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国际医疗器械监管机构论坛

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Preface/前言

The document herein was produced by the International Medical Device Regulators Forum (IMDRF), a voluntary group of medical device regulators from around the world. The document has been subject to consultation throughout its development.
本文件由国际医疗器械监管机构论坛(IMDRF)制定，该论坛是由来自世界各地的医疗器械监管机构组成的自愿小组。该文件在制定过程中始终在征求意见。

1.Introduction/引言

What is clinical investigation?
什么是临床试验？

A clinical investigation is defined as "any systematic investigation or study in or on one or more human subjects, undertaken to assess the safety, clinical performance, and/or effectiveness of a medical device". (ISO 14155:2011)
临床试验的定义为"在一例或多例受试者中开展的，用于评价医疗器械的安全性临床性能、和/或有效性的任何系统性的试验或研究"。 (ISO 14155:2011)

The undertaking of a clinical investigation is a scientific process that represents one method of generating clinical data.
临床试验的开展是一个科学的过程，代表了一种产生临床数据的方法。

What is the objective of a clinical investigation?
临床试验的目的是什么？

The objective of a clinical investigation is to assess the safety, clinical performance and/or effectiveness of a medical device for a particular indication or intended use.
临床试验的目的是评价医疗器械在特定适应症或预期用途下的安全性、临床性能、和/或有效性。

How is a clinical investigation conducted?
临床试验是如何开展的？

ISO 14155: 2011 *Clinical Investigation of Medical Devices for Human Subjects — Good clinical practice*-details the requirements for the conduct of clinical investigations. Clinical investigations must take into account scientific principles underlying the collection of clinical data along with accepted ethical standards surrounding the use of human subjects.

ISO 14155: 2011 *适用于人类受试者的医疗器械临床试验—临床试验质量管理规范*—详细说明了开展临床试验的要求。—临床试验必须考虑临床数据收集的科学原理以及围绕受试者使用的公认伦理标准。

This document supersedes an earlier version produced under the Global Harmonization Task Force (GHTF) with the same title in May, 2007 (GHTF/SG5/N3:2010).

本文件取代了全球协调工作组（GHTF）于 2007 年 5 月制作的同一标题的早期版本（GHTF/SG5/N3：2010）。

2. Scope/范围

The primary purpose of this document is to provide guidance in relation to:
本文件的主要目的是提供以下方面的指导：

- when a clinical investigation should be undertaken for a medical device to demonstrate compliance with the relevant Essential Principles (see IMDRF/GRRP WG/N47 FINAL:2018 "*Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices*"); and
- 何时应开展医疗器械的临床试验，以证明其符合相关的基本原则（参见 IMDRF/GRRP WG/N47 FINAL:2018"*医疗器械及体外诊断器械安全性与性能的基本原则*"）；以及

- the general principles of clinical investigation involving medical devices.
- 关于医疗器械临床试验的一般原则。

Given the wide diversity of medical devices and their associated risks, this document is not intended to provide comprehensive guidance for clinical investigations of specific medical devices.
鉴于医疗器械的多样性及其相关风险，本文件不会为特定医疗器械的临床试验提供全面的指导。

The guidance contained within this document is intended to apply to medical devices generally and combination products regulated as medical devices. It is not intended to cover *in vitro* diagnostic medical devices. Additionally, this document was drafted primarily to address the use of Clinical Investigations to support a marketing authorization application. Some aspects of this document may apply to studies conducted following commercial release of a device. Future GHTF documents will specifically address post-market clinical follow-up studies.
本文中包含的指南适用于一般医疗器械和作为医疗器械监管的组合产品。不包括体外诊断器械。此外，本文件的起草主要是为了解决使用临床试验来支持上市授权申请的问题。本文的某些方面可能适用于器械上市后开展的研究。未来的 GHTF 文件将专门针对上市后临床随访研究。

3. Reference/参考文献

IMDRF/GHTF final documents
IMDRF/GHTF 最终文件

GHTF SG1/N011:2008 *Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED)*
GHTF SG1/N011:2008 *证明符合医疗器械安全性与性能基本原则的汇总技术文件 (STED)*

