# Impact of the new versions of the Declaration of Helsinki, ICH E6 R3 and WHO guidance for the conduct of clinical trials

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# Conflict of Interest Statement

- The presenter is :
- The Immediate Past President of the International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine - IFAPP and current IFAPP Executive Board Member
- Executive Committee Member of the Council of International Organisations of Medical Sciences -CIOMS
- There are no commercial or financial interests of the presenter or the associations in the work to be presented.

# Outline

DECLARATION OF HELSINKI ,10TH REVISION 2024

ICH GCP E6 R3 REVISION 2025

WHO BEST PRACTICES FOR CLINICAL TRIALS GUIDANCE 2024

WMA

- Declaration of Helsinki (10th Rev. October 2024)
- Ethical principles for medical research involving humans.
- Broad: all medical research involving human participants.

ICH

- ICH E6(R3) (2025)
- Harmonize Good Clinical Practice (GCP) for regulatory trials of investigational products
- Focused: investigational product trials for regulatory submission.

WHO

- WHO 2024 Best Practices in Clinical Trials
- Provide global, equitable guidance for ethical and scientifically sound trials, especially in LMICs.
- Broad: includes public health emergencies, non-commercial trials, and implementation research.

# Important International Organisations for Clinical Trials

WMA* Declaration of Helsinki (DoH): High Level Ethical Principles

CIOMS**Guidelines : Implementation Guidelines on Health Research ,Policies & Ethics

ICH*** Documents : Regulatory Standards by the regulatory authorities and pharmaceutical industry

*WMA: World Medical Association
**Council for International Organizations of Medical Sciences (CIOMS)
***International Conference Harmonisation (ICH)

# Declaration of Helsinki

- This  is the World Medical Association's (WMA) best-known policy statement.
- The first version was adopted in 1964 and has been amended several times since, **most recently at the General Assembly in October 2024.**
- The current 10th version is the **only official one**; all previous versions* have been replaced and should not be used or cited except for historical purposes.
- In 2024, the WMA produced a celebratory publication to mark the **60th anniversary of the adoption of the Declaration of Helsinki.**
- Since 2016, the Declaration of Taipei on Ethical Considerations regarding Health Databases and Biobanks has complemented the Declaration of Helsinki.

Declaration of Helsinki
10th Revision:

# Ethical Standards for Strengthening Clinical Research involving Humans

## Process supported by public consultations

- It was **a mammoth revision process spanning 30 months,** and the World Medical Association extends its heartfelt thanks to everyone who participated," **Dr Ashok Philip, President of the World Medical Association.**
- "The new version of the Declaration says that as physicians, **it's part of our moral obligation to ensure that our patients and the participants in research are respected and treated with dignity," said Dr Jack Resneck Jr.**

# Declaration of Helsinki 10th Revision: Eight Regional Meetings in preparation of DoH

- Tel Aviv: Implications of Big Data, Machine Learning, AI **(IFAPP delegation onsite)**
- São Paulo: Ethical Considerations on Use of Placebo (IFAPP delegation online)
- Copenhagen: Emerging Trial Designs **(IFAPP delegation onsite )**
- Tokyo: Research During Public Health Emergencies **(IFAPP delegation onsite)**
- Vatican: Research in Resource-Poor Settings, Global Justice (IFAPP delegation online)
- Johannesburg: Community Inclusiveness, Post-Trial Access, Vulnerability (IFAPP delegation online)
- Munich: Specific and Particularly Vulnerable Groups (IFAPP delegation online)
- Washington, DC: Final Consolidation **(IFAPP delegation onsite)**

# IFAPP proposed changes to the 10th Revision of the DoH

- 1. Connection of Declaration of Helsinki (DoH) & Declaration of Taipei (DoT) – included
- 2. Ethical approval & consent for secondary use of data- included
- 3. Incidental findings- not included
- 4. Registration of "data sharing plan" and study results in public databases- included
- 5. Shared responsibility- included
- 6. Patient & Public involvement plan - pending
- 7. Diversity of membership & qualified experience of Research Ethics Committees (REC)-included
- 8. Terminology aspects of human subjects & humans, participants, instead of human subjects - included.
- 9. Medical research for common nomenclature between organisations- included
- 10. Placebo use wording & alignment of wording CIOMS & WMA (paragraph 33 DoH)- not achieved
- 11. Vulnerable population – included
- 12. Post-trial access –not totally clarified –partly arranged

# Substantive changes of the Declaration of Helsinki by WMA

- The **substantive changes** to the Declaration of Helsinki can be categorised in two areas:
- **Participant-centered inclusion, respect and protection**, including recognition of **participant vulnerability**, calls for **community engagement**, pursuit of **global justice**, obtaining **informed consent**, and use of **participant-centered language**.
- **Research beneficence and value**, including the pursuit of "**individual and public health**", upholding **scientific rigor** and **integrity**, and considered **distribution of benefits, risks and burdens.**

# Key Positive Changes of the Declaration of Helsinki

Reprint from the Helsinki Statement
http://cont.o.oo7.jp/52pop/52pop_contents_e.html
Kurihara C ,Matsuyama K., Baroutsou V.

