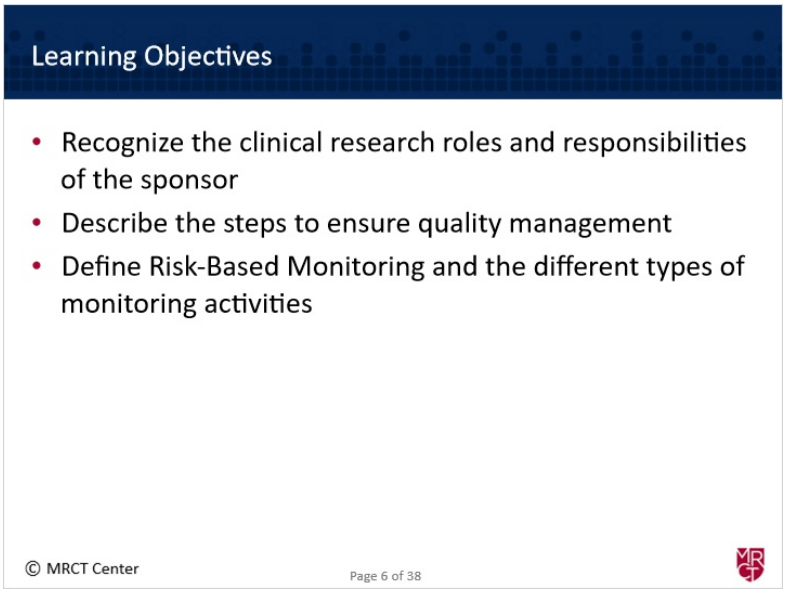
1.5 Overview of Training



Notes:

In Module 5 we will focus on describing the sponsor responsibilities of ICH GCP as outlined in the guideline.

1.6 Learning Objectives

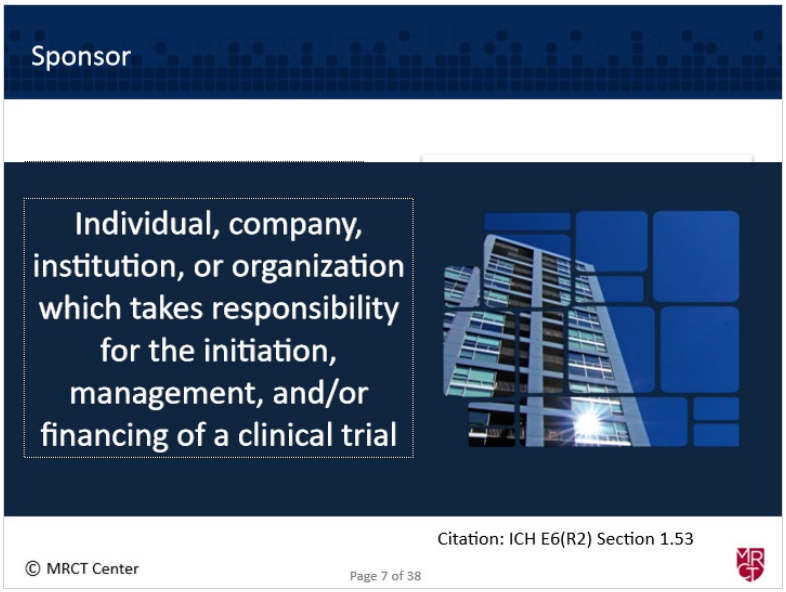


Notes:

By the end of this module you are expected to be able to:

- Recognize the clinical research roles and responsibilities of the sponsor
- Describe the steps to ensure quality management
- Define Risk-Based Monitoring and the different types of monitoring activities

1.7 Sponsor



Notes:

A sponsor is defined as an Individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.,

1.8 Sponsor Responsibilities - Overview

Notes:

Sponsors responsibilities are varied and maintained throughout the clinical trial. This module will provide an overview of the responsibilities. Sponsors:

- Develop and prepare the protocol, case report form (CRF) and Investigator Brochure
- Develop and provide the tools (drug, protocol, CRF) to conduct the clinical investigation
- Conduct clinical trial oversight, which may include selecting monitors and auditors to oversee the clinical investigation
- Submit and maintain the Investigational New Product applications and New Product or marketing applications to regulatory authorities
- Manage quality throughout the clinical trial process by implementing and maintaining quality assurance and quality control systems

Prior to initiating a trial, the sponsor should define, establish, and allocate all trial-related duties and functions.7)

1.9 Sponsor Responsibilities - Overview

Notes:

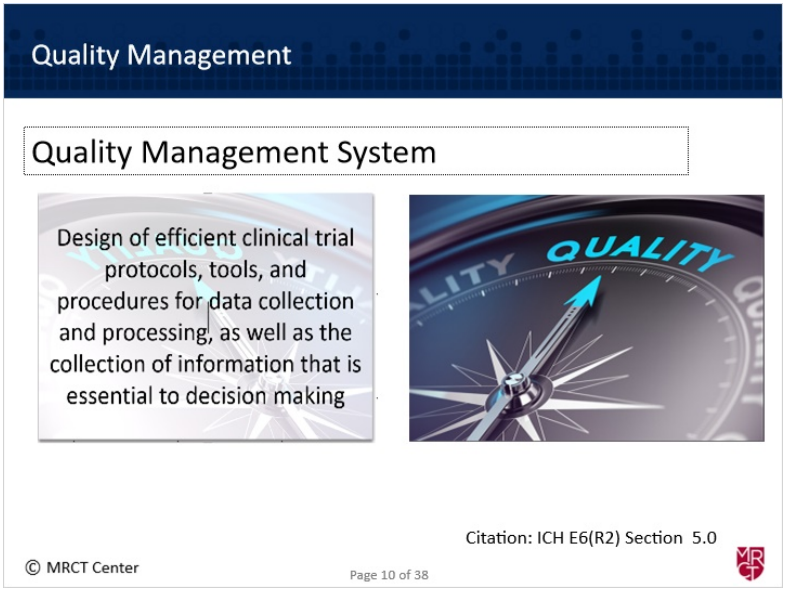
The sponsor maintains clinical trial documentation demonstrating adherence to GCP obligations and manages quality throughout the clinical trial process by implementing and maintaining quality assurance and quality control systems with written SOPs, study plans, and monitoring plans. The Sponsor establishes requirements for completeness, accuracy, reliability, and consistent intended performance for electronic trial data handling systems

The sponsor must ensure:

- The conduct of the trial and its data management is documented and reported in compliance with the protocol, regulations and regulator requirements
- Direct access to all trial related sites source data/document and reports for all parties involved for the purpose of monitoring, inspecting and auditing
- All data are processed correctly and is reliable
- All agreements are in writing with all parties involved in the trials

- Essential documents are retained for the appropriate length of time

1.10 Quality Management

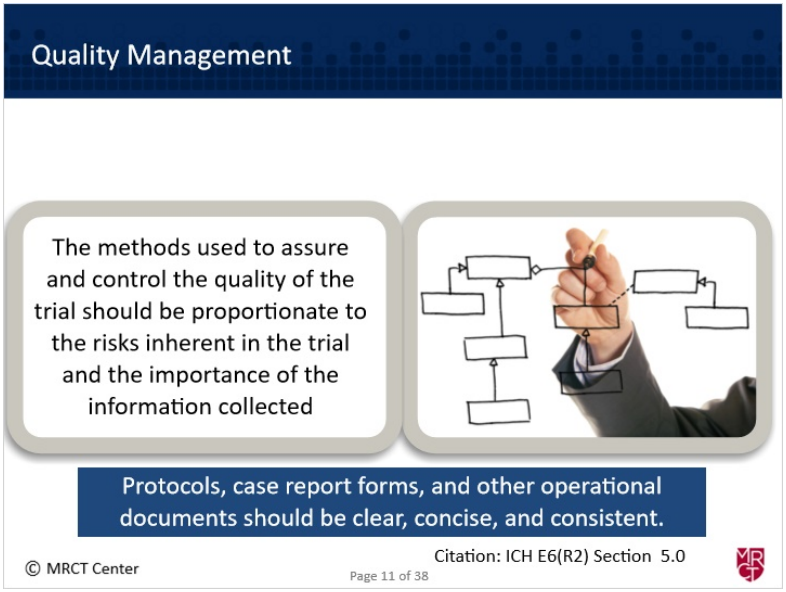


Notes:

The sponsor should implement a system to manage quality throughout all stages of the trial process and should focus on trial activities essential to ensuring human subject protection and the reliability of trial results.

Quality management includes the design of efficient clinical trial protocols, tools, and procedures for data collection and processing, as well as the collection of information that is essential to decision making.