GHTF SG1/N029:2005 *Information Document Concerning the Definition of the Term "Medical Device"*
GHTF SG1/N029:2005 *关于'医疗器械'术语定义的信息文件*

IMDRF GRRP WG/N47 FINAL: 2018 *Essential Principles of Safety and Performance of Medical Devices and IVD Medical Device*
IMDRF GRRP WG/N47 FINAL:2018 *医疗器械及体外诊断器械安全性和性能基本原则*

GHTF SG1/N78:2012 *Principles of Conformity Assessment for Medical Devices*
GHTF SG1/N78:2012 *医疗器械符合性评价原则*

GHTF SG1/N43:2005 *Labelling for Medical Devices*
GHTF SG1/N43:2005 *医疗器械的标签*

IMDRF MDCE WG (PD1)/N57 *Clinical Evidence – Key definitions and Concepts*
IMDRF MDCE WG (PD1)/N57 *临床证据 – 主要定义与概念*

IMDRF MDCE WG (PD1)/N55 *Clinical Evaluation*
IMDRF MDCE WG (PD1)/N55 *临床评价*

International standards/国际标准

ISO 14155 2011 *Clinical investigation of medical devices for human subjects — Good clinical practice*
ISO 14155-2011 *适用于人类受试者的医疗器械临床试验—临床试验质量管理规范*

ISO 14971: 2007 *Medical devices -Application of risk management to medical devices*
ISO 14971: 2007 *医疗器械 -医疗器械风险管理的应用*

Other References/其他参考文献

World Medical Association – Declaration of Helsinki - Ethical principles for medical research involving human subjects
世界医学会–赫尔辛基宣言–涉及人类受试者的医学研究的伦理原则

4. Definitions/定义

Clinical Data: Safety, clinical performance, and/or effectiveness information that is generated from the clinical use of a medical device.
临床数据: 在医疗器械临床使用过程中所产生的安全性，临床性能，和/或有效性的信息。

Clinical Evaluation: A set of ongoing activities that use scientifically sound methods for the assessment and analysis of clinical data to verify the safety, clinical performance, and/or effectiveness of the device when used as intended by the manufacturer.
临床评价: 采用科学合理的方法评价和分析临床数据以验证器械在生产商宣称的预期使用下的安全性、临床性能和/或有效性的一套持续开展的活动。

Clinical Evidence: The clinical data and the clinical evaluation report pertaining to a medical device.
临床证据: 与医疗器械相关的临床数据和临床评价报告。

Clinical Investigation: Any systematic investigation or study in or on one or more human subjects, undertaken to assess the safety, clinical performance, and/or effectiveness of a medical device.
临床试验: 在一例或多例受试者中开展的，用于评价医疗器械安全性、临床性能、和/或有效性的任何系统性的试验或研究。

Clinical Investigation Plan: Document that states the rationale, objectives, design and pre-specified analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation.
临床试验方案: 阐明临床试验的依据、目的、设计及预先设定的分析手段、方法学、监视、执行以及记录保存的文件。

Clinical Performance: The ability of a medical device to achieve its intended purpose as claimed by the manufacturer.

临床性能: 医疗器械实现生产商宣称的预期目的的能力。

Effectiveness: The ability of a medical device to achieve clinical outcome(s) in its intended use as claimed by the manufacturer.

有效性: 医疗器械实现生产商宣称的预期用途下的临床结果的能力。

Safety: Acceptable risks as weighed against benefits, when using the device according to the manufacturer's Instructions for Use.

安全性: 在根据生产商使用说明书使用器械时，与受益相比，风险可接受

Conformity Assessment: The systematic examination of evidence generated and procedures undertaken by the manufacturer, under requirements established by the Regulatory Authority, to determine that a medical device is safe and performs as intended by the manufacturer and, therefore, conforms to the *Essential Principles of Safety and Performance for Medical Devices and IVD Medical Device* (IMDRF GRRP WG/N47 FINAL:2018) .

