

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

1.1 Interpretation and Application of ICH E6(R2)

ICH E6(R2)的解读和应用



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

Interpretation and Application of ICH E6(R2)

Module 6+7: Clinical Trial Protocol and Protocol
Amendment(s) and Investigator Brochure

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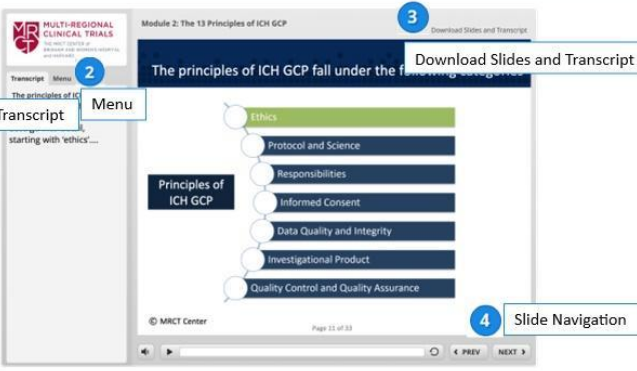
Notes:

Welcome to Module 6+7 of this training on the interpretation and application of ICH E6(R2)

欢迎来到 ICH E6(R2)的解读和应用培训的第六和第七讲。

1.2 How to use these modules

How to use these modules



1 Transcript

2 Menu

3 Download Slides and Transcript

4 Slide Navigation

5 Quiz: The last few slides include quiz questions. Please read the answers, choose a response and click "Submit." You will have multiple attempts.

6 Certificate of completion: If you complete all 10 Modules with at least 80%, you will have the option to obtain a certificate of completion.

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1.4 Outline

Outline

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




1.5 Overview of Training

培训概览

Overview of Training

- Module 1** – What is ICH E6(R2) and how does it apply to regulators?
- Module 2** – Section 2 of Guideline: The 13 Principles of ICH GCP
- Module 3** – Section 3 of Guideline: IRB Responsibilities
- Module 4** – Section 4 of Guideline: Investigator Qualifications and Responsibilities
- Module 5** – Section 5 of Guideline: Sponsor Responsibilities
- Module 6+7** – Key Documents of ICH E6(R2)-Protocol and Investigator’s Brochure
- Module 8** – Key Documents of ICH E6(R2)-Essential Documents
- Module 9** – GCP in Practice for Reviewers: Risk-based Monitoring as an element of Quality by Design
- Module 10** – GCP in Practice for Inspectors
- Module 11** – Summary of Key Takeaways for Regulators

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Notes:

In 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).

在本模块中，我们结合 ICH E6(R2)指南第 6 和第 7 部分的信息，概述了两个关键研究文件，即临床试验研究方案（及相关修订）和研究者手册（IB）。

1.6 Learning Objectives

教学目标

Learning Objectives

- Gain general information about the goals and basic contents of a clinical trial research protocol and Investigator Brochure (IB).
- Understand how investigators, regulators and Institutional Review Boards/Independent Ethics Committees (IRB/IECs) use the protocol and IB documents at the time of protocol implementation.
- Understand how regulators and inspectors use the protocol during the marketing application and review processes.



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.

这两个模块的学习完成时，您将获得更多关于临床试验研究方案和研究者手册的目标和基本内容方面的信息，更深入地了解临床试验利益相关方在研究方案实施时以及在上市申请和审查过程中如何使用研究方案和研究者手册。

1.7 Clinical Trial Protocol

临床试验研究方案



Notes:

We will first look at the Clinical Trial Protocol.

我们首先来学习临床试验研究方案。

1.8

什么是临床试验研究方案？

What is a Clinical Trial Protocol?

A clinical trial protocol

Clinical trial protocols must:

Citation: ICH E6(R2) Section 1.44

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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.

