# Session 1: Good Clinical Practice (GCP) Harmonization: Updates to ICH E6(R3)

Joint US-FDA | MHRA-UK | Health Canada Good Clinical Practice & Pharmacovigilance Symposium
February 13, 2024 – 9:00 – 10:00 AM


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# Updates: ICH E6(R3) Good Clinical Practice Draft Guideline

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A Joint US-FDA | MHRA-UK | Health Canada Good Clinical Practice & Pharmacovigilance Compliance Workshop
February 13, 2024

# Disclaimer

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

# Overview

- General overview of ICH E6
- Why changes ICH E6(R2) → E6(R3) ?
- Changes to the Principles
- Annex 1 highlights: Important changes in relation to Investigator and Sponsor responsibilities
- MHRA consultation responses
- Data Governance changes
- Appendix C: Detailed coverage of changes to Essential Records
- Annex 2

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# ICH-E6: Global Standard for Clinical Trial Conduct

- **E6: Good Clinical Practice (GCP) – 1996**
  - Described the responsibilities and expectations of stakeholders in the conduct of clinical trials;
  - Covered aspects of monitoring, reporting, and archiving of clinical trials;
  - Included sections for essential documents and investigator brochures
- **E6 (R2) – 2016**
  - Included integrated addendum to encourage implementation of improved and more efficient approaches to GCP, while continuing to ensure human subject protections;
  - Updated standards for electronic records.


https://admin.ich.org/sites/default/files/2021-05/ICH_ReflectionPaper_GCPRenovation_2021_0519.pdf

# Why E6 (R2) Improvement?

**Gap Analyses of E6 (R2)**

- Peer-review publications
- Academic Opinions
- Open letter sent to EMA & ICH
- Responses to CTTI survey
- Input taken from regional public engagements
- ICH Guideline Analysis

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# ICH E6 (R3): Purpose of the Update

- To provide guidance that is applicable to different clinical trial designs and facilitate innovation
  - Modernize, harmonize and adapt
- To further advance focus on a proportionate, risk-based approach to the design and conduct of clinical trials
- Address the complexities of clinical trials in the current global regulatory climate

# E6(R3) Development Process

1) Involving engagement with academic stakeholders

2) Publishing draft principles

3) Holding a global conference to provide updates

4) Holding EWG Meetings

Ensuring Agency internal clearances

Endorsement by ICH

# Development Strategy for E6(R3)

## Annex 1

- Considerations for interventional clinical trials

## Annex 2

- Additional considerations

When complete, E6(R3) will be composed of an overarching principles and objectives, Annex 1, and Annex 2.

**Draft Published** | **In the Making**

https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Annex2_ConceptPaper_2023_0405.pdf

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# Overview of Key Changes

- Principles of ICH GCP
- Investigator Responsibilities
- Sponsor Responsibilities

# ICH E6(R3): Updates

- Principles of ICH GCP:
  - Designed to be flexible and applicable to a broad range of Clinical Trials (CTs).
- Annex 1: Considerations for interventional CTs
  - Provides information on how the principles can be appropriately applied to clinical trials.
- Annex 2: Additional considerations for interventional CTs
  - How GCP principles may be applied across a variety of trial designs and data sources (Decentralised CT, Pragmatic Elements, Real-world data, Digital Health Technologies …).

# E6(R3) vs E6(R2) Structure

| E6(R3) Table Of Contents | E6(R2) Table Of Contents |
|---|---|
| I. Introduction<br>II. Principles of ICH GCP<br>III. Annex 1<br>1. Institutional Review Board/Independent Ethics Committee (IRB/IEC)<br>2. Investigator<br>3. Sponsor<br>4. Data Governance – Investigator And Sponsor (New Section)<br>Glossary<br>Appendices<br>Appendix A. Investigator's Brochure<br>Appendix B. Clinical Trial Protocol …<br>Appendix C. Essential Records … | Introduction<br>1. Glossary (Moved To The End)<br>2. The principles of ICH GCP<br>3. Institutional Review Board/Independent Ethics Committee (IRB/IEC)<br>4. Investigator<br>5. Sponsor<br>6. Clinical trial protocol and protocol amendment(s) (Appendix B)<br>7. Investigator's brochure (Appendix A)<br>8. Essential documents for the conduct of a clinical trial (Appendix C) |

# Principles of ICH GCP

- The principles are intended to apply across clinical trial types and settings and to remain relevant as technological and methodological advances occur.

- The principles outlined in the ICH E6(R3) guideline may be satisfied using differing approaches and should be applied to fit the intended purpose of the clinical trial (CT).

Source: https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf

# ICH E6 (R3) Principles: Key changes

Principles are interdependent and should be considered in their totality to assure ethical CT conduct and reliable results.

1. CTs should be conducted in accordance with the ethical principles … and that are consistent with GCP and applicable regulatory requirement(s). CTs should be designed and conducted in ways that ensure the rights, safety and well-being of participants. (E6(R2) 2.1, 2.2 2.3, 2.7, 2.11)

2. Informed consent is an integral feature of the ethical conduct of a trial. CT participation should be voluntary and based on a consent process that ensures participants ... are well-informed. (E6(R2) 2.9)

Source: https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf

# ICH E6 (R3) Principles: Key changes

3. CTs should be subject to an independent review by an institutional review board/independent ethics committee. (E6(R2) 2.6)

4. CTs should be scientifically sound for their intended purpose and based on robust and current scientific knowledge and approaches. (E6(R2) 2.4, 2.5)

5. CTs should be designed and conducted by qualified individuals. (E6(R2) 2.8)

6. Quality should be built into the scientific and operational design and conduct of CTs. (E6(R2) 2.13)

7. CT processes, measures and approaches should be implemented in a way that is proportionate to the risks to participants and to the importance of the data collected. (New)

Source: https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf

# ICH E6 (R3) Principles: Key changes

8. CTs should be described in a clear, concise and operationally feasible. (E6(R2) 2.5)
9. CTs should generate reliable results. (E6(R2) 2.10, 2.13)
10. Roles and responsibilities in CTs should be clear and documented appropriately. (New)
11. Investigational products used in a CT should be manufactured in accordance with applicable Good Manufacturing Practice ….. and be stored, shipped, handled and disposed of in accordance with the product specifications ….. (E6(R2) 2.12)

Source: https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf

# Investigator Responsibilities: Key Changes

Flexibility and clarity are provided under the responsibilities:

- Investigator retains the **ultimate responsibility** for appropriate **supervision** of the persons/parties undertaking the delegated activities …. (2.3.1)
- Trial-related **training** to persons assisting in the trial **should correspond to what is necessary** to enable them to fulfill their delegated trial activities that go beyond usual training/experience. (2.3.2 )
- Where the CT activities are performed in accordance with routine clinical care, **delegation documentation may not be required**. (2.3.3)