符合性评价: 由生产商开展的，通过对按照监管机构的要求所生成的证据和过程进行系统性检查，以确定医疗器械是否具有生产商预期的安全性及性能，且因此符合*医疗器械及 IVD 器械安全性和性能基本原则* (IMDRF GRRP WG/N47 FINAL:2018)。

Endpoint: An indicator used for providing the evidence for safety, clinical performance, and/or effectiveness in a clinical investigation (ISO 14155:2011, modified).

终点: 临床试验中提供安全性、临床性能、和/或有效性证据的指标 (ISO 14155:2011, 修订版)。

Multi-Regional Clinical Investigation: A clinical investigation conducted in more than one region under a single protocol.

多区域临床试验:遵循同一方案在一个以上区域开展的临床试验。

Region: A geographical region, country or regulatory region.

区域:某一地理区域、国家或监管区域。

Regulatory Region: A region comprised of countries for which a common set of regulatory requirements applies for medical device approval (e.g., EU).

监管区域: 由对医疗器械批准采用共同监管要求的国家组成的区域(如，欧盟).

Residual Risk: Risk remaining after risk control measures have been taken (ISO 14971:2007).

剩余风险: 实施风险控制措施后仍存在的风险 (ISO 14971:2007)。

Risk Management: Systematic application of management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk (ISO 14971).

风险管理: 将管理政策、程序和实践系统性地应用于对风险的分析、评估、控制和监视(ISO 14971)。

5. General Principles When Considering the Need for a Clinical Investigation/ 考虑需进行临床试验的基本原则

When should a clinical investigation be undertaken?
何时应开展临床试验?

Clinical investigations are necessary to provide data not available through other sources (such as literature or preclinical testing) required to demonstrate compliance with the relevant Essential Principles (including safety, clinical performance and acceptability of benefit/risk associated with its use). When a clinical investigation is conducted, the data obtained is used in the clinical evaluation process and is part of the clinical evidence for the device (see IMDRF MDCE WG (PD1)/N55 "*Clinical Evaluation"*).
当其他数据来源（如文献或非临床实验）不能提供证明符合相关基本原则（包括与器械使用相关的安全性、临床性能及可接受的受益/风险）所需的数据时，必须开展临床试验。当进行临床试验时，获得的数据用于该器械的临床评价过程且作为临床证据的一部分（见 IMDRF MDCE WG (PD1)/N55 *"临床评价"*）

When considering the need for a clinical investigation, one should consider whether there are new questions of safety, clinical performance and/or effectiveness for the particular device and intended use that need to be addressed in a clinical investigation. Generally, such questions are more likely to be generated for high risk and/or novel devices.
在考虑是否需开展临床试验时，应考虑对于特定器械及预期用途是否存在需在临床试验中解决的安全性、临床性能和/或有效性的新问题。通常，此类问题更多见于高风险和/或创新器械。

For long established technologies, the clinical investigation data that might be required for novel technologies may not be necessary. The available clinical data in the form of, for example, published literature, reports of clinical experience, post-market reports and adverse event data may, in principle, be adequate to establish the safety, clinical performance, and/or effectiveness of the device, provided that new risks have not been identified, and that the intended

use(s)/purpose(s) has/have not changed.对创新技术可能会被要求的临床试验数据，对于成熟技术则可能不是必须的。已有的临床数据，诸如已发表的文献、临床经验报告、上市后报告和不良事件数据，可能在原则上已足够用于确认产品的安全性、临床性能、和/或有效性，证明未识别新的风险，且预期用途/目的并未改变。

What are the key considerations in clarifying the need for clinical investigations?
明确是否需要开展临床试验的主要考量是什么

1. Identifying relevant clinical **Essential Principles** (for example, specifics of safety, clinical performance, acceptability of benefit/risk) for the device and its intended use/purpose(s) (see IMDRF/GRRP WG/N47 FINAL:2018-*Essential Principles of Safety and Performance of Medical Devices and IVD Medical Device*);
1. 识别器械及其预期用途/目的的相关临床**基本原则**（例如，安全性、临床性能、受益/风险的可接受性）（参见 IMDRF/GRRP WG/N47 FINAL:2018 *医疗器械和 IVD 医疗器械安全和性能的基本原则*）；