研究方案是临床试验的路线图和“驾驶员”。

临床试验研究方案

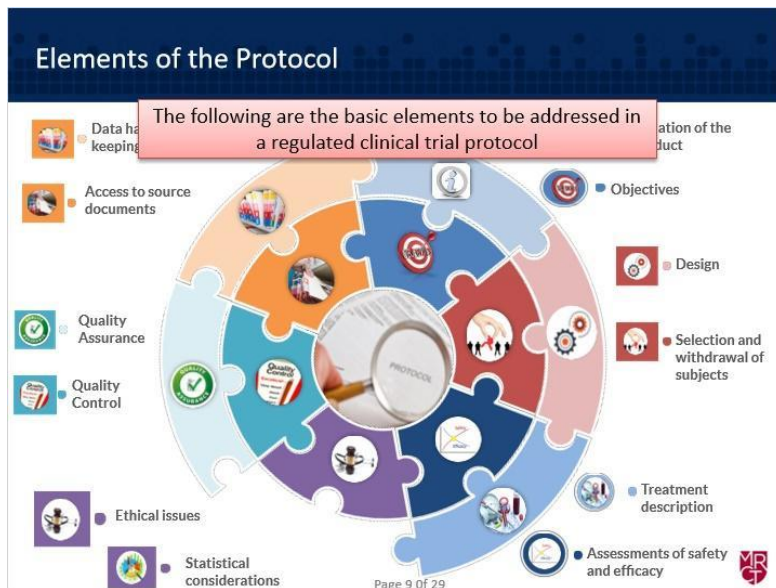
- 是一份规范的文件，描述了目标和目的、临床设计、活动和统计方面的考虑。
- 提供进行临床研究的背景和理论依据，强调要解决的具体研究问题。
- 包含涉及质量标准、伦理问题、出版政策以及临床方案具体问题的章节，如特定设备的使用、新型数据收集方法等。

并且临床试验研究方案必须

- 证明符合 ICH E6(R2) 药品临床试验管理规范(GCP)的要求
- 符合当地法规和机构审查委员会/独立伦理委员会(IRB/IEC)的要求。

1.9 Elements of the Protocol

研究方案的要素



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

以下是 ICH E6(R2)GCP 中规定的临床试验研究方案中应涉及的基本内容。


- 临床试验用产品的背景信息
- 目标
- 设计
- 受试者的筛选和退出
- 治疗描述
- 安全性和保护效力的评估
- 统计学方面的考虑
- 伦理问题
- 质量保证
- 质量控制
- 数据处理和记录保存
- 获取源文件

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

其中一些信息可以在其他研究方案参考文件，如研究者手册中找到。

1.10 Examples Specific Protocol Elements

研究方案具体要素举例



Examples Specific Protocol Elements

- 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.

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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,

这张幻灯片涉及到研究方案具体章节中要描述的内容。

- 研究方案的目标部分告诉我们为什么要进行这项研究。
- 伦理问题部分阐述的内容包括知情同意和隐私问题。
- 研究方案设计部分包括的问题有：研究是否随机，是否开放标签的；如何选择研究对象；关于研究对象何时退出研究的规则。

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.

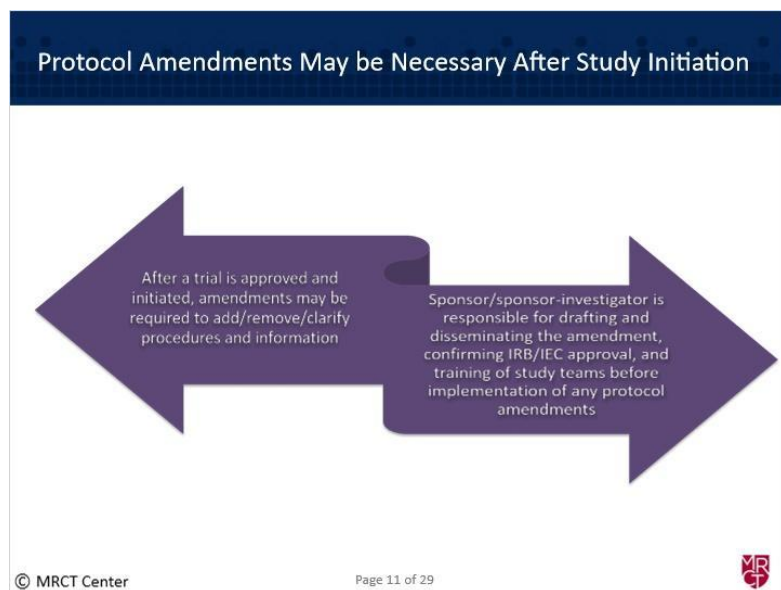
- 研究方案还要描述临床试验用产品，它是药物、设备、还是生物制品；治疗方式（如给药方式）；以及治疗频率。

- 研究方案要细致描述安全性和保护效力的评估方法，并提供数据分析的初步统计方法。

- 研究方案还提供数据处理、记录保存和数据来源的细节，以及质量保证和质量控制的方法。

1.11 Protocol Amendments May be Necessary After Study Initiation

研究启动后可能需要修订研究方案



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.