- Throughout the Declaration, the words "research subjects" are replaced with **"research participants".**
- Although the recommendations are directed to **physicians,** their scope should be also applied to non-physi**cians, research teams and organizations. (§2*)**
- In recognition of "various structural inequalities" in research, considerations on **benefits, risks, and burdens must be reinforced**. (§6)
- **Meaningful engagement with participants and their communities** is fundamental and should be required at all stages of the research. (§6)
- The principles of the Declaration must also be upheld during **public health crises**. (§8)
- The contextual and **dynamic nature of vulnerability** must be recognized and it is important to emphasise that the exclusion of vulnerable can exacerbate their disparities. Therefore, their inclusion in research aiming at their benefit must be promoted, with adequate protection. (§19, 20)
- The functions of **research ethics committees have been strengthened. And the committee must be familiar with the local context and involve at least one member of the general public**. (§23)
- The **preferences and values of incapable research participants shall be considered** during the process of deciding to participate in research. (§28, 29)
- Data or specimens from research shall be handled in **accordance with the "Declaration of Taipei"** on Health Databases and Biobanks. (§32)
- Clinical use of **unproven intervention must never be undertaken to circumvent the protection** set forth in the DoH, and must be the **object of research to evaluate safety and efficacy. (§37)**

The significant revisions to the 2024 DoH are not fully described here, but can be found on the WMA website :https://www.wma.net/policiespost/wma-declaration-of-helsinki/

# Key Challenges of the Declaration of Helsinki-2

Reprint from the Helsinki Statement
http://cont.o.oo7.jp/52pop/52pop_contents_e.html
Kurihara C ,Matsuyama K., Baroutsou V.

- Lack of a **plain language version** that is understandable to **research participants.**
- Thus, **social value must be reinforced in order to implement relevant research and also to ensure that benefits are shared through co-creation with community.**
- **The use of placebo in clinical trials can only be acceptable when there is no proven effective and safe comparator**. This was stated in the 2000 DoH, in accordance with DoH's fundamental principle that the purpose of research "*never takes precedence*" over the rights and interests of individual participants which is not so clearly stated in the current version.
- The 2008 DoH accepted level of risk to the participant was kept in the DoH 2024 ,despite it is higher than CIOMS' latest update with greater patient involvement & contextualized minimal risk tolerance

- **At the end of the trial, research participants who still need interventions that have been shown to be safe and effective must have access to them ensured by the sponsor(s).**
- The **2024 DoH post trial access is a lot weaker than the 2000 one in relation to participant rights., since** it just says that it must be "arranged"(§ 34).
- **The timely dissemination of research results and technology transfer of the products of research involving humans must be recognised as public goods**, so that **transparency is ensured and everyone can have fair and equitable access to the research results and benefits**.

- **2024 DoH in §33, placebo can be used, even if there is proven intervention, when the participant "will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention**".

The significant revisions to the 2024 DoH are not fully described here, but can be found

on the WMA website at :https://www.wma.net/policiespost/wma-declaration-of-helsinki/

# The Declaration of Helsinki Evaluations from NHS

- **Terminology update**: the term "subjects" has been replaced with **"participants"** throughout the document to respect the rights and agency of individuals involved in research. Gender-neutral language has also been adopted.
- **Inclusive applicability**: the Declaration now **addresses all individuals, teams**, and organisations involved in medical research**, not just physicians.** This change acknowledges the interdisciplinary nature of modern research and holds all researchers to the same ethical standards.
- **Participant engagement**: new provisions emphasise **meaningful engagement with research participants and their communities before, during, and after studies. This recognises participants as partners in the research process.**
- **Distributive and global justice**: researchers are now called upon to carefully consider **how the benefits, risks, and burdens of research are distributed, addressing issues of equity and justice on a global scale.**
- **Vulnerability and inclusion**: significant revisions acknowledge that **vulnerability is contextual and dynamic.** The Declaration promotes fair and responsible inclusion of vulnerable populations**, balancing the harms of inclusion and exclusion while** providing adequate support.