2. Performing **risk management** (ISO 14971:2007) activities such as a risk analysis will help in identifying the clinical data necessary to address residual risks and aspects of clinical performance not completely resolved by available information (e.g. design solutions, preclinical and material/technical evaluation, conformity with relevant standards, labelling).
2. 执行如风险分析等**风险管理**（ISO 14971:2007）措施将有助于识别必要的临床数据，以解决剩余风险和临床性能方面未能通过现有信息（如方案设计，临床前和材料/技术评价，所符合相关标准，标签）完全解决的问题。

   Risk control measures include inherent safety by design, protective measures in the medical device itself or in the manufacturing process, and information for safety. The decision to use a medical device in the context of a clinical procedure requires the residual risk to be balanced against the anticipated benefits of the procedure. A clinical investigation may be required to further elucidate the benefit/risk in a defined patient population;
   风险控制措施包括产品设计带来的固有安全性、医疗器械本身或制造过程中的保护措施、以及产品安全性信息。决定在临床程序中使用医疗器械需将剩余风险与该程序的预期受益相平衡。可能需要临床试验以进一步阐明特定患者群体中的风险/受益;

3. Conducting a proper **clinical evaluation** will demonstrate which clinical data are necessary, and can be adequately contributed to by sources such as literature searching,

prior clinical investigations (including clinical data generated in other jurisdictions), clinical experience, or clinical data available from comparable devices, and which clinical data should be generated from clinical investigation(s) when data are unavailable or insufficient to demonstrate conformity to the Essential Principles. Available clinical data from comparable devices should be carefully examined for comparability and adequacy (see IMDRF MDCE WG (PD1)/N55 *Clinical Evaluation).*

3. 进行适当的**临床评价**将证明哪些临床数据是必要的，且可以通过文献检索、已完成的临床试验（包括在其他司法管辖区产生的临床数据）、临床经验数据、或来自对比器械的临床数据等来源为临床评价提供充分数据。当数据缺乏或不足以证明符合基本原则时，相应临床数据应从临床试验中产生。应谨慎评价来自对比器械的可用临床数据的可比性和充分性（参见 IMDRF MDCE WG (PD1)/N55 *临床评价*）。

Key considerations for clarifying the need for clinical investigations are illustrated by the flowchart in Figure 1.
图 1 中的流程图展示了明确是否需要开展临床试验的主要考虑因素。

Where uncertainty exists as to whether current data are sufficient to demonstrate conformity with the Essential Principles, discussion with the relevant regulatory authorities or conformity assessment bodies may be appropriate.
如果现有数据是否足以证明符合基本原则存在不确定性，则可能需要与相关监管机构或符合性评价机构进行讨论。

Note: This exercise is applicable for the introduction of a new device as well as for planned changes of a device, its intended use and/or claims.
注意：这一流程适用于引入新器械以及计划性的器械的预期用途和/或宣称的变更。