Source: https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf

# Investigator Responsibilities: Key Changes

- 2.4 Communication with IRB/IEC
  - Submission to the IRB/IEC **may be made by** the investigator / institution **or sponsor** in accordance with applicable regulatory requirements. (2.4.1)

- 2.5 Compliance with Protocol
  - **For important deviations,** the investigator should explain the deviation and implement appropriate measures to prevent a recurrence. (2.5.2 )

- 2.7 Participant Medical Care and Safety Reporting
  - **Other qualified healthcare professionals** ….. could have the overall **responsibility for trial-related medical care and decisions.** (2.7.1(b))

Source: https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf

# Investigator Responsibilities: Key Changes

- 2.8 Informed Consent of Trial Participants
  - The information should be as clear and concise as possible … (2.8.1(b))
  - Varied approaches …. may be used in the informed consent process…. **Obtaining consent remotely may be considered** … (2.8.1(c) )

- 2.12 Records
  - … should ensure that such data are protected from unauthorised access, disclosure, dissemination or alteration and from inappropriate destruction or accidental loss. (2.12.8)
  - When using computerised systems …should … **(b)** …. ensure that **the requirements for computerised systems in section 4 (Data Governance) are addressed**. (2.12.9)

Source: https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf

# Sponsor Responsibilities: Key Changes

Clarity provided for sponsors' responsibilities

- 3.1 Trial Design
  - Sponsors should incorporate **quality into the design of the clinical trial** by identifying factors that are critical to the quality of the trial and by managing risks to those factors. (3.1.2)

- 3.6 Agreements
  - Sponsor should **ensure appropriate oversight** of important trial-related activities that are transferred to **service providers** … (3.6.10)
  - A **clinical trial may have one or several sponsors** …. (3.6.12 )

Source: https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf

# Sponsor Responsibilities: Key Changes

- 3.9 Sponsor Oversight
  - The sponsor should determine necessary **trial-specific criteria for classifying protocol deviations as important.** (3.9.3)

- 3.10 Quality Management
  - The sponsor should adopt **a proportionate and risk-based approach to quality management**, which involves incorporating **quality into the design** of the CT.

Source: https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf

# Sponsor Responsibilities: Key Changes

- 3.11.4 Monitoring: Is one of the principal quality control activities ... Monitoring activities may include site monitoring (performed on-site or remotely) and **centralised monitoring**…
  - **Centralised Monitoring** clarified through 3.11.4.2(a), (b), (c)

- 3.16 Data and Records
  - Data Handling: (d) The sponsor should ensure data acquisition tools are **fit for purpose** and designed to capture the information required by the protocol. (3.16.1)
    - ….. **computerised systems** in a CT ….. (w) (i) to (vi)

Source: https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf

# References

ICH
harmonisation for better health

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Home \ ICH Guidelines \ Efficacy Guidelines

## Efficacy Guidelines

The work carried out by ICH under the Efficacy heading is concerned with the design, conduct, safety and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/ pharmacogenomics techniques to produce better targeted medicines.

### E6 Good Clinical Practice

- E6(R2) Good Clinical Practice (GCP)
- E6(R3) EWG Good Clinical Practice (GCP)

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# MHRA Consultation

Web Portal Used to Ask MHRA Specific Questions with reference to the following (in addition to completion of an Excel® spreadsheet for detailed comments)

- ICH Reflection paper on Renovation of Good Clinical Practice (January 2017 [updated May 2021])
- ICH E6(R3) Concept Paper (17 November 2019)
- ICH E6 (R3) Business Plan (17 November 2019)

<u>Response</u>

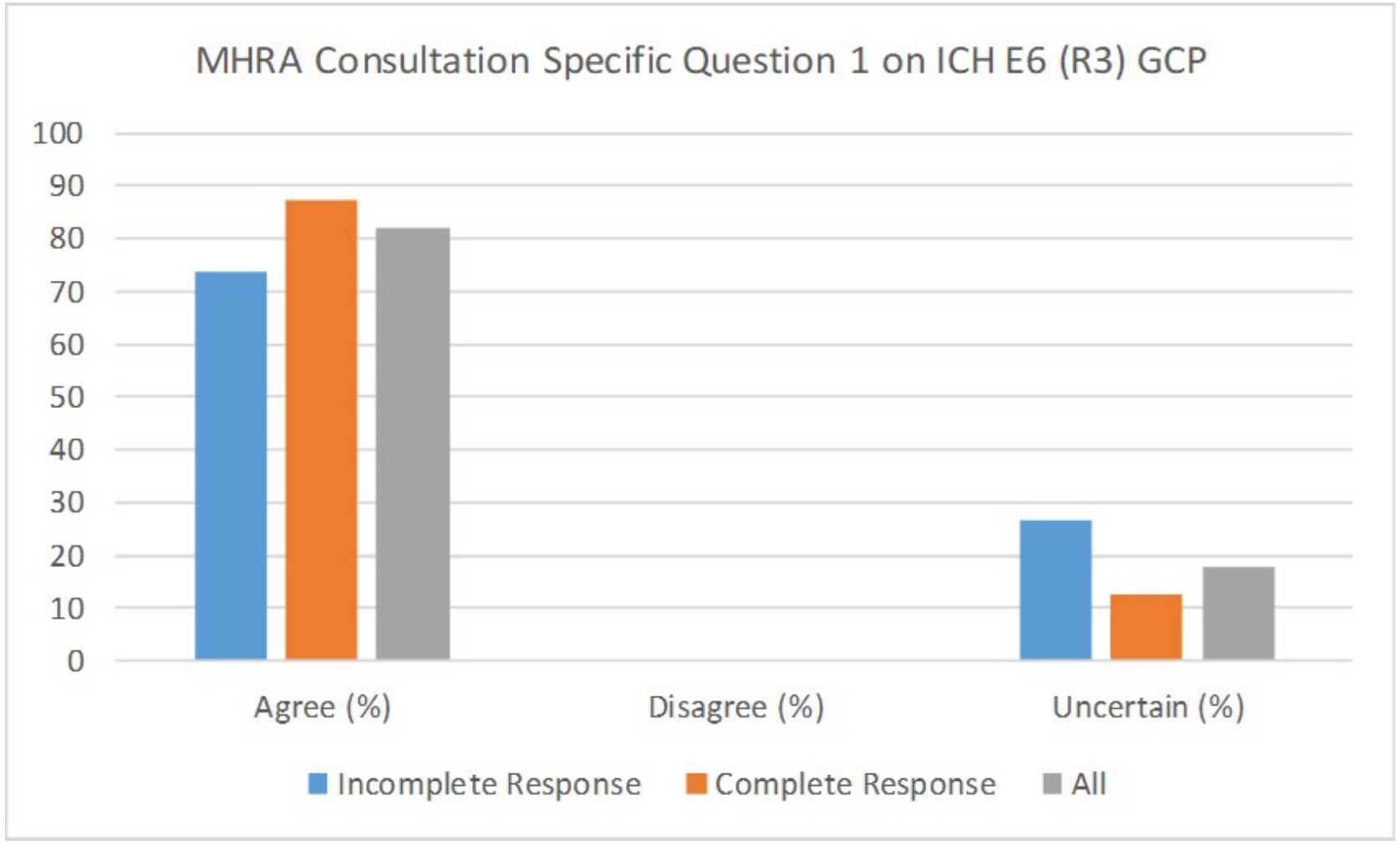
56 complete responses (answered questions, uploaded spreadsheet and submitted)