1.11 Quality Management

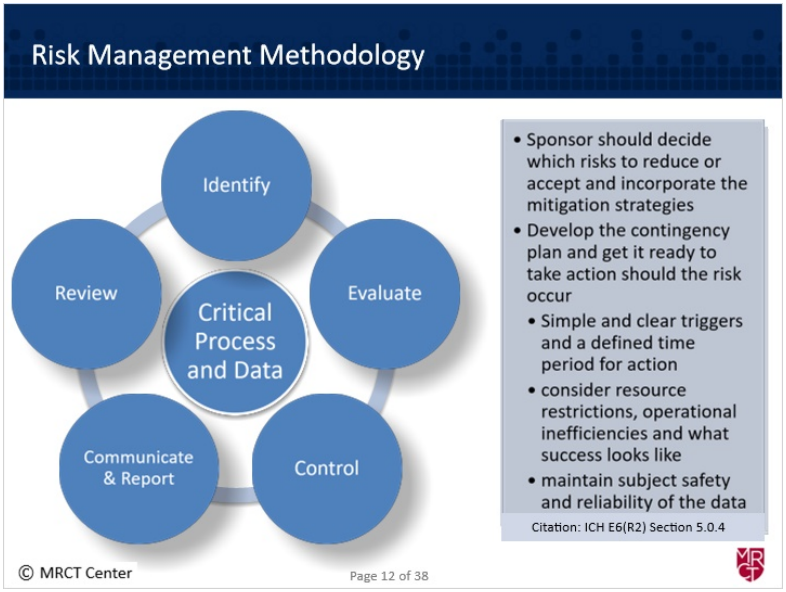


Notes:

The methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected.

The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures, and data collection. Protocols, case report forms, and other operational documents should be clear, concise, and consistent.

1.12 Risk Management Methodology



Notes:

Sponsors should develop a quality management system using a risk based approach. Risk Management methodology uses Critical Process and Data Identification to ensure human subject protection and the reliability of trial results.

This includes:

Risk Identification

The sponsor should identify risks to critical trial processes and data. Risks should be considered at both the system level (e.g., standard operating procedures, computerized systems, and personnel) and clinical trial level (e.g., trial design, data collection, and informed consent process).

Risk Evaluation

The sponsor should evaluate the identified risks, against existing risk controls by

considering:

The likelihood of errors occurring.

The extent to which such errors would be detectable.

The impact of such errors on human subject protection and reliability of trial results.

Risk Control

The sponsor should decide which risks to reduce and/or which risks to accept. The approach used to reduce risk to an acceptable level should be proportionate to the significance of the risk.

The Sponsor should develop the contingency plan and get it ready to take action should the risk occur as well as Simple and clear triggers and a defined time period for action

The Sponsor should:

- consider resource restrictions, operational inefficiencies and what success looks like
- maintain subject safety and reliability of the data

Risk Communication & Reporting

The sponsor should communicate quality management activities to those who are involved in or affected by such activities, to facilitate risk review and continual improvement during clinical trial execution.

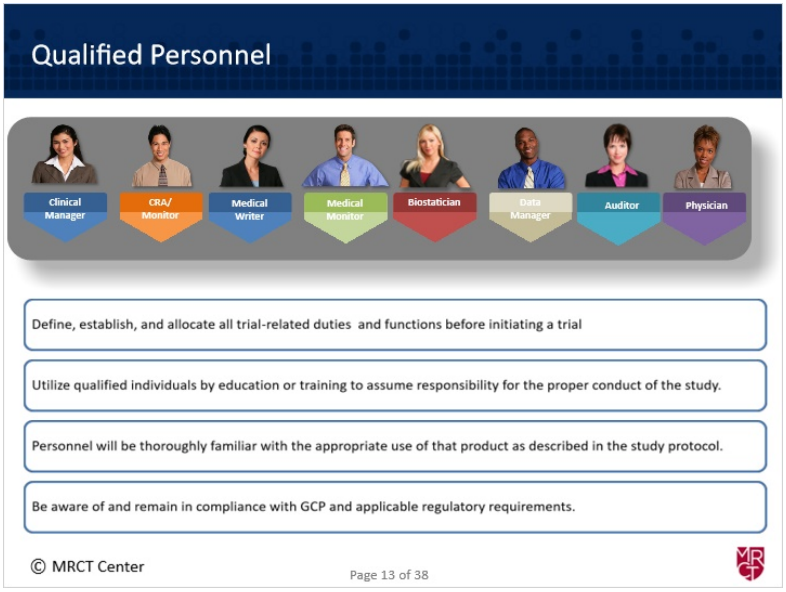
The sponsor should document quality management activities, as well as summarize important deviations from the predefined quality tolerance limits and remedial actions taken in the clinical study report

Risk Review

The sponsor should periodically review risk control measures to determine whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience.

Please refer to Module 9 of the training for additional details on risk management.

1.13 Qualified Personnel



Notes:

The sponsor should utilize qualified individuals (e.g., biostatisticians, monitors, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analyzing and preparing interim and final clinical trial reports.