6. General Principles of Clinical Investigation Design/ 临床试验设计的一般原则

Any clinical investigation must:
任何临床试验必须：

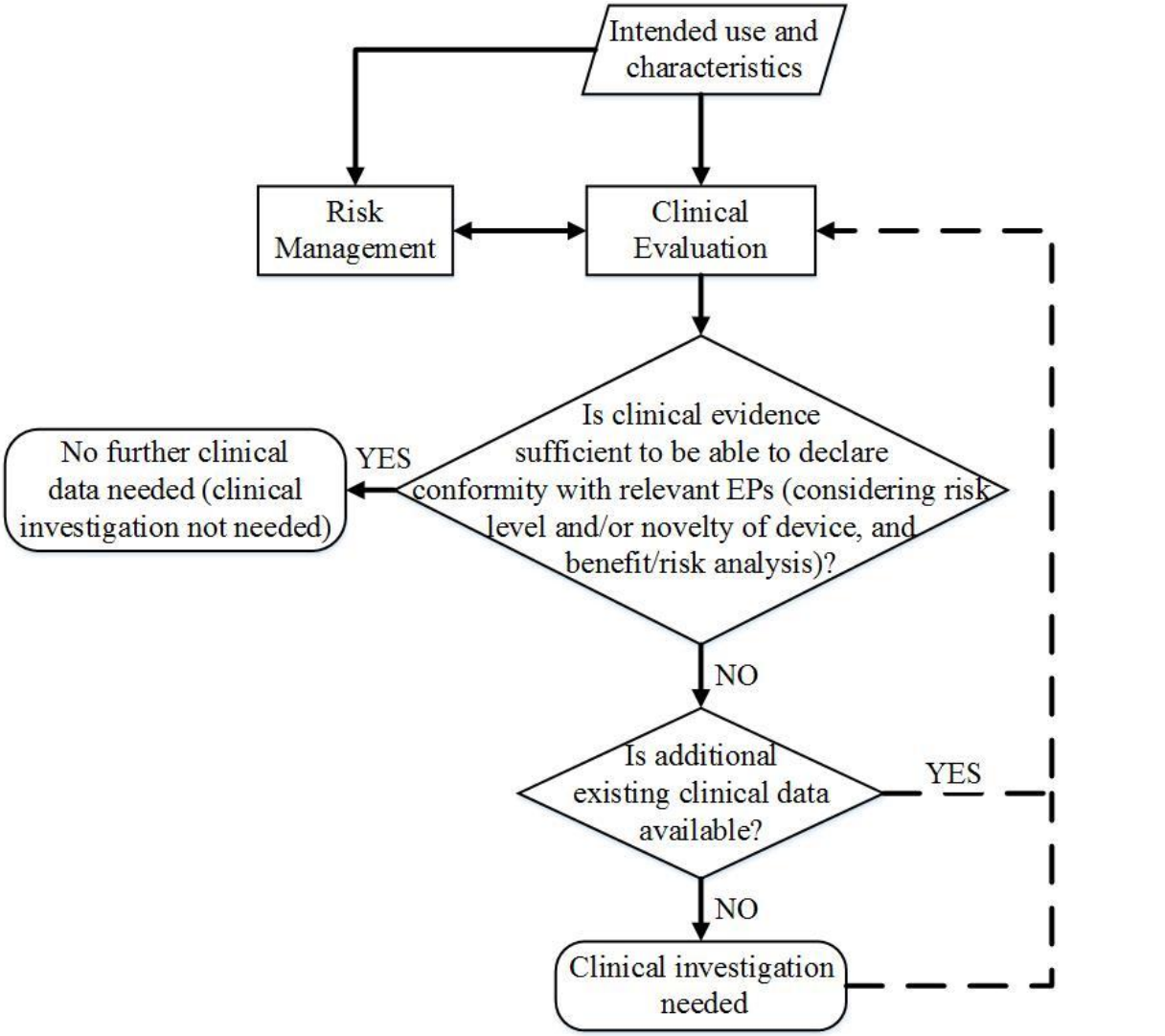
- be based on the results of the clinical evaluation process;
- 基于临床评价过程的结果;
- follow a proper risk management procedure to avoid undue risks;

- 遵循适当的风险管理程序，以避免不合理的风险;
- be compliant with all relevant legal and regulatory requirements;
- 遵守所有相关的法律和监管要求;
- be appropriately planned, conducted, analysed and reported;
- 进行适当的计划，实施，分析和报告;
- follow appropriate ethical principles (see Section 7).
- 遵循适当的伦理原则（参见第 7 节）。

The design of the clinical investigation, including the study objectives and statistical considerations, should provide the clinical data necessary to address the residual risks, including 临床试验的设计，包括研究目标和统计考虑，应提供解决剩余风险所必需的临床数据，包括临床性能方面。可能影响数据要求程度的一些因素包括但不限于以下内容：