World Medical Association announces adoption of the 2024 Revision of the Declaration of Helsinki - Health Research Authority

# The Declaration of Helsinki Evaluations from NHS-2

- **Protections for vulnerable groups**: specific protections remain for **particularly vulnerable individuals** (e.g., incarcerated persons or those unable to consent), including requirements **that research address their health needs and that they benefit from the outcomes.**
- **Data and biobanking**: paragraph 32 has been rewritten to address **informed consent for the collection, processing, storage, and secondary use of biological materials and data.** It also recognises situations where obtaining consent for unforeseen secondary research is impracticable, requiring ethics committee approval in such cases.
- **Reference to Declaration of Taipei**: the updated Declaration cross-references the WMA Declaration of Taipei, providing detailed guidelines on the governance of **health databases and biobanks, especially for data collected for multiple and indefinite uses.**
- **Public health emergencies**: a new paragraph asserts that ethical principles must be fully upheld even during public health emergencies**, emphasising that urgency should not compromise ethical standards**.
- World Medical Association announces adoption of the 2024 Revision of the Declaration of Helsinki - Health Research Authority

# The Declaration of Helsinki Evaluations from NHS-3

- **Unproven interventions**: revisions clarify the use of unproven interventions aimed at alleviating suffering, ensuring they are **not used to bypass ethical protections or evade rigorous clinical trials.**
- **Environmental sustainability and research integrity**: modifications strengthen commitments **to environmental sustainability, promote rigorous study designs to prevent research waste, and underscore the importance of scientific integrity**.
- **Ethics committees**: the Declaration now insists on **sufficient resources and strengthened independence for research ethics committees to ensure they can effectively oversee research practices.**
- **Participant preferences**: new language calls for considering participants**' previously expressed preferences and values when consent is obtained from legally authorised representatives on their behalf.**

World Medical Association announces adoption of the 2024 Revision of the Declaration of Helsinki - Health Research Authority

# Declaration of Helsinki

This Issue | Views 6,309 | Citations 7 | Altmetric 192 | Comments 2

**Viewpoint** | Integrating Clinical Trials and Practice

June 20, 2024

## Protecting Participants Is Not the Top Priority in Clinical Research

Jerry Menikoff, MD, JD[1]

Author Affiliations

JAMA. 2024;332(3):195-196. doi:10.1001/jama.2024.7677

The Declaration of Helsinki,[1] adopted 60 years ago by the World Medical Association, is widely viewed as "t
nerstone' document pertaining to medical research ethics."[2] Yet it endorses a core premise that is wildly inc
with the long-accepted understanding of the ethics of research with human participants. Its endorsement o
premise has real consequences that are harmful to the ability to conduct research ethically. It is long overdu
that position to change. And there is now a particular opportunity to make that change: the World Medical
Association is currently engaged in a procedure to revise the declaration.

https://jamanetwork.com/journals/jama/article-abstract/2820280

- "What's Our First Priority in Clinical Research: Generating Data or Protecting Participants?".
- When we conduct clinical trials, what should our primary goal be?

# Declaration of Helsinki

Is it about ensuring the safety and protection of research participants and the optimisation of their outcomes?

Or, as others argue, is it the collection of scientifically sound data that we can use to make evidence-based medical decisions for future patients - even if this means that individual research participants may not have the best outcomes?