34 incomplete responses (answered questions, no spreadsheet, not submitted)

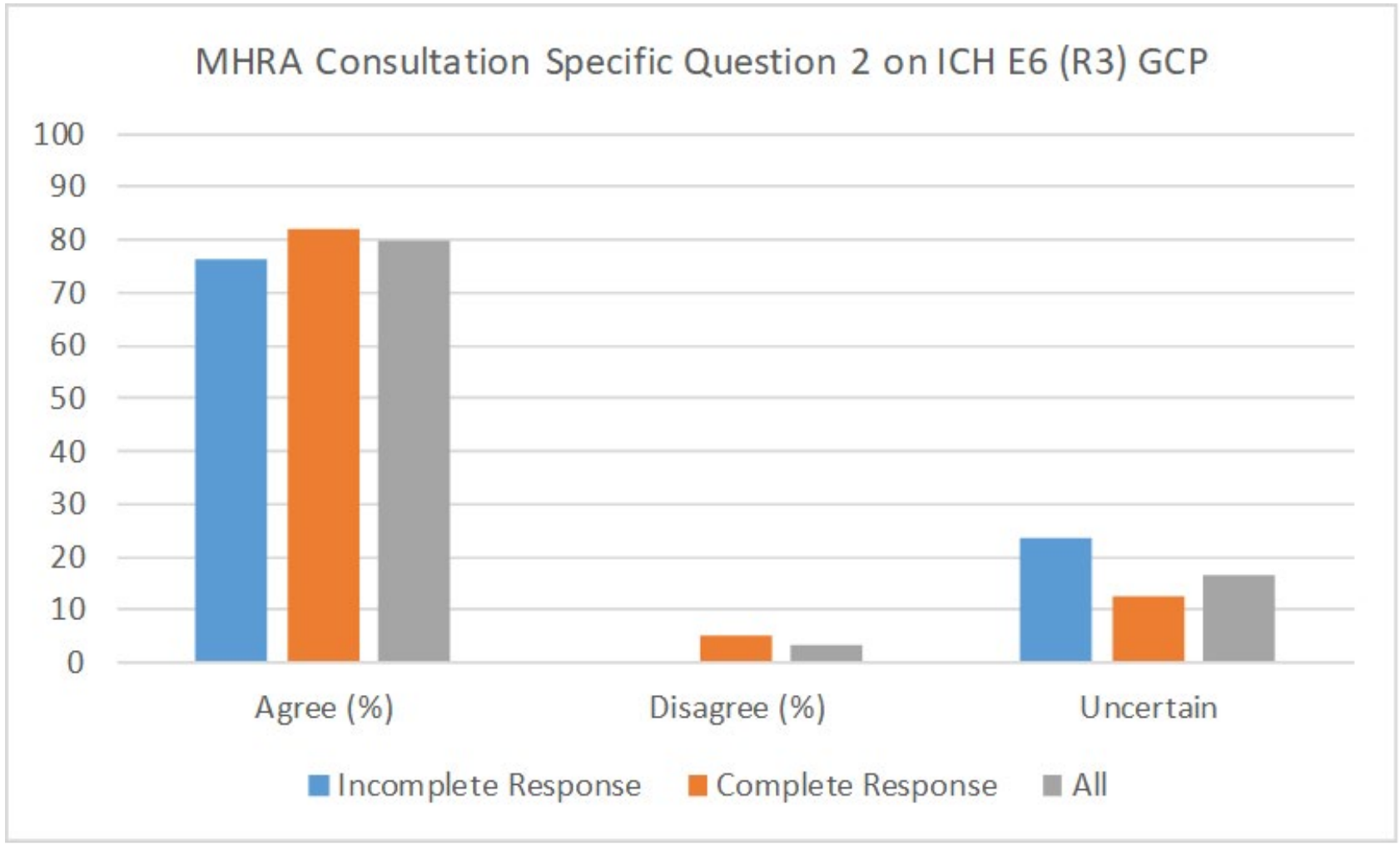
Broad range of responders

| | INCOMPETE | COMPLETE | ALL |
|---|---|---|---|
| Charity/Society/Not for Profit/Network including CT funding and sponsorship | 1 | 3 | **4** |
| Commercial Investigator Site Organisation (excluding Phase 1 Clinical Trialsnit) | | 1 | **1** |
| Contract Research Organisation (for clinical trial operations) | | 5 | **5** |
| Disease-Specific Charity/Society/Not for Profit/Network including CT funding sponsorship | | 1 | **1** |
| eSYSTEM Vendor/Service Provider | | 1 | **1** |
| Government Body | | 2 | **2** |
| IMP Manufacturer/Distributor | | 1 | **1** |
| Individual (Academic) | 2 | | **2** |
| Individual (Freelance Consultant) | 2 | 3 | **5** |
| Individual (Funder Employee) | 1 | | **1** |
| Individual (Investigator/Researcher) | 7 | 3 | **10** |
| Individual (Participant/Carer) | 3 | | **3** |
| Individual (QP) | 2 | | **2** |
| Individual (Sponsor Employee) | 7 | 2 | **9** |
| Medical Device Company | | 1 | **1** |
| NHS Central | | 4 | **4** |
| NHS Hospital (Trust/Board) | 1 | 6 | **7** |
| Non-Commercial Clinical Trials Unit | 2 | 2 | **4** |
| Pharmaceutical/Biotechnology Company (Commercial Sponsor) | 2 | 3 | **5** |
| Phase 1 Clinical Trials Unit | | 3 | **3** |
| Site Management Organisation/Investigator Site Service Provider | 1 | | **1** |
| Trade Union/Professional Association/Society for Individual Membership | 1 | 4 | **5** |
| Trade/Professional Association/Society for Organisational Membership | | 6 | **6** |
| UK University | 2 | 5 | **7** |
| **ALL** | **34** | **56** | **90** |