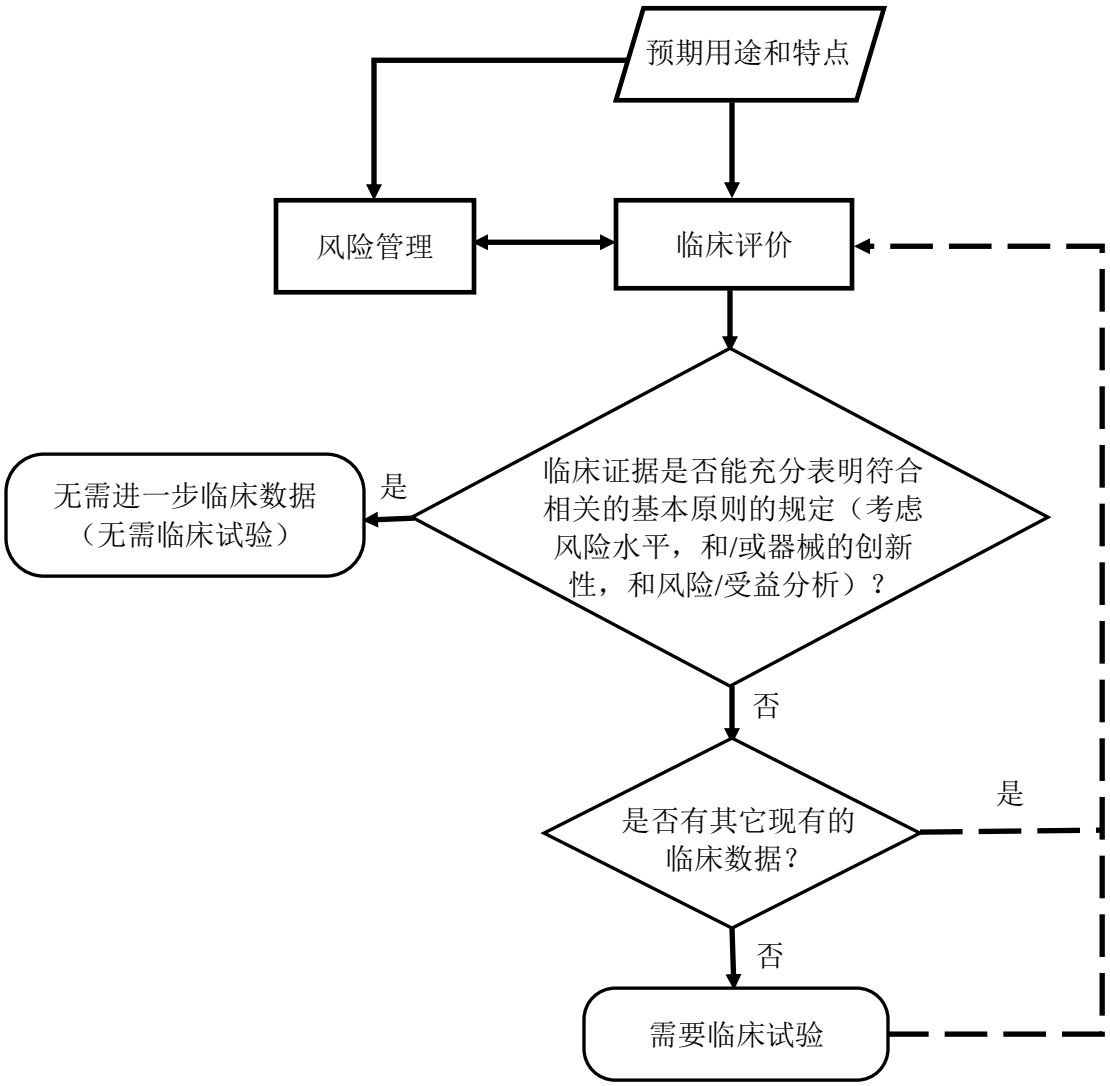
- type of device and/or regulatory classification;
- 器械类型和/或监管分类
- novel technology/relevant previous experience;
- 新技术/相关的先前经验
- clinical application/indications;
- 临床应用/适应症
- nature of exposure to the product, e.g.: surface contact, implantation, ingestion;
- 器械与人体的接触方式，例如：表面接触，植入，吸收；
- risks inherent in the use of the product, e.g.: risk associated with the procedure;
- 产品使用中固有的风险，例如：与过程相关的风险；
- performance claims made in the device labeling (including instructions for use) and/or promotional materials;
- 器械标签（包括说明书）和/或宣传材料中的性能宣称；
- component materials or substances;
- 组成材料或成分；
- disease process (including severity) and patient population being treated;
- 疾病过程（包括严重程度）和正在接受治疗的患者人群；
- demographic, geographic and cultural considerations (e.g.: age, ethnicity, gender, etc.);
- 人口学、地理和文化方面的考虑（例如：年龄，种族，性别等）；
- potential impact of device failure;
- 器械故障的潜在影响；
- period of exposure to the device;
- 器械与人体接触时间；