在研究过程中，为了增加、删除和/或澄清程序和/或信息而修订研究方案是很常见的。由于发生了不可预见的事件，取消或修改纳入或排除标准，或者为了实施某些程序的改变，例如，根据临床现场的反馈，采取更容易实施的操作方式，都需要修订研究方案。

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

申办者/申办方研究者负责起草和宣传修订，确认 IRB/IEC 会对修订的批准，并在实施任何修订之前培训研究人员。

1.12 Important Points for Regulatory Reviewers

监管审评员须知的要点

Important Points for Regulatory Reviewers

1. A clinical trial that will be used to support a marketing application will have been vetted by reviewers within regulatory agencies such as FDA, EMA, CFDA and PMDA.
2. Any differences of opinions between the regulators and study sponsors in terms of study design or content should be documented, thus establishing a clarity of intent and acceptance of the final protocol.
3. Thus, at the time of regulatory review of the marketing application, unless there were major unanticipated events or the protocol was not followed, the study should still be acceptable

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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

监管审评员应考虑到，任何用于支持上市申请的临床试验研究方案都应事先经过监管机构审评员的审核，

在接受研究方案终稿之前，监管人员和研究申办者之间的任何意见分歧都应记录在案。

如果按照商定的研究方案实施和执行，临床试验结果应支持监管部门对上市申请的决策。除非有

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.

重大的意外事件或没有遵守研究方案，否则监管部门应接受该研究。

1.13 Important Points for Regulatory Inspectors

监管检查员须知的要点



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

监管机构的评审部门对上市申请进行初步评估后，检查员会对临床现场、申办者和合同研究机构进行检查，以确保各方都遵守了研究方案并符合 GCP。这些检查被称为批准前检查。

训练有素的检查员会访问临床研究现场、申办者、合同研究机构和关键供应商，以保证各方都遵守了研究方案。

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.

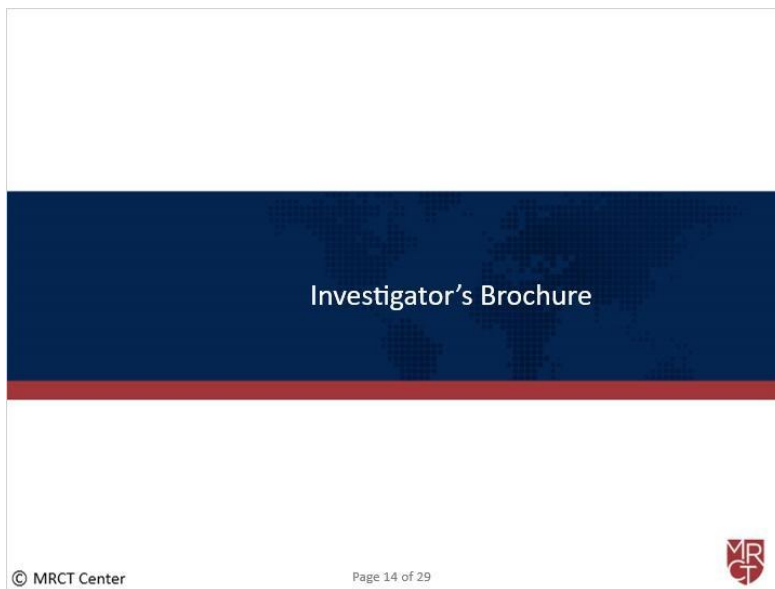
This overall study conduct, including, for example, protocol study procedures, data collection techniques, and the way the CRFs are signed electronically should be considered acceptable by the Inspectors if the approved study protocol was followed.

检查员还评估各方对 GCP 的遵守情况，确保研究的高质量（例如，没有重要的错误），以及研究数据将适用于目的。

整体的研究行为——包括例如研究程序、数据收集技术和 CRF 的电子签名方式等，——如果遵守了批准的研究方案，检查员应该认为该研究是可以接受的。

1.14 Investigator's Brochure

研究者手册



Notes:

We will now look at the Investigator's Brochure.