Sponsors must

- Define, establish, and allocate all trial-related duties and functions before initiating a trial
- Ensure personnel responsible for the execution of trial related duties must be qualified by education, training, and experience to assume responsibility for the proper conduct of the study
- Ensure personnel is thoroughly familiar with the appropriate use of the investigational product as described in the study protocol
- Ensure personnel is aware of and remain in compliance with GCP and applicable regulatory requirements.

1.14 Clinical Research Organization (CRO)

Notes:

A Clinical Research Organization or CRO is defined as a person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions. This includes all vendors to which trial-related duties have been contracted, such as site management organizations and data handling/processing companies.

A sponsor may transfer a portion of trial-related duties to a CRO. And in some cases a sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO. It is important to remember the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.

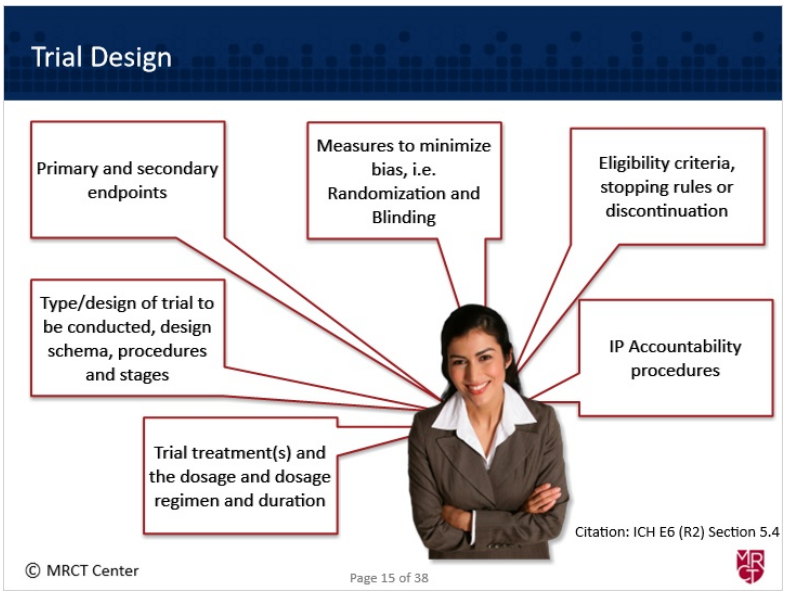
The CRO should implement quality assurance and quality control measures.

Any trial-related duty and function that is transferred to and assumed by a

CRO should be specified in writing.

The sponsor should ensure oversight of the trial-related duties carried out on its behalf by the CRO.

1.15 Trial Design



Notes:

As stated before, the sponsor will design the protocol, the CRFs, conduct analysis and prepare interim and final clinical study reports. The scientific integrity of the trial and the credibility of the data from the trial depends substantially on the trial design.

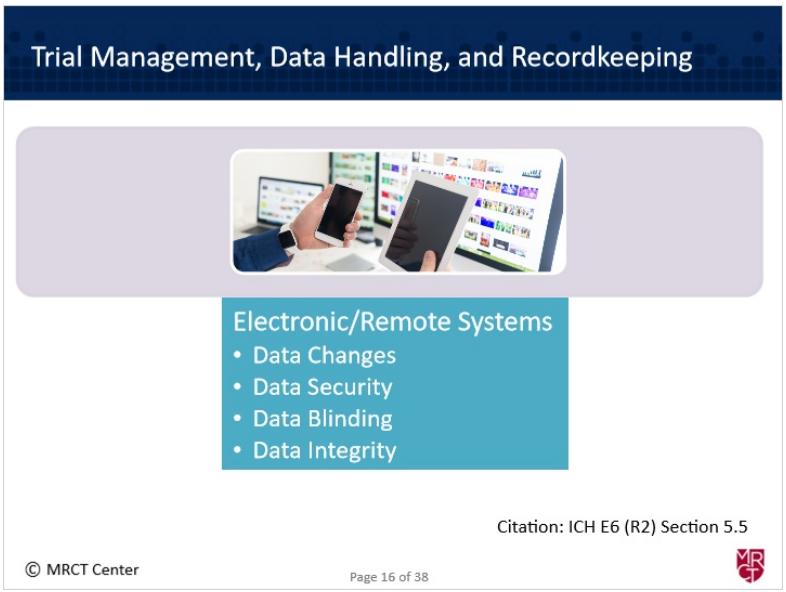
When designing clinical trials sponsors need to consider:

- Primary and secondary endpoints
- Type/design of trial to be conducted, design schema, procedures and stages
- Measures to minimize bias, i.e. Randomization and Blinding
- Trial treatment(s) and the dosage and dosage regimen and duration

- Eligibility criteria, stopping rules or discontinuation
- Intellectual Property Accountability procedures

Please see module 6 for more detailed information about the protocol.