- expected lifetime of the device;
- 器械的预期使用寿命；
- availability of alternative treatments and current standard of care; and
- 可用的替代治疗和现行的标准治疗；以及
- ethical considerations.
- 伦理考量。



EPs = Essential Principles of safety and performance of medical devices;
* - Conformance to performance standards may be sufficient to demonstrate compliance to relevant Essential Principles.

Figure 1 Key considerations for clarifying the need for clinical investigations



基本原则 = 医疗器械的安全性与性能的基本原则;
*–符合于性能标准可能能够充分地证明遵从相关的基本原则

图 1 明确是否需要开展临床试验的关键考虑因素

Considerations for Device Study Protocols/器械试验方案的注意事项

Factors needing consideration in study protocols include:
试验方案中需要考虑的因素包括：

- clear statement of objectives
- 明确的试验目的
- primary and secondary endpoints, or composite endpoints if applicable

- 主要和次要终点，或复合终点，如适用
- appropriate subject population(s)
- 适当的受试者人群
- minimization of bias (e.g., randomization, blinding/masking, concealment of allocation)
- 最小化偏倚（例如：随机化，盲法，随机分配方案隐藏）
- identification of confounding factors (e.g., concurrent medications, co-morbidities)
- 识别混杂因素（例如：合并用药，合并症）
- choice of appropriate controls (e.g., active control, sham, historical), where necessary
- 选择适当的对照（例如：阳性对照，假手术，历史对照），如必要
- design configuration (e.g., parallel, crossover, cohort study, single arm)
- 设计类型（例如：平行，交叉，队列研究，单臂）
- type of comparison (e.g., superiority, non-inferiority, equivalence)
- 检验类型（例如：优效性，非劣效性，等效性）
- follow-up duration and monitoring, where necessary
- 随访时间和监查，如必要

In designing the study, statistical considerations should be prospectively specified and be based on sound scientific principles and methodology. Care must be taken in developing a statistical plan that includes consideration of, for example, the following:
在设计试验时，应该前瞻性地规定统计学要求，并以科学合理的原理和方法为基础。必须谨慎的制定统计计划，考虑诸如以下因素：

- clinically relevant endpoints
- 临床相关终点
- analysis population (e.g. intention-to-treat, per-protocol)
- 分析人群（例如：意向性治疗人群，符合方案人群）
- statistical significance levels, power
- 统计学显著性水平，把握度
- sample size calculation and justification
- 样本量计算和依据
- analysis methodology (including sensitivity analyses)
- 分析方法（包括敏感性分析）
- accounting for learning curve or run-in issues
- 考虑学习曲线和导入期问题
- the provision for an interim analysis, where applicable
- 中期分析的条件，如适用

- management of potential confounding factors (e.g. adjustment, stratification or stratified randomization)
- 管理潜在的混杂因素（例如：调整，分层和分层随机化）
- describe procedures for multiplicity control and adjustment of error probabilities, if applicable
- 描述多重控制和错误概率调整的程序，如适用
- the specification of subgroups for analysis, if applicable
- 对亚组分析的要求，如适用
- the handling of missing, unused or spurious data, including drop-outs
- 对缺失、未使用、和虚假数据的处理，包括脱落
- procedures for reporting any deviation(s) from the original statistical analysis plan
- 报告对原始统计分析计划任何偏离的程序