# Clinical Trials Regulations & ICH Guidelines

IFAPP contributed to EMA, ICH and WHO public consultations

V.Baroutsou DoH, ICH E(6) R(3),WHO Best Practices for Clinical Trials

**Regulations**

***EU : EMA & EC CTR, MDR***

*Cited, together with SOPs, by inspectors & auditors*

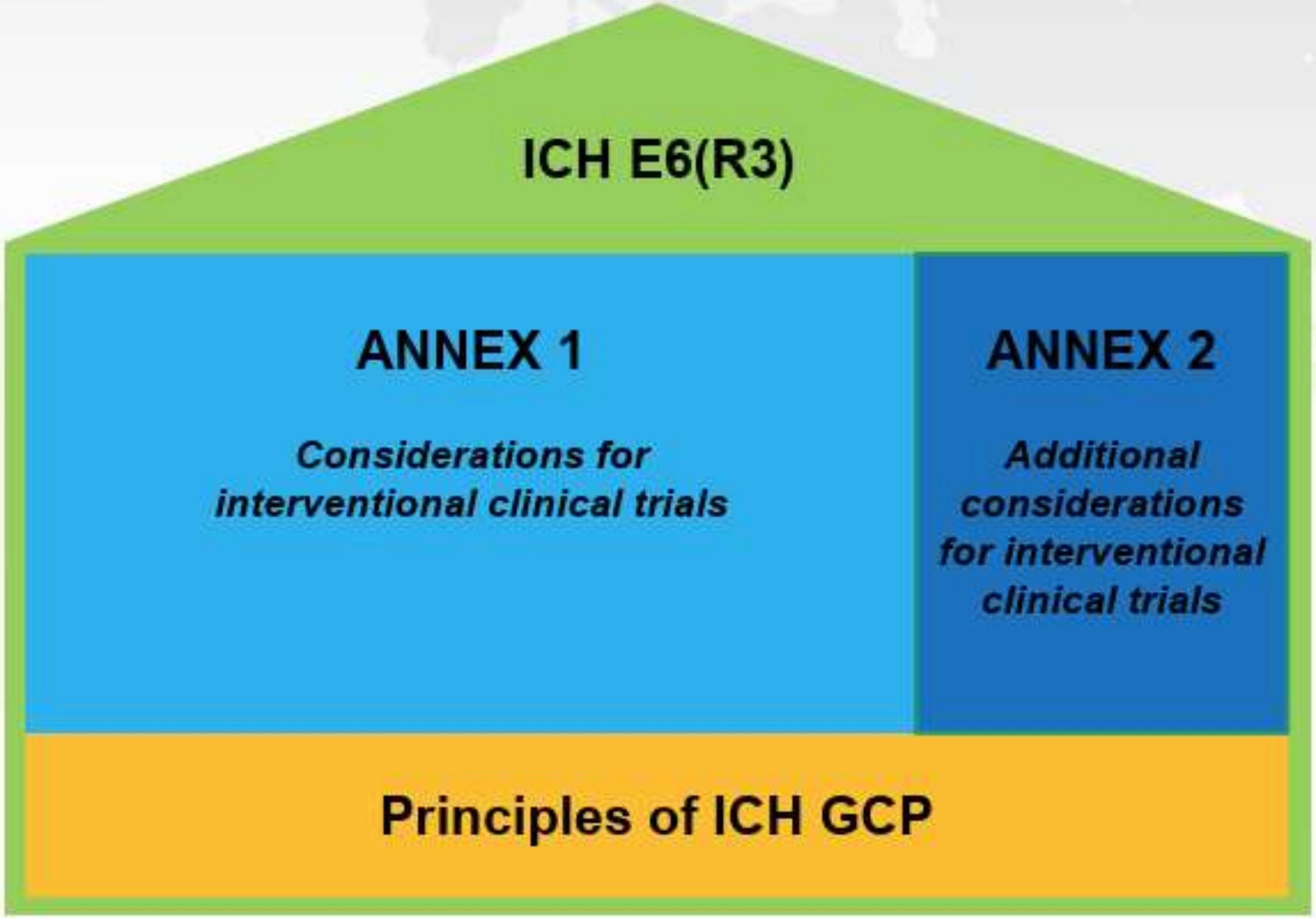
**Guidelines**

*Current thinking, not recipes*

*FDA, EMA, MHRA, PMDA etc*

*ICH, WHO*

# OVERVIEW OF ICH E6(R3)



ICH E6(R3)

**ANNEX 1**

*Considerations for interventional clinical trials*

**ANNEX 2**

*Additional considerations for interventional clinical trials*

**Principles of ICH GCP**

# ICH GCP E6 (Revision 3)
## New structure

**I. INTRODUCTION**

**II. PRINCIPLES OF ICH GCP**

**III. ANNEX 1**

1. Institutional Review Board/Independent Ethics Committee (IRB/IEC)
2. Investigator
3. Sponsor
4. Data Governance – Investigator and Sponsor

**GLOSSARY**

**APPENDICES**

Appendix A. Investigator’s Brochure
Appendix B. Clinical Trial Protocol and Protocol Amendment(s)
Appendix C. Essential Records for the Conduct of a Clinical Trial