我们现在来讲研究者手册。

1.15 What is an Investigator Brochure?

什么是研究者手册？

What is an Investigator's Brochure?

The Investigator's Brochure (IB) is a comprehensive document which provides a summary of the available information about an investigational product.

The IB compiles chemistry information as well as non-clinical and clinical data relevant to studies of the investigational product.

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

The IB is updated annually with new information, or sooner if there are significant findings.

Citation: ICH E6(R2) Section 7

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Notes:

The Investigator Brochure is a summary of what is currently known about the investigational product, 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.

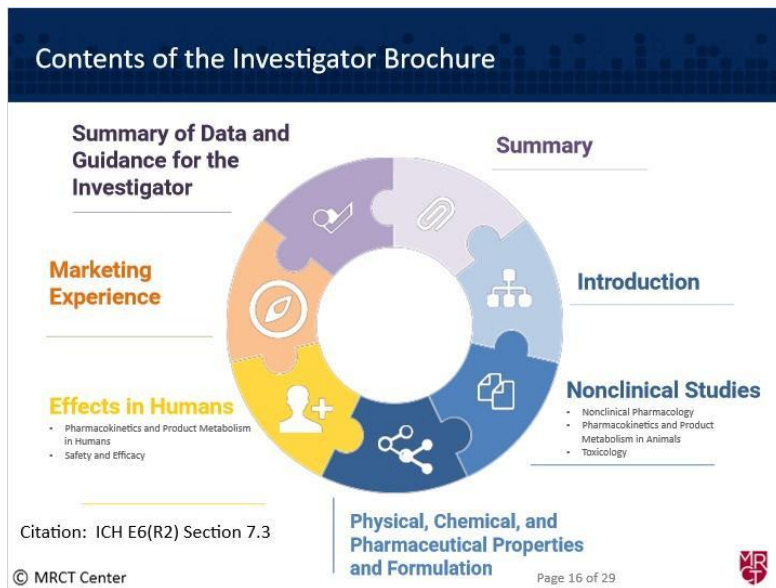
研究者手册是对目前已知的临床试验用产品的总结，包括化学信息以及相关的非临床和临床数据。

监管者将研究者手册作为监管评审过程的一部分进行评审，研究者和 IRB/IEC 也将研究者手册作为临床试验用产品的主要信息来源。

研究者手册至少每年更新一次，如果有重大发现，则应及时更新。

1.16 Contents of the Investigator Brochure

研究者手册的内容



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 pharmaceutical 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

研究者手册的内容包括：

- 摘要

- 介绍

- 关于非临床研究的信息，包括动物毒理学研究的具体结果

- 物理、化学和药学特性及配方——包括有效期

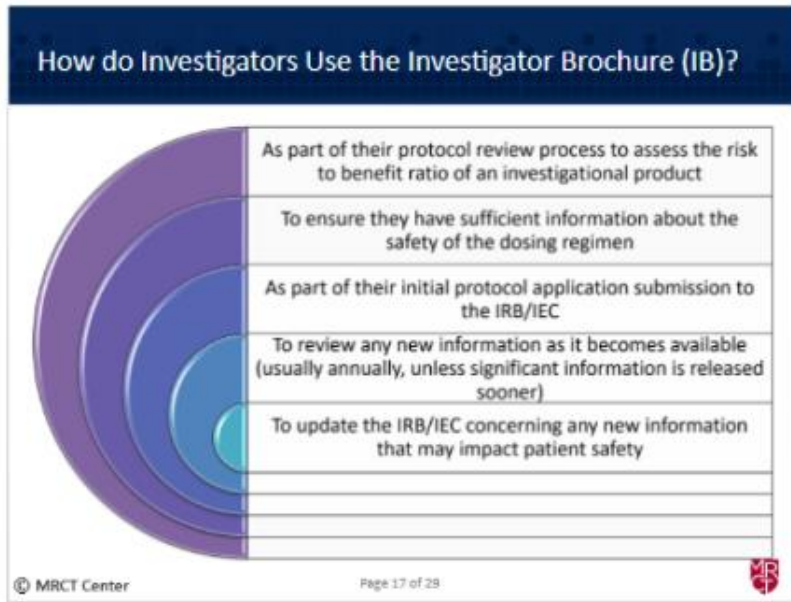
- 对人体的影响，包括相关临床试验的具体结果和人类使用该临床试验用药品的其他经验

- 市场经验，以及

- 提供给研究者的数据和指导的总结

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

研究者如何使用研究者手册？



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.