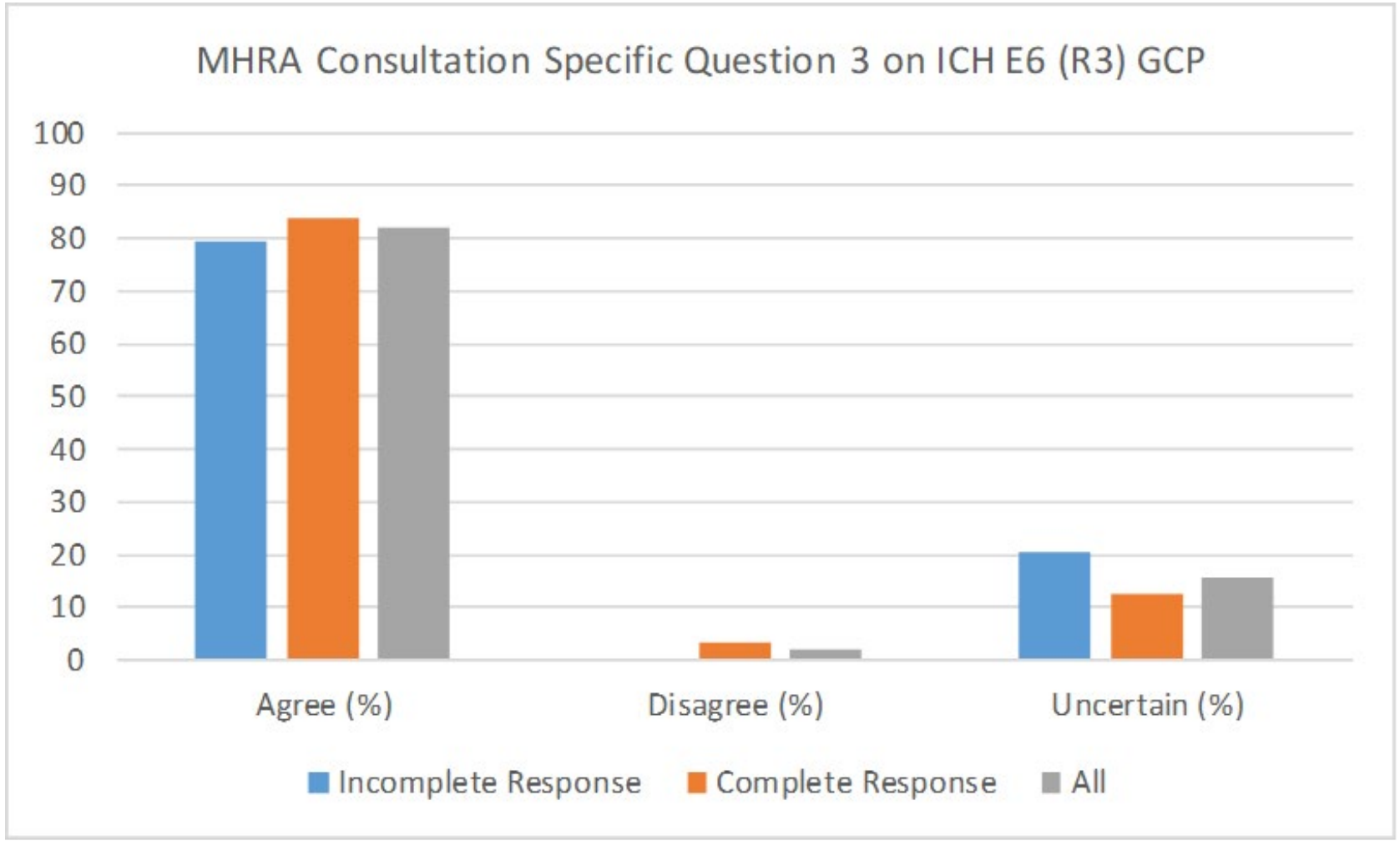
## Question 1: The E6 (R3) Principles and Annexe 1 Guideline further advance the concept of a proportionate, risk-based approach to the design and conduct of clinical trials. Do you agree or disagree?



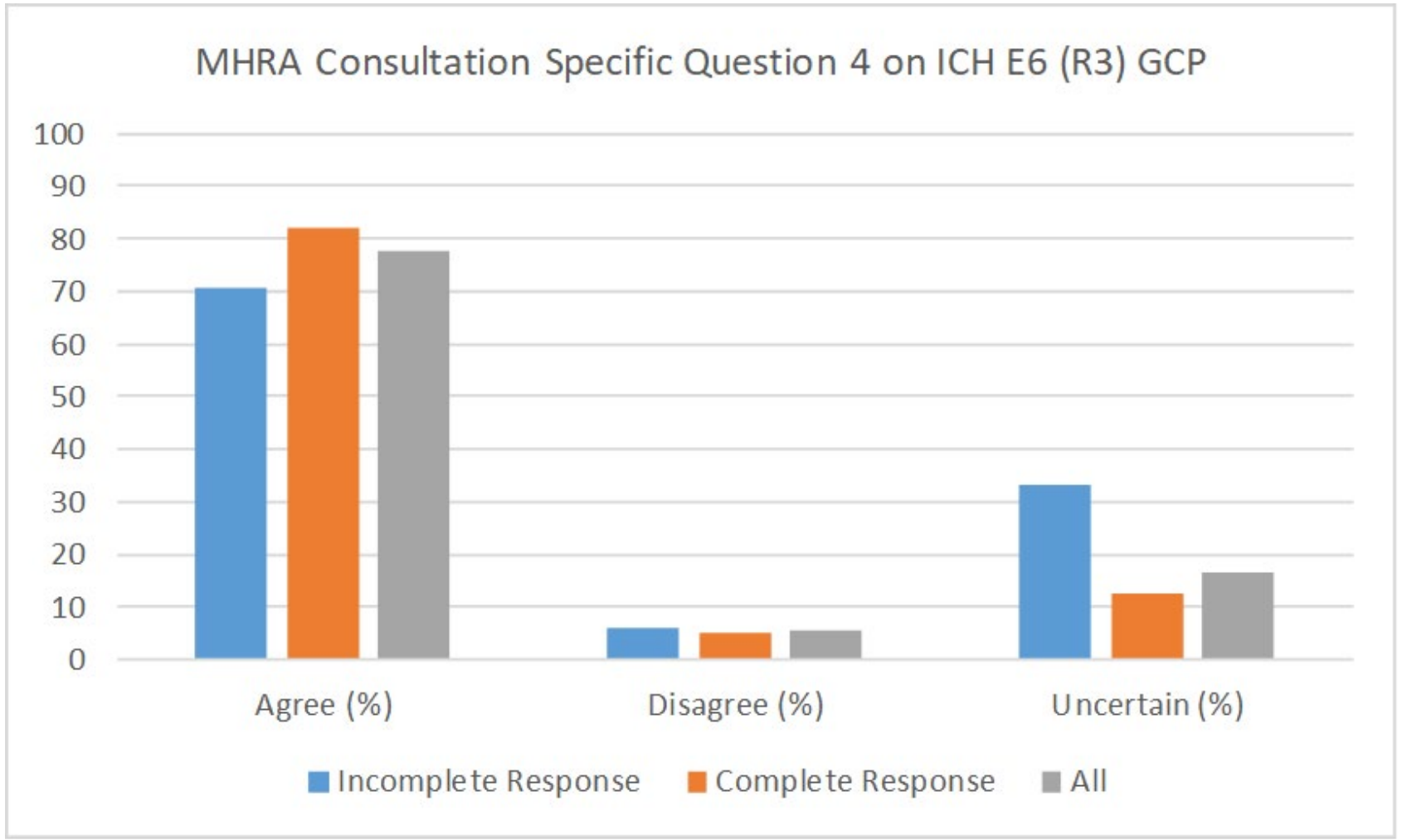
## Question 2: The E6 (R3) Principles and Annexe 1 Guideline encourage relevant parties to utilise a proportionate, risk-based approach and focus on the protection of clinical trial participants and the reliability of the trial results. Do you agree or disagree?