# ICH GCP E6 (R3)
# II. Principles of GCP

| ICH E6 (R3) PRINCIPLE | TOPIC | ICH E6 (R2) REF |
|---|---|---|
| 1 | Ethical Principles | 2.1, 2.2, 2.3, 2.7, 2.11 |
| 2 | Informed Consent | 2.9 |
| 3 | IRB/IEC Review | 2.6 |
| 4 | Science | 2.4, 2.5 |
| 5 | Qualified Individuals | 2.8 |
| 6 | Quality | 2.13 |
| 7 | Risk Proportionality | N/A |
| 8 | Protocol | 2.5 |
| 9 | Reliable Results | 2.10 |
| 10 | Roles and Responsibilities | N/A |
| 11 | Investigational Products | 2.12 |

# Data Governance (New)
# Annex 1.4

| ICH E6 (R3) Section | ICH E6 (R2) Ref. |
|---|---|
| 4.1 – Safeguard Blinding in Data Governance | NA – Major Revamp |
| 4.2 – Data Life Cycle Elements | |
| 4.3 – Computerised Systems | |
| 4.4 – Security of Computerised Systems | |
| 4.5 – Validation of Computerised Systems | |
| 4.6 – System Failure | |
| 4.7 – Technical Support | |
| 4.8 – User Management | |