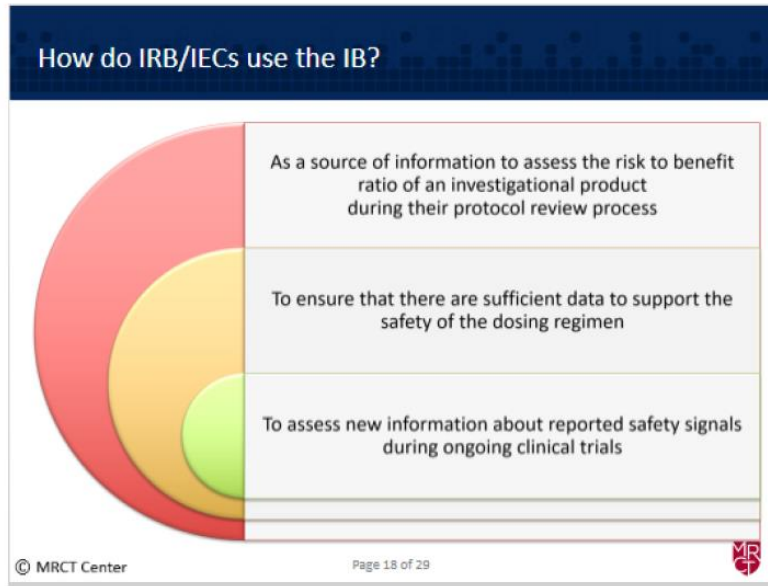
临床研究者应审评研究者手册，评估临床试验用产品的风险收益比，并确保有足够的关于剂量安全性的信息。

研究者将研究者手册提交给 IRB/IEC，作为研究方案审评过程的一部分，并在有新信息时进行审评（通常每年一次，除非提前有重要信息发布）。

研究者应向 IRB/IEC 及时更新患者安全性相关数据，这些数据来自于正在进行的临床试验或非临床研究。

1.18 How do IRB/IECs use the IB?

IRB/IEC 如何使用研究者手册？



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.

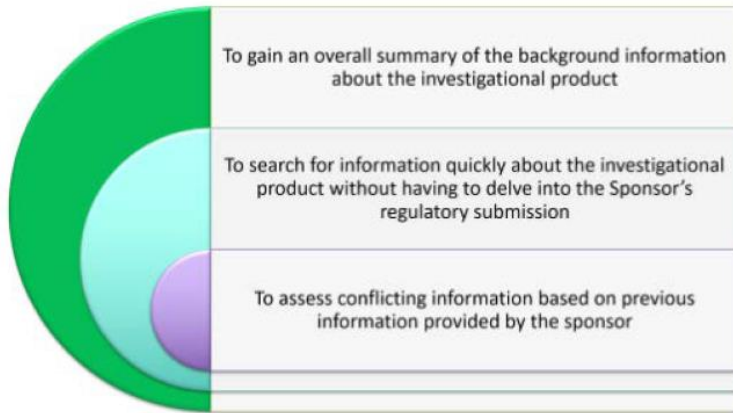
研究者手册允许 IRB/IEC 在研究方案审评过程中评估研究性产品的风险收益比，以确保有足够的证据支持给药方案的安全性。

在正在进行的临床试验中，研究者手册也被用于评估上报的安全信号的新信息。

1.19 How do Regulators Use the IB?

监管者如何使用研究者手册？

How do Regulators Use the IB?



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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.

监管者可以利用研究者手册更好地了解临床试验用药品的安全性和有效性，搜索信息，而不必深入研究申办者的申请材料，并根据申办者以前提供的信息评估相互冲突的信息。

1.20 Summary

总结

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

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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.

综上所述：

- 研究方案和研究者手册是与临床试验相关的基本文件。
- 研究方案是临床试验相关的程序和活动的路线图。
- 研究者手册是关于临床试验用产品的安全性和潜在有效性的现有信息的百科全书。
- 所有利益相关者都会使用研究者手册来了解所有可用信息，以最大限度地保证参与临床研究的受试者的安全。


1.21 Quiz

Quiz



Please
move on
to the
Quiz

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Notes:

Please review and respond to the following questions at your own pace.

When complete, please click Submit.