1.16 Trial Management, Data Handling, and Recordkeeping



Notes:

Sponsors need to maintain the standard operating procedures (SOPs) for trial management, data handling, and recordkeeping.
These SOPs should
Ensure systems maintain an audit trail, data trail, edit trail
Maintain a security system that prevents unauthorized access to the data.
Safeguard the blinding, if any (e.g. maintain the blinding during data entry and processing).
Ensure the integrity of the data. This is particularly important when making changes to the computerized systems, such as software upgrades or migration of data.
The sponsor should base their approach to validation of such systems on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and

reliability of trial results.

1.17 Investigator Selection

Notes:

Sponsors must select investigators whom by training or expertise will expertly oversee and conduct the trial.

The Investigator should be based at the institutions/hospitals and have sufficient resources to properly conduct the trial. This include any third party retained by the investigator or institution to whom the investigator delegates trial-related duties and functions

Sponsors use an Investigator Agreement to document that the investigator agrees to

- Conduct the trial in compliance with GCP
- Comply with procedures for data recording
- Allow monitoring, auditing and inspections
- Retain the trial related essential documents until the sponsor informs

the investigator these documents are no longer needed

- Provide access to source data/documents

1.18 Investigator and Subject Compensation

Notes:

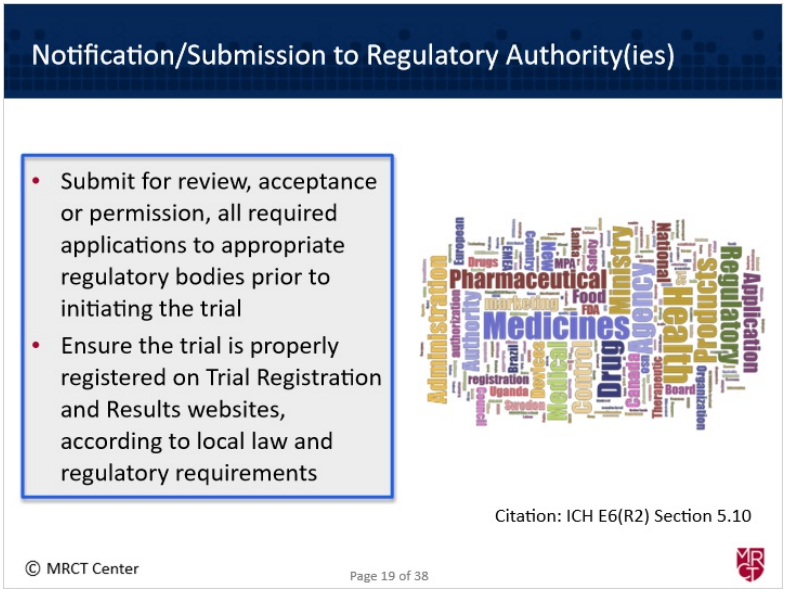
The sponsor should maintain SOPs to: address insurance or indemnification against claims arising from the trial for the investigator/institution

This does not include malpractice or negligence

Address treatment cost in the event of trial-related injuries

Ensure all compensation agreements are in compliance with regulatory requirements

1.19 Notification/Submission to Regulatory Authority(ies)



Notes:

Before initiating a clinical trial, the sponsor should submit for review, acceptance or permission, all required applications to appropriate regulatory bodies.

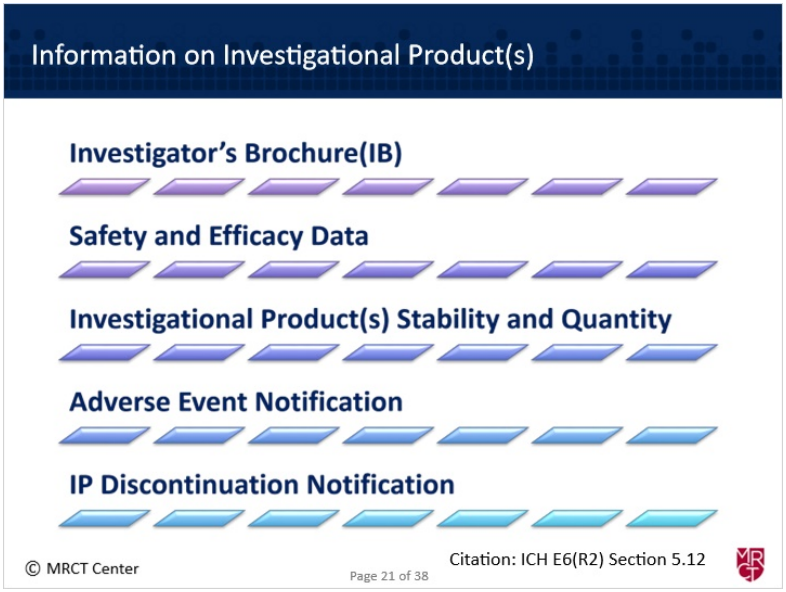
Sponsors are responsible for the Trial Registration on appropriate websites, according to local law, regulatory requirements and timeliness.