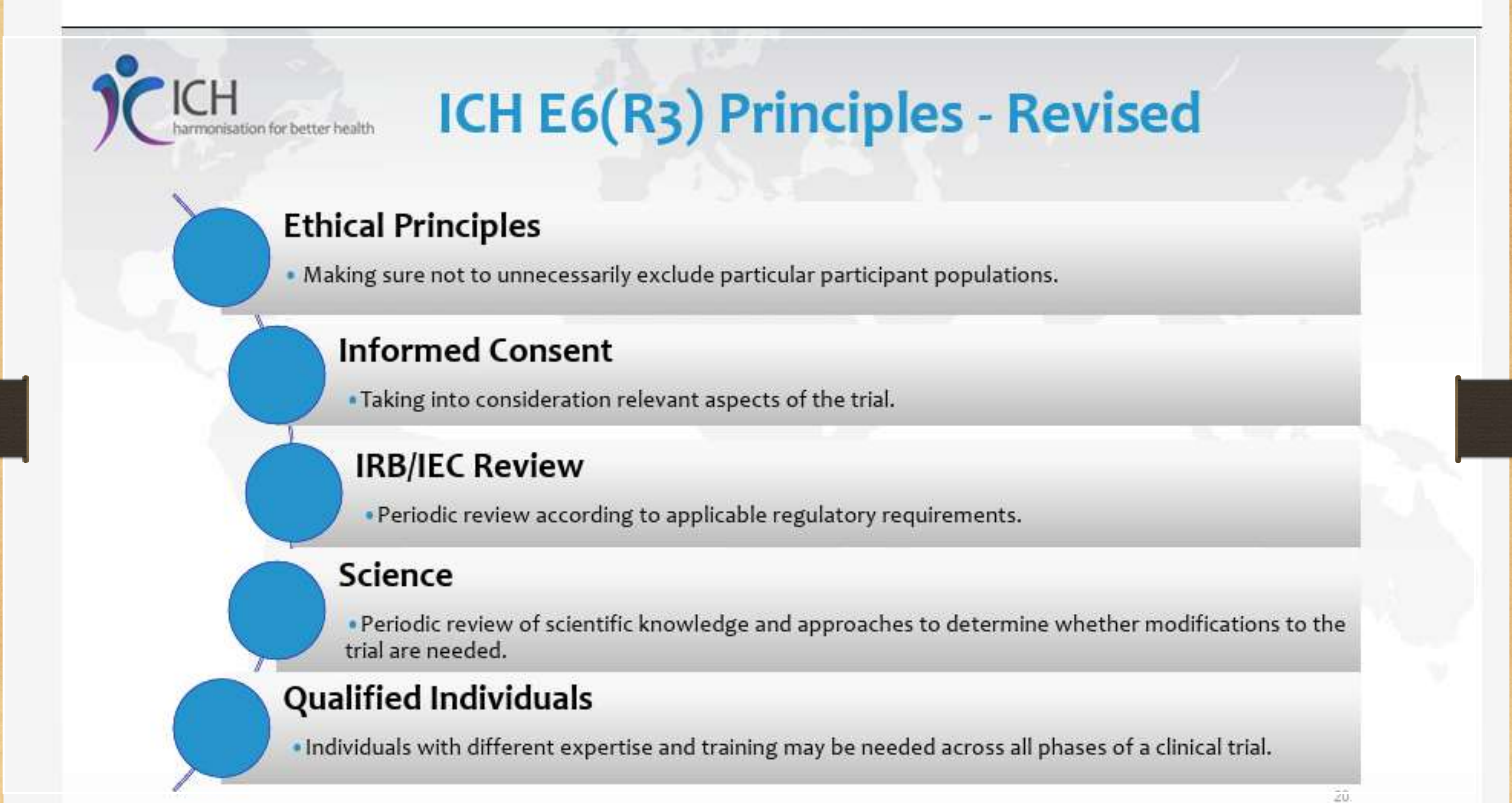
# ICH E6(R3) Principles - New

## Proportionality, risk-based

- Focus on participant's safety and reliability of results.
- Focus on the risks associated with trial participation.
- Focus on risks beyond those associated with usual medical care for clinical trials involving patients.

## Roles and Responsibilities

- Clarification of transfer of activities by the Sponsor and delegation by the Investigator.
- Maintenance of appropriate oversight.



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harmonisation for better health

# ICH E6(R3) Principles - Revised

**Ethical Principles**
- Making sure not to unnecessarily exclude particular participant populations.

**Informed Consent**
- Taking into consideration relevant aspects of the trial.

**IRB/IEC Review**
- Periodic review according to applicable regulatory requirements.

**Science**
- Periodic review of scientific knowledge and approaches to determine whether modifications to the trial are needed.

**Qualified Individuals**
- Individuals with different expertise and training may be needed across all phases of a clinical trial.

# ICH E6(R3) Principles – Revised (2)

**Quality**

- The quality and amount of the information generated should support good decision making.

**Protocol**

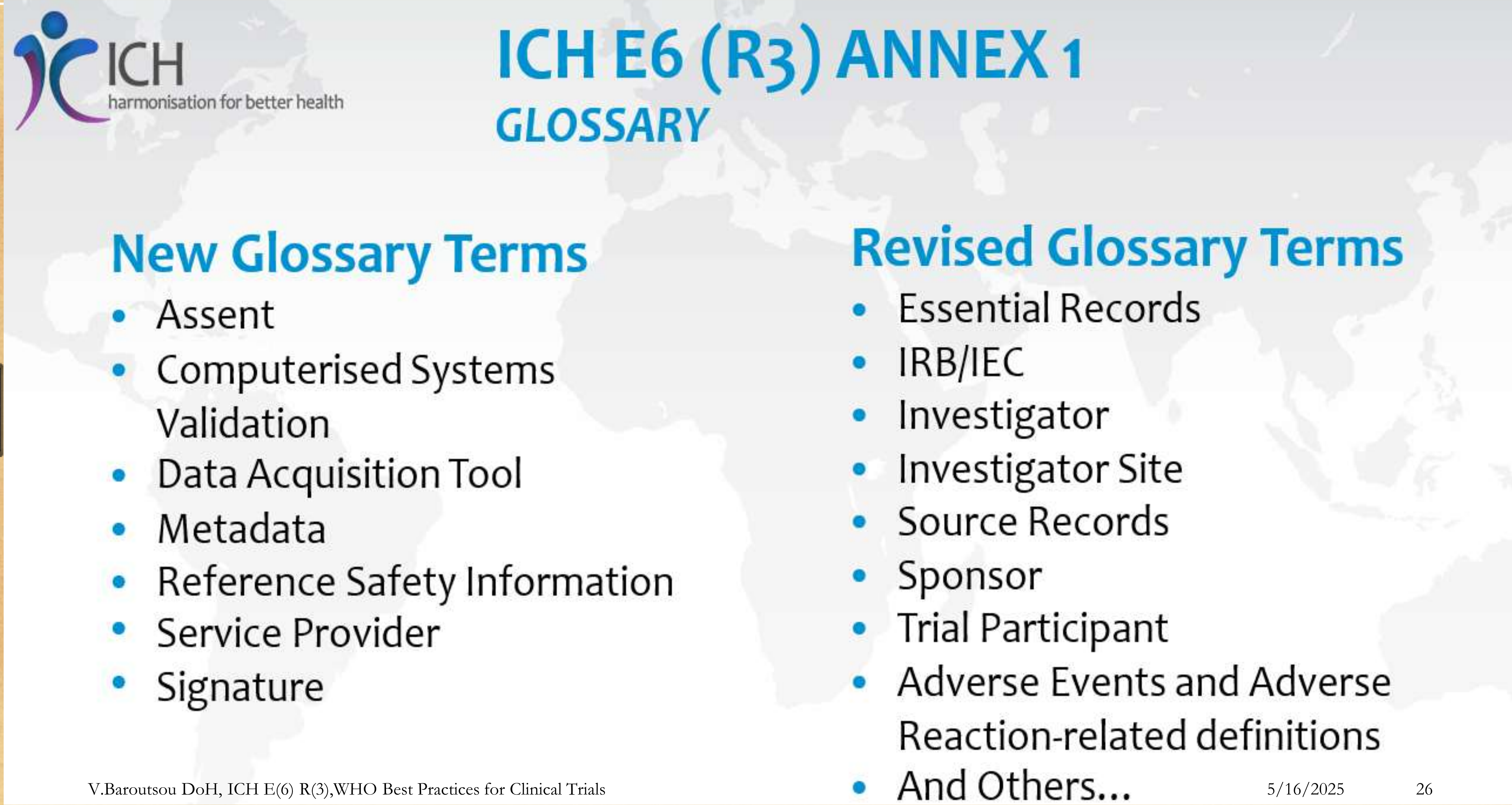
- A well-designed trial protocol is fundamental to the protection of participants and for the generation of reliable results.
- The protocol and other documents (e.g., statistical analysis plan, data management plan) for trial execution should be clear, concise and operationally feasible.