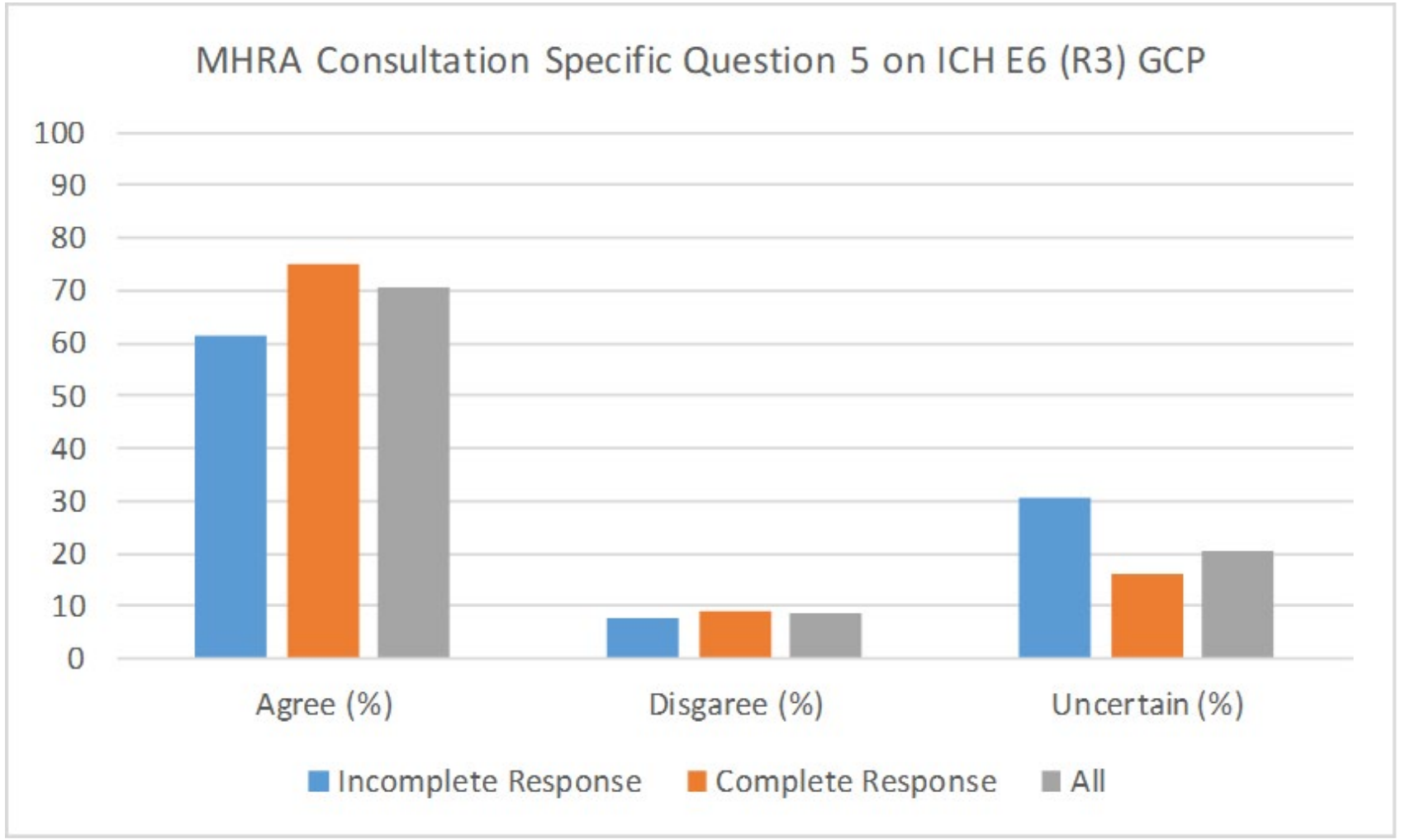
## Question 3: The E6 (R3) Principles and Annexe 1 guideline conveys that the implementation of GCP principles should be a thoughtful, deliberative, and risk-based process (as clinical trials can vary greatly and certain aspects of GCP may not be applicable to every trial). Do you agree or disagree?



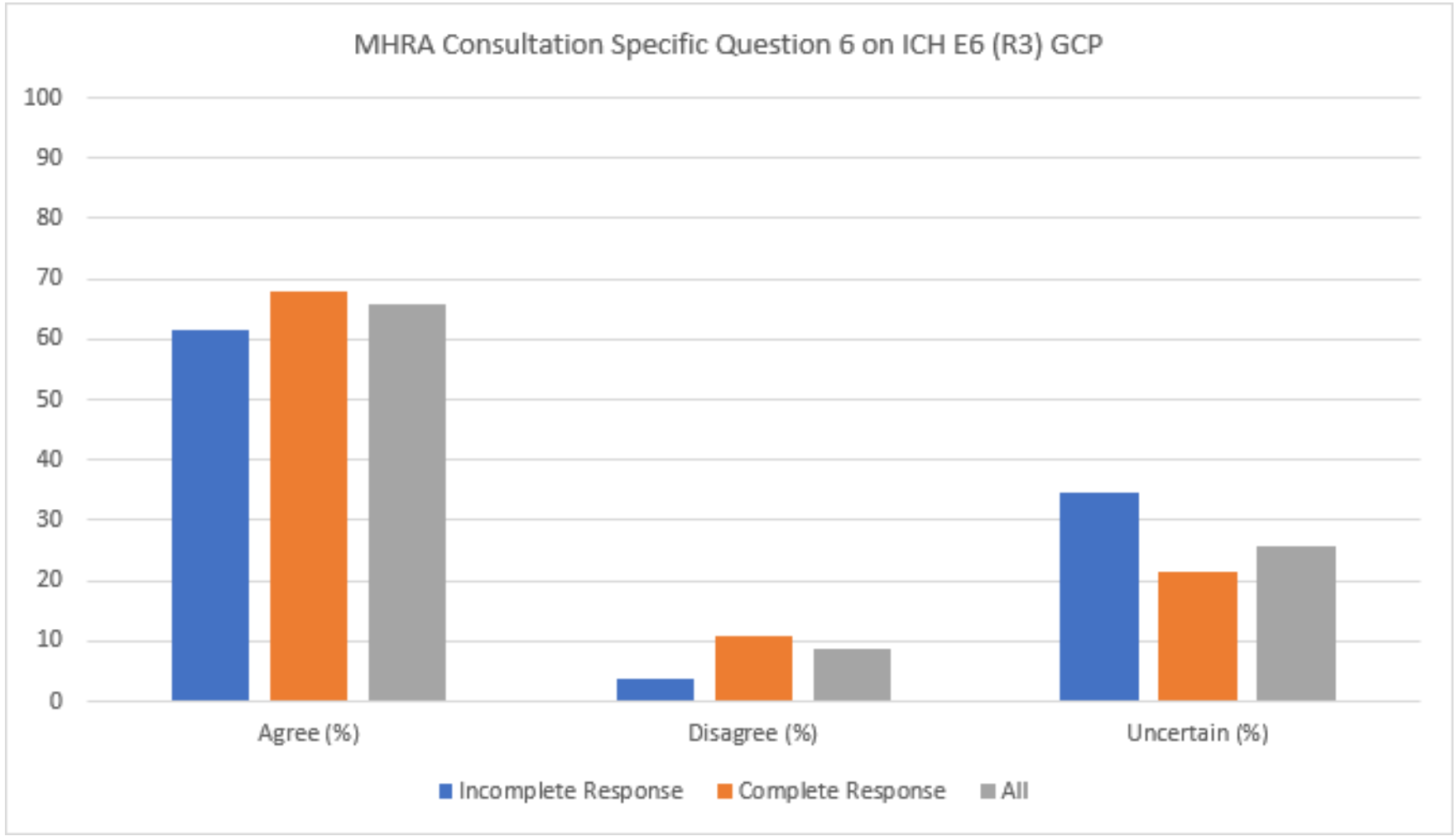
# Question 4: The E6(R3) Principles and Annexe 1 guideline highlights that achieving compliance with GCP principles can be accomplished using multiple tools and methods? Do you agree or disagree?