1.20 Confirmation of Review by IRB/IEC

Notes:

Sponsors need to ascertain that all investigator sites have approval from their IRB/IEC to conduct the trial, and in addition, confirm that the IRB/IEC operates according to applicable local laws, regulations and GCP. The sponsor should maintain all relevant IEC/IRB documentation on file.

1.21 Information on Investigational Product(s)



Notes:

When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied.

The sponsor should ensure that:

The Investigator's Brochure(IB) is made available to the investigator(s) and the investigators are responsible for providing the up-to-date IB to the responsible IRBs/IECs.

Sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied

The Investigational product(s) are stable over the period of use and that ongoing safety evaluations are performed on the investigational product(s)

Notify all related parties of findings that may adversely affect subjects, trial conduct or approval from IRB/IEC or if the development of the Investigational Product is discontinued

Additional detail about the Investigator's Brochure is presented in Module 6

1.22 Investigational Product Oversight

Notes:

For investigational product oversight, the sponsor is required to

- Supply all required documentation including approval from IRB and regulatory authorities before supplying the investigator with the Investigational Products, including Comparator(s) and Placebo if applicable. This includes a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding

- Sponsors must Maintain records of the quantities of Investigational Product with proper batch numbers, Determine acceptable storage temperature, conditions, time, reconstitution fluids and procedures and devices for product infusion characterized as appropriate to the stage of development of the product(s)

- Ensure all product(s) are manufactured in accordance with any applicable GMP, appropriately coded, packaged to prevent contamination and unacceptable deterioration during transport and storage; and Labelled in a manner that protects the blinding, if applicable and that it complies with applicable regulatory requirements

- And finally sponsors ensure that the investigational product(s) are stable over the period of use and timely delivered to the investigator(s).

1.23 Adverse Drug Reaction Reporting

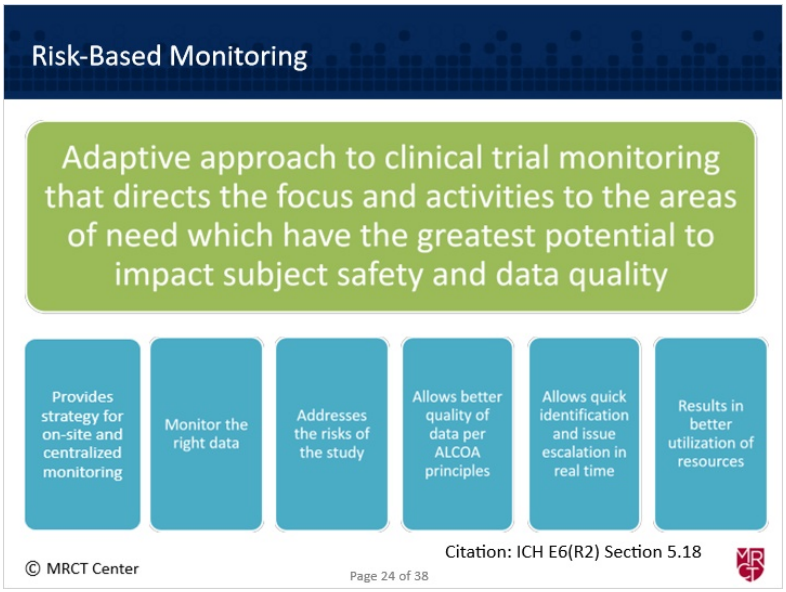
Notes:

Sponsors submit to the regulatory authority all safety updates and periodic

reports, as required by applicable regulatory requirements.

All adverse drug reactions (ADRs) that are both serious and unexpected reporting must be expedited to all concerned investigators and institutions, where required, and to the regulatory authorities.

1.24 Risk-Based Monitoring



Notes:

The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials that directs the focus on activities to the areas of need which have the greatest potential to impact subject safety and data quality.

The sponsor should document the rationale for the chosen monitoring strategy (e.g., in the monitoring plan). The monitoring plan needs to be tailored to the specific human subject protection and data integrity risks of the trial.