**Reliable Results**

- Trial processes should support the key trial objectives.
- Clinical trials should incorporate efficient and well-controlled processes for managing records through appropriate management of data integrity.
- The transparency of clinical trials should involve registration on publicly accessible databases and the public posting of clinical trial results.

**Investigational Product**

- Investigational products should be carefully managed to align with treatment assignment and maintain blinding, where applicable.
- The investigational product provided to the trial participant should retain its quality.



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# ICH E6 (R3) ANNEX 1

## *GLOSSARY*

### New Glossary Terms

- Assent
- Computerised Systems Validation
- Data Acquisition Tool
- Metadata
- Reference Safety Information
- Service Provider
- Signature

### Revised Glossary Terms

- Essential Records
- IRB/IEC
- Investigator
- Investigator Site
- Source Records
- Sponsor
- Trial Participant
- Adverse Events and Adverse Reaction-related definitions
- And Others…

# Annex II of the ICH E6(R3) Status

- **Annex II of the ICH E6(R3) Good Clinical Practice (GCP) guideline** is currently in **Step 3** of the ICH guideline development process, which involves regulatory consultation and discussion. According to the latest updates:
- **Annex II was released as a draft for public comment on December 30, 2024**.
- The **comment period was reopened in March 2025** and closed on **March 31, 2025**, to allow additional feedback
- If the current timelines are maintained, **Annex II is expected to be finalized and adopted later in 2025**, following the adoption of the Principles and Annex I, which are set to become effective in **June–July 20252**

# Summary of Key Changes in the ICH E6 (R3) Guidelines

The final version of ICH E6 (R3) (.PDF) Good Clinical Practice (GCP) Guidelines was published on 6th January, 25 and recommended for adoption by regulatory bodies.

The changes reflect advancements in **trial design**, **technology** and the **digital ecosystem** for trials, with expanded content on **data governance and computerised systems.**

There is also an emphasis on **Quality-by-Design** - a methodology that proactively designs quality into a trial **to prevent errors that could significantly impact patient safety and data** reliability (see CTTI Guidance).

# Summary of Key Changes in the ICH E6 (R3) Guidelines

The implementation of **key trial design principles**, with a **strong emphasis on proportionality** and **fitness-for-purpose,** aiming to **improve trial efficiency** and **extend the applicability of GCP to a broader range of trials**.

**Transparency** in the trial process is also emphasised. For teams conducting trials that incorporate **decentralised, pragmatic or real-world** elements, additional considerations are outlined in the draft Annex 2 of ICH E6 (R3 (.PDF)).

New sections, particularly Section 3.16 and Section 4 (relating to **data governance**), warrant thorough review.

# ICH Guidelines

Clinical Trial Execution and Reporting only ?

and

Which ICH Guidelines to Consider from Trial Design to Reporting and Importance ?

Quality of protocol

Sound design
E4, E8, E9, E10, E20

Research Methodology
E8, E9

Quality of analysis
E6

Scientific & ethical integrity
E2, E3, E6, E9

Participant protection & safety
E2, E3, E6, E7, E19

Safety of participants
E6, E19

Clinically relevant
E4, E7, E10, E14, E17, E20, E21, E22

Quality of recruitment
E10, E17

Compliance, adherence
E6

Essential data
E2, E3, E9

CRF quality
E9

Quality of data
E6

Quality of results

E3, ISO 14155

**Submission:** M4 Common Technical Document

# The first step is to read , understand and apply critical thinking

## Read

Read the actual regulations & guidelines, not just their interpretation in your SOPs, and encourage your teams to do the same.