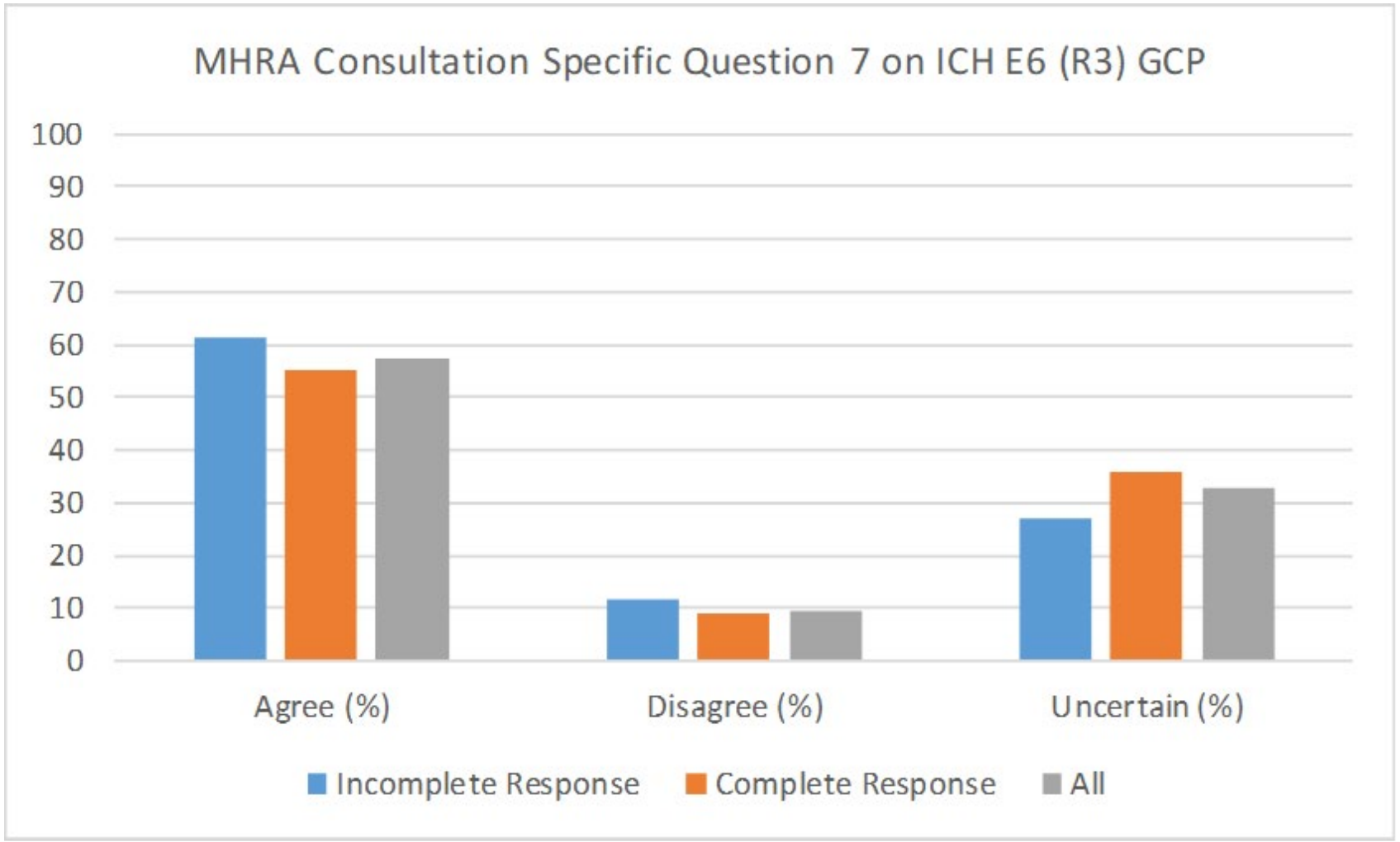
**Question 5: The E6(R3) Principles and Annexe 1 guideline, in particular the inclusion of the new section on Data Governance, flexibly addresses the requirements of the increased use of technology in clinical trials, for example validity of electronic systems, data sources and data integrity. Do you agree or disagree?**