No single approach is appropriate for every clinical trial, therefore risk-based monitoring approach

- Provides strategy for on-site and centralized monitoring
- Allows sponsor Monitor the right data (Identified Risks)
- Addresses the risks of the study (Risk Mitigation Plan)
- Allows better quality of data per ALCOA principles - Accurate, Legible, Contemporaneous, Original and Attributable.
- Allows quick identification and issue escalation in real time
- Results in better utilization of resources

1.25 Monitoring

Notes:

Sponsors determine the extent and nature of monitoring activities to ensure that the trials are adequately monitored and document the rationale for the monitoring strategy in the monitoring plan. Included in the monitoring plan is the extent and nature of on-site and central monitoring activities

Activities may vary for a specific trial or the extent and nature of the monitoring activity. Included activities for on-site monitoring may be:

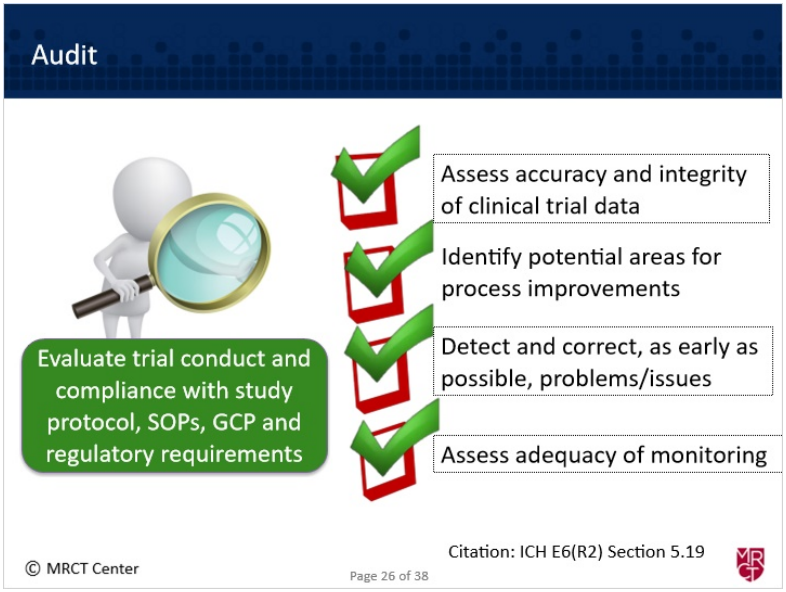
- Schedule (Location visit or conferencing technology)
- Site Management
- Performance gaps
- Adherence to study documents and procedures
- Documentation
-

Centralized Monitoring is a remote evaluation of aggregated data and is generally different from on-site and remote monitoring. Activities include:

- Data Analytics (Examine data trends such as the range, consistency, and variability of data within and across sites, including analysis of site characteristics and other performance metrics)
- Outlier Oversight (Identify missing data, inconsistent data, data outliers, unexpected lack of variability and protocol deviations)
- Data Errors (Evaluate for systematic or significant errors in data collection and reporting at a site or across sites; or potential data manipulation or data integrity problems)
- Select sites and/or processes for targeted on-site monitoring

The sponsor must confirm that all reports, Central or On-Site monitoring contain sufficient information to allow verification of compliance with monitoring plan, contain a summary of what was reviewed, significant findings, deviations and deficiencies, conclusions and actions recommended or taken to secure compliance

1.26 Audit



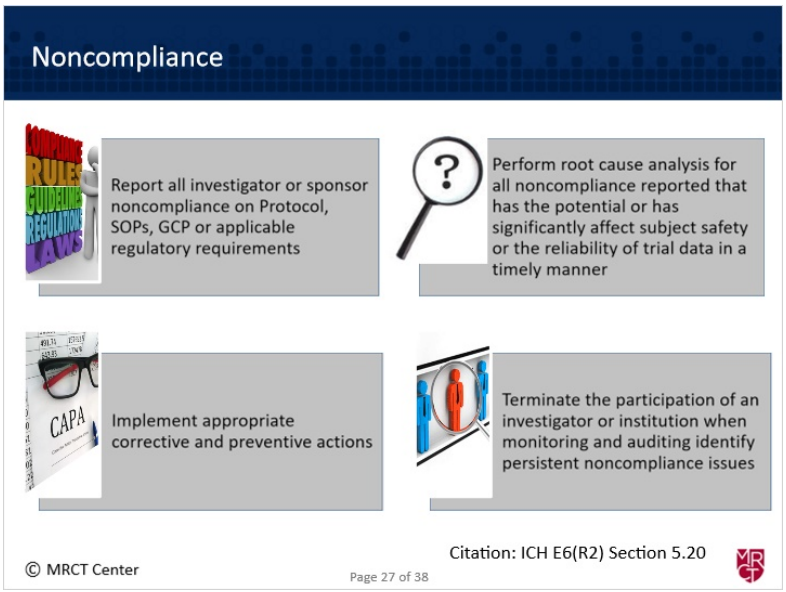
Notes:

A sponsor audit is an independent and separate activity from monitoring, and is usually a more formal approach to evaluating a study's conduct by professionals who are independent of the research. It evaluates the trial conduct and compliance with the protocol, SOPs, GCPs, and the applicable regulatory requirements.