## Read

First, read those directly relevant to your area of responsibility, then look at the related ones; there is no standard reading list for all.

## Use

If you want to include ICH guidelines in your SOPs, use critical thinking and assess applicability to your organization.

# WHO GUIDANCE
for best practices for clinical trials

Published on

24 September 2024

Video available

https://www.youtube.com/watch?v=LDEq7-f6z_c&ab_channel=TheGlobalHealthNetwork

## Guidance for best practices for clinical trials

25 September 2024 | Guideline

**Overview**

This document responds to requests by the World Health Assembly to the Director-General in resolution WHA75.8 (2022) on strengthening clinical trials to provide high-quality evidence on health interventions and to improve research quality and coordination to identify and propose best practices and other measures to strengthen the global clinical trial ecosystem and to review existing guidance and develop new guidance as needed on best practices for clinical trials. This guidance updates and adapts the previous work of the World Health Organization (WHO) on research capacity for the context of well-designed and well-implemented clinical trials as framed in resolution WHA75.8 (2022). It aims to enhance clinical research efficiency, minimize research waste and provide guidance on sustained clinical trials that are always functional and active for endemic conditions and can pivot in time of emergency or pandemics.

**WHO TEAM**
Research for Health (RFH)

**EDITORS**
World Health Organization

**NUMBER OF PAGES**
76

**REFERENCE NUMBERS**
ISBN: 978-92-4-009771-1

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https://iris.who.int/bitstream/handle/10665/378782/9789240097711-eng.pdf?sequence=1

# Guidance for Best Practices for Clinical Trials by WHO

- The **World Health Organization (WHO)** published its updated **"Guidance for Best Practices for Clinical Trials"** in September 2024 in response to World Health Assembly resolution WHA75.8 (2022). This document aims to strengthen the global clinical trial ecosystem by improving the quality, coordination, and efficiency of clinical research.
- IFAPP contributed to WHO public consultation

# WHO Key Objectives

- Firstly, **patient, participant and community engagement** are placed centrally in the trial planning and implementation phases to ensure the research meets public needs and maintains **trust.**
- Secondly, major new recommendations are included on reforms that enable trials in underrepresented populations such as **children, pregnant women and older adults**.
- Thirdly, the guidance lays out how to **focus trial design and oversight on the key scientific and ethical considerations that determine whether trials are ethical, efficient and informative**. Here risk based and **proportionate approaches** are advocated so that we move away from one size fits all **oversight or audit**, to those that are **tailored to risk.**

# Key Highlights of the WHO Best Practices for Clinical Trials

1. **Purpose and Scope**:
    1. Enhance the quality and reliability of clinical trials.
    2. Minimize research waste and duplication.
    3. Ensure trials are adaptable for both endemic conditions and emergency situations (e.g., pandemics).
2. **Core Principles**:
    1. **Scientific Rigor**: Trials must be well-designed and methodologically sound.
    2. **Ethical Conduct**: Uphold participant rights, safety, and informed consent.
    3. **Transparency**: Promote open access to trial protocols, data, and results.
    4. **Inclusivity**: Encourage diverse participant representation and equitable access to research benefits.

# Key Highlights of the WHO Best Practices for Clinical Trials

**3. Operational Best Practices**:

1. **Sustainable Infrastructure**: Support continuous trial readiness and capacity.
2. **Collaboration and Coordination**: Foster partnerships across countries and institutions.
3. **Regulatory Alignment**: Harmonize standards and streamline approval processes.
4. **Digital Innovation**: Leverage digital tools for data collection, monitoring, and remote participation.

**4.Emergency Preparedness**:

1. Establish mechanisms for rapid trial activation during health emergencies.
2. Maintain "always-on" trial platforms that can pivot quickly in response to emerging threats.

**5. Capacity Building**:

1. Invest in training, mentorship, and infrastructure in low- and middle-income countries.
2. Promote equitable global participation in research leadership and authorship.

# Thank you for your attention

Discussion

# References

- WMA Declaration of Helsinki https://www.wma.net/policies-post/wma-declaration-of-helsinki/
- WMA Declaration of Taipei https://www.wma.net/what-we-do/medical-ethics/declaration-of-taipei/
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, https://ich.org/
- https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Step%204_Presentation_2025_0123.pdf
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