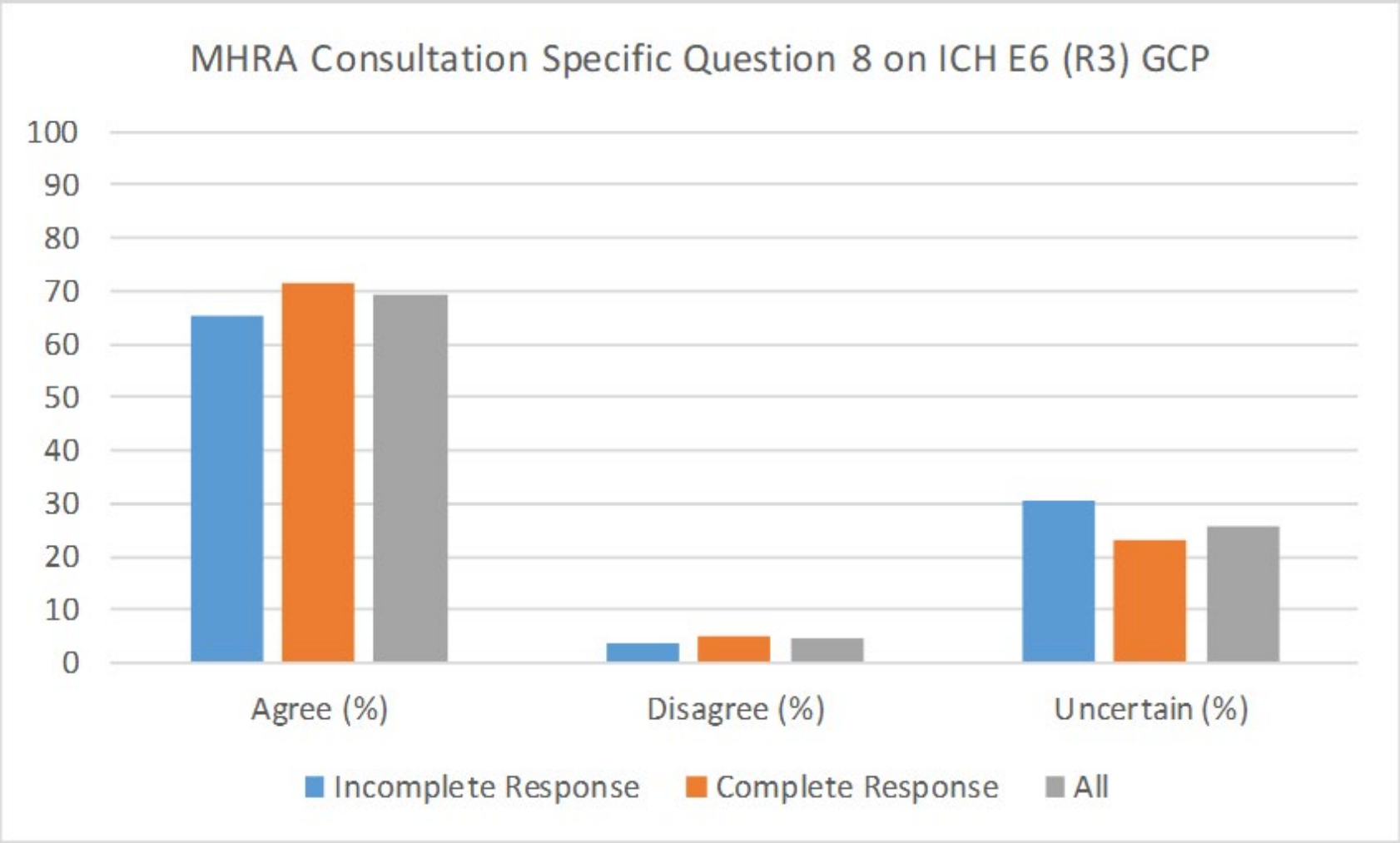
# Question 6: The E6(R3) Principles and Annexe 1 guideline, in particular Appendix C, concerning essential records, allows a more thoughtful, flexible and proportionate approach to the collection and retention of essential records. Do you agree or disagree?



# Question 7: The E6(R3) Principles and Annexe 1 guideline flexibly addresses innovations and complexities in investigator sites, test facilities or service provider activities in trial designs. Do you agree or disagree?



## Question 8: The E6(R3) Principles can be successfully and proportionately applied to all clinical trials of medicines that require a clinical trial authorisation (or notification of low interventional trials as per the consultation on legislative proposals for clinical trials) from the MHRA. Do you agree or disagree?



# ICH E6 (R3) Data Governance - Significant Changes Made

Entire new section to address data life cycle and computerised systems

Additional text added to sponsor and investigator sections

**More details in session 4 this afternoon**

# Significant changes from ICH E6 (R2) Concerning Essential Documents

- Revised definitions
- More detail on record management to update for complexity and new technology
- More guidance on what makes a record essential
- Simplification of the tabulations

# Investigator Responsibilities in Relation to Essential Records

Maintain the (specified) trial records and as required by the applicable regulatory requirement(s)

Have control of all essential records generated by the investigator /institution before, during and after the trial

Take measures to prevent accidental or premature destruction of these records

If the investigator closes a site or leaves a site during or after the end of the clinical trial, the sponsor should be notified of the appropriate individual responsible for retention of the site's essential records

Retain the essential records for the required retention period in accordance with applicable regulatory requirements or until the sponsor informs the investigator/institution that these records are no longer needed, whichever is the longer

Upon request of the monitor, auditor, IRB/IEC or regulatory authority, the investigator/ institution should make available for direct access all requested trial related records

# Sponsor Responsibilities in Relation to Essential Records

Sponsor's Monitor confirming the investigator is maintaining the essential records and the arrangement for the retention of the essential records

The sponsor (or subsequent owners of the data) should retain all of the sponsor-specific essential records pertaining to the trial in conformance with the applicable regulatory requirement(s).

The sponsor should inform the investigator(s)/institution(s) and service providers, when appropriate, in writing of the need for essential records retention and should notify the investigator(s)/institution(s) and service providers, when appropriate, in writing when the trial-related records are no longer needed.

The sponsor should report any transfer of ownership of the essential records to the appropriate authority(ies) as required by the applicable regulatory requirement(s).

# ICH E6 (R3) Essential Documents - glossary

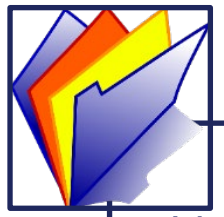
Change from “Essential Documents” to “Essential Records”

“Documentation”, “Source Data”, “Source Documents” amalgamated to “Source Records”

# Essential Records

| | |
|---|---|
| Records are always created | • Before and during the conduct of a clinical trial. |
| A proportionate collection of records is produced | • Dependent upon the trial design, its conduct, application of proportional approaches and the importance and relevance of that record to the trial. |
| The essential records permit and contribute to the evaluation of the conduct of a trial and the reliability of the results produced | • Sponsor oversight or investigator supervision<br>• Demonstrate compliance<br>• Used by the auditors and inspectors |

# Management of Essential Records (1)



## Type and Quality of

- Identifiable
- version controlled
- include authors, reviewers and approvers as appropriate
- Include date and signature (electronic or wet ink), where necessary
- Alteration to the essential records should be traceable
- a copy is used to permanently replace the original, it should fulfil the requirements for certified copies
- Certain essential records may not be specific to a trial but may be related to the systems and processes involved in running multiple trials and retained outside the trial-specific repositories