Sponsors appoint individuals qualified by training and experience to conduct audits. Auditors evaluate trial conduct and compliance with study protocol, SOPs, GCP and regulatory requirements to:

- Assess accuracy and integrity of clinical trial data
- Identify potential areas for process improvements
- Detect and correct, as early as possible, of problems/issues
- Assess the adequacy of monitoring

1.27 Noncompliance



Notes:

Any non compliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

If noncompliance that significantly affects or has the potential to significantly affect human subject protection or reliability of trial results is discovered, the sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions.

If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution's participation in the trial. When an investigator's/institution's participation is terminated because of noncompliance, the sponsor should notify promptly the regulatory authority(ies).

1.28 Premature Termination or Suspension of Study

Notes:

In case the sponsor chooses or is required to terminate prematurely, or suspend the study, then the sponsor should notify the investigators, institutions, the ethics committee and the regulatory authorities accordingly. The notification should document the reasons for the termination or suspension.

1.29 Clinical Trial / Study Reports

Notes:

A clinical trial/study report is defined under Section 1.12 as a written description of a trial/study conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report.

As trials conclude or are halted by the sponsor, clinical trial reports should be prepared and submitted to the regulatory agencies.

Reports should:

describe the quality management approach implemented in the trial in the clinical study report

And Summarize important deviations from the predefined quality tolerance limits and remedial actions taken in the clinical study report

Reports must meet ICH guidelines and submission schedules

Finally, Sponsors are responsible for Results Posting on appropriate websites, according to local law, regulatory requirements

1.30 Multicenter Trials

Notes:

A multicenter trial is defined in GCP guidelines as a clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

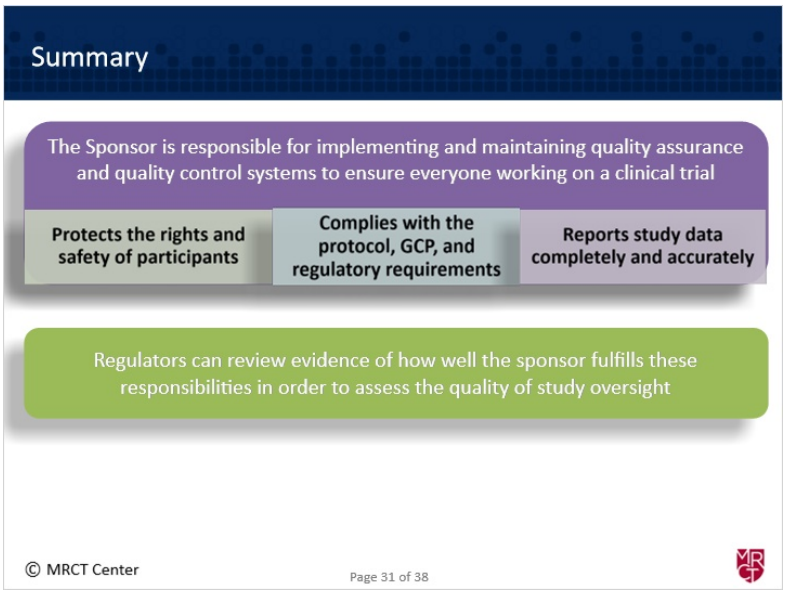
Effective oversight of a multicenter trial includes:

ensuring that all investigator and other institution personnel involved with the trials follows strict adherence to the trial protocol as well as GCP guidelines,

The Investigators and site staff should receive adequate training and, comply with a uniform set of standards for trial

Sponsors must ensure clear and consistent communications, and roles and responsibilities are clearly delineated for all sites.

1.31 Summary



Notes:

In summary, The Sponsor is responsible for implementing and maintaining quality assurance and quality control systems to ensure everyone working on a clinical trial

- Protects the rights and safety of participants
- Complies with the protocol, GCP, and regulatory requirements
- Reports study data completely and accurately

Regulators can review evidence of how well the sponsor fulfills these responsibilities in order to assess the quality of study oversight.