The design should ensure that the statistical evaluation derived from the investigation reflects a meaningful, clinically significant outcome.
试验设计应确保基于试验进行的统计评估能反映有意义的、具有临床显著性的结果。

Multi-regional clinical investigation designs may be considered to facilitate more efficient medical device development, thus providing earlier access to new medical devices worldwide. For multi-regional clinical investigation designs, the potential differences between two or more regions that might affect study results should be carefully considered.
可以考虑多区域临床试验设计以促进更有效的医疗器械的开发，从而促进全球更早获得新的医疗器械。对于多区域临床试验设计，应谨慎考虑可能影响试验结果的两个或多个区域之间的潜在差异。

Discussion with the relevant regulatory authorities or conformity assessment bodies may be appropriate when there is uncertainty as to whether the proposed clinical investigational plan is sufficient.
当不确定临床试验方案是否充分时，与相关监管机构或符合性评价机构进行讨论可能是适当的。

Conduct of Clinical Investigations/临床试验的实施

A properly conducted clinical investigation, including compliance to the clinical investigation plan and local laws and regulations, ensures the protection of human subjects, the integrity of the data and that the data obtained is acceptable for the purpose of demonstrating conformity to the

Essential Principles. ISO 14155 outlines good clinical practice for clinical investigations of medical devices.
开展一项高质量的临床试验，应符合临床试验方案和当地法律法规，确保对人类受试者的保护，数据的完整性以及获得数据可被用于证明符合基本原则。 ISO 14155 概述了医疗器械临床试验的临床试验质量管理规范。

Final Study Report/最终的试验报告

The outcome of a clinical investigation should be documented in a final study report. This then forms part of the clinical data that is included in the clinical evaluation process and ultimately becomes integrated into the clinical evaluation report (see IMDRF MDCE WG (PD1)/N55 Clinical Evaluation) for the purposes of conformity assessment.
临床试验的结果应记录在最终试验报告中。这构成临床评价程序中所包含的临床数据的部分，并最终纳入临床评价报告（参见 *IMDRF MDCE WG (PD1)/N55 临床评价*），以达到一致性评定的目的。

7. Ethical Considerations for Clinical Investigations/临床试验伦理考量

As a general principle, "the rights, safety and wellbeing of clinical investigation subjects shall be protected consistent with the ethical principles laid down in the Declaration of Helsinki" and the applicable regulatory requirements or other relevant standards (ISO 14155:2011).
作为一般原则，"对临床试验受试者权利、安全和福祉的保护应符合赫尔辛基宣言中规定的伦理原则"和适用的监管要求或其他相关标准（ISO 14155:2011）。

It is ethically important in deciding to conduct a clinical investigation that it should generate new data and answer specific safety, clinical performance, and/or effectiveness questions that remain unanswered by the current body of knowledge. The desire to protect human subjects from unnecessary or inappropriate experimentation must be balanced with the need to protect public health through the use of clinical investigations where they are indicated. In all cases, however, care must be taken to ensure that the necessary data are obtained through a scientific and ethical investigational process that does not expose subjects to undue risks or discomfort. The rights, safety and well-being of subjects are paramount, and appropriate trial design and conduct is essential to generate meaningful data.

在决定进行临床试验时，它应该生成新数据并回答当前知识体系尚未解答的特定安全性、临床性能和/或有效性问题，这在伦理上具有重要意义。保护人类受试者免受不必要或不适当试验的愿望必须与保护公共健康的需求相平衡，即在需要的地方开展临床试验。但是，在任何情况下，都必须注意确保必要的数据是通过科学及符合伦理的试验过程获得的，这些过程不会使受试者面临不适当的风险或不适。受试者的权利、安全和福祉是至关重要的，适当的试验设计和实施对于获得有意义的数据至关重要。