## Sharing of Records

- In order to fulfil their responsibilities in the conduct of the trial, the sponsor and investigator/institution may need access to or copies of one another's relevant essential records before, during and after the trial is completed. This will determine whether the record resides in the repositories of the sponsor, the investigator/institution, or both
- There should be careful consideration of sharing of records subject to data protection legislation and blinding considerations in line with applicable regulatory requirements

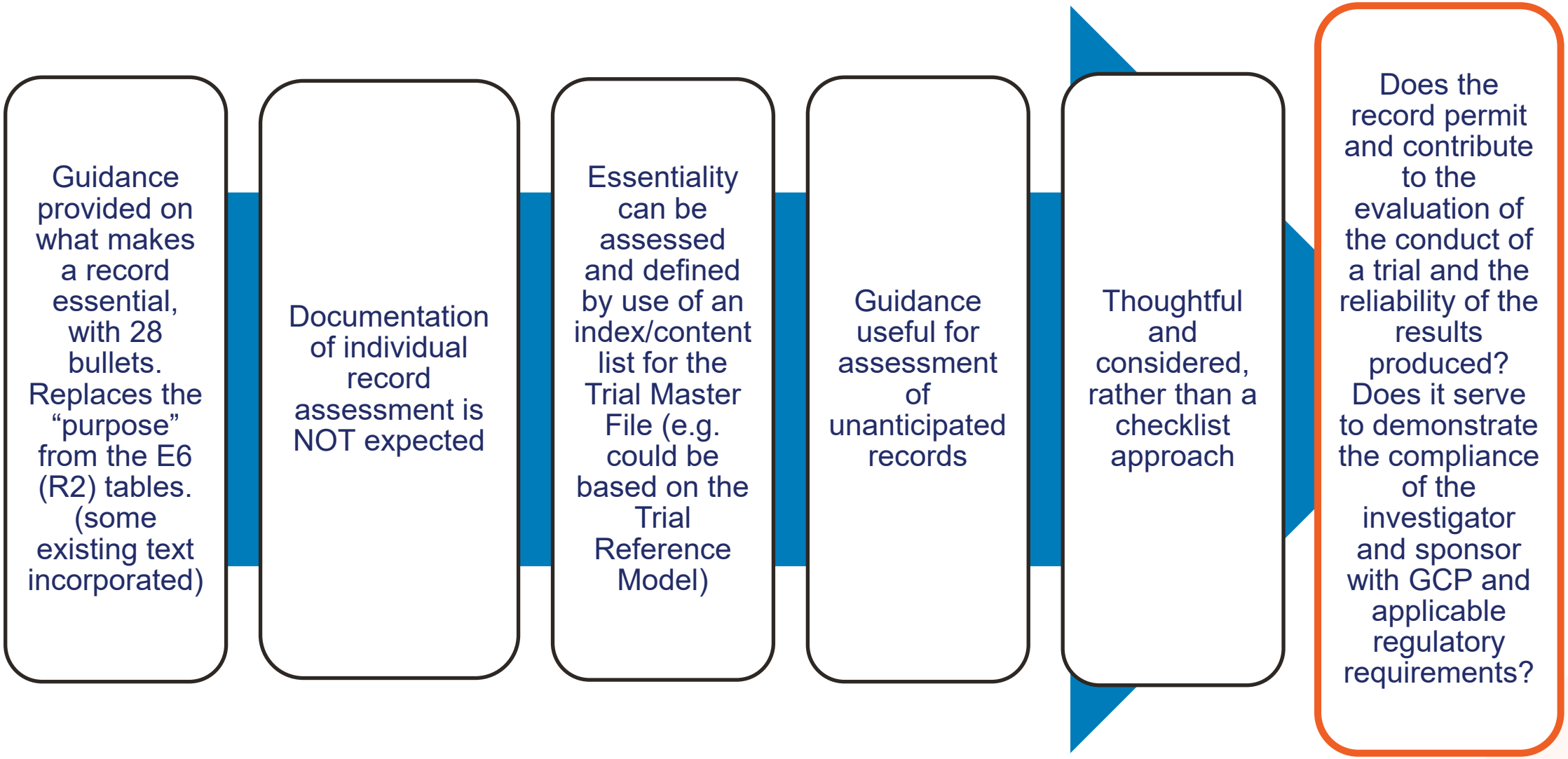
## Use of Service

- For activities that are transferred or delegated to service providers by the sponsor or investigator/institution respectively, arrangements should be made for the access and management of the essential records throughout the trial and for their retention following completion of the trial

# Management of Essential Records (2)

| Storage of Records | | | | | | |
|---|---|---|---|---|---|---|
| The original version of the essential record should be retained by the responsible party (sponsor or investigator). | The investigator/institution should have access to and the ability to maintain and retain the essential records generated by the investigator/institution before, during and after the trial. | These essential records should be maintained in or referred to from repositories, including, for example, the trial master file (TMF) held by the sponsor or investigator site file (ISF). | The sponsor and investigator/institution should maintain a record of where essential records are located, including source records. | The storage system(s) used during the trial and for archiving (irrespective of the type of media used) should provide for appropriate identification, version history, search and retrieval of trial records. | The sponsor and investigator/institution should ensure that the essential records are collected and filed in a timely manner, including those required to be in place prior to the trial start, which can greatly assist in the successful management of a trial. | The sponsor and investigator/institution should retain the essential records in a way that ensures that they remain complete, readable and readily available and are directly accessible upon request by regulatory authorities. |

# Essentiality and the Tables



# Changes to the tabulations of essential records – have your say now!

## What would you prefer?


**(A)** The tabulations in ICH E6 (R2) with updates to include new records, but keeping the purpose, location, copy or not and availability before/during/after structure **("the current way")**


**(B)** The approach in ICH E6 (R3) which lists essential records to be retained for all trials and those that, if produced, should also be retained and use of the guidance on management and essentiality. **("the proposed way")**


**(C)** No tabulations at all, instead to rely completely on the guidance on management and essentiality. **("the alternative way")**

# Copyright information

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# Annex 2 Purpose

- Intended to address growing interest in clinical trials using various operational approaches and data sources.
- Intended to provide additional GCP considerations, focusing on examples of trials that incorporate:
  1. Decentralized elements
  2. Pragmatic elements
  3. Real-world data (RWD) sources

# Timelines

- Final Concept Paper for Annex-2: https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Annex2_ConceptPaper_2023_0405.pdf
  - Endorsed by the ICH Management Committee April 28, 2023
- Draft subject to public consultation is expected approx. 12-18 months from the date of endorsement
- When Annex 2 completes, E6(R3) will be composed of 2 Annexes
  - **Annex 1:** considerations for interventional clinical trials, and
  - **Annex 2:** additional considerations for interventional clinical trials

# Summary

- Has the updated ICH (so far) achieved its goal?
  - Thoughtful, transparent, collaborative
- How guidelines apply to your trial and applied appropriately
  - Not one-size-fits-all: risk based
- Training aspect

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