ICH E6(R3) Guideline for Good Clinical Practice (GCP)

Update on Progress

WELCOME!

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ICH E6(R3) EWG Rapporteur

May 18 & 19, 2021
Today’s Agenda

Session 1 – General Introduction
A – Welcome, Opening Remarks
B – ICH Guideline Development Process and the Initial Approach to ICH E6(R3) Video

Session 2 – E6(R3) GCP Expert Working Group Vision & Engagement
A – Vision and Goals for the Work to Update E6(R3) GCP Guideline
B – Lessons Learned from Public Input & Stakeholder Feedback
C – Questions & Answers

Session 3 – Principles & Stakeholder Reflections
A – Draft “Work-in-Progress” Principles
B – Stakeholder Reflections and Vision Questions & Answers for Stakeholders

Closing Remarks & Summary

Adjournment
Welcome

• This webinar is being recorded and will be posted to the ICH Website & CTTI website.

• All participants are muted upon entry.

• Questions can be entered in the designated Q&A box during the webinar.

• There will be a time for “Questions & Answers” at the end of session 2 and 3.
ICH Guideline Development Process and the Initial Approach to ICH E6(R3)

This video session will explain the ICH guideline development process and provide a brief description of the approach to updating the ICH E6(R3) Good Clinical Practice (GCP) guideline.
Vision and Goals for the Work to Update E6(R3) GCP Guideline

The Continuum of Clinical Trial Design and Conduct

ICH E8 and ICH E6

Dr. Fergus Sweeney, EMA
ICH E6(R3) EWG Regulatory Chair
ICH E8(R1) EWG Regulatory Chair

May 18 & 19, 2021
We Need to be Responsive to a Rapidly Evolving Ecosystem

Advancing Evidence Generation

Increasingly Digital World

Innovative Clinical Trial Designs
ICH E6 Good Clinical Practice: An Important Global Standard for Clinical Trial Conduct

ICH Reflection on “GCP Renovation”: Modernization of ICH E8 and Subsequent Renovation of ICH E6

ICH is inviting public review and comment on a reflection paper on Good Clinical Practice (GCP) “Renovation”, which contains the ICH proposal for further modernization of the ICH Guidelines related to clinical trial design, planning, management, and conduct. The scope of the proposed renovation includes the current E8 General Considerations for Clinical Trials and further revision to the E6 Guideline for Good Clinical Practice, which is already undergoing modernization with the recent production of ICH E6(R2).

The goal of the potential renovation is to provide updated guidance that is both appropriate and flexible enough to address the increasing diversity of study types and data sources that are being employed to support regulatory and other health policy decisions, as appropriate. The underlying principles of subject protection and data quality would remain. ICH’s decision to invite stakeholder comment on the...
Purpose of GCP Renovation

• Emphasise the role of achieving quality by good design and conduct
• Ensure that innovations in technology and design and facilitated and encouraged
• Ensure the involvement of all parties up front in study planning and conduct whenever appropriate (sponsors, patients, trial participants, investigators, healthcare professionals, regulatory agencies).
• Set the foundation for responsible and efficient clinical trial conduct
• Provide principles that remain relevant as technology, methods, and design evolve

This is about doing things differently
– change –
We should not just add more to the status quo
• Establish a quality continuum throughout design and conduct
• Link to and emphasise ICH E8 focus on achieving quality by good design
• ICH E8 General Considerations on Clinical Trials and E6 GCP need modernising to prepare for the future –
  - future medicines, future trial designs, future technologies, future data sources
• Set the foundation for new study designs and conduct, technologies and data sources
ICH E8 General Considerations on Clinical Studies:
Key aspects linking to ICH E6 GCP

• General Principles
  o Protection of clinical study participants
  o Scientific approach in clinical study design, conduct and analysis
  o Patient input into study design

• Designing Quality into Clinical Studies
  o Quality by Design of clinical studies
  o Critical to quality factors
  o Approach to identifying critical to quality factors
ICH E8 Quality of a clinical study

• Quality of a clinical study is … fitness for purpose.

• Purpose of a clinical study is to generate reliable information to answer the research questions and support decision making while protecting study participants. The quality of the information generated should therefore be sufficient to support good decision making.

• Quality by design … to ensure that the quality of a study is driven proactively by designing quality into the study protocol and processes.
  
  o use prospective, multidisciplinary approach to promote the quality of protocol and process design,

  o in a manner proportionate to the risks involved,

  o clear communication of how this will be achieved.
• Establishing a Culture that Supports Open Dialogue:
  o … values and rewards critical thinking and open dialogue about quality … beyond sole reliance on tools and checklists.

• Focusing on Activities Essential to the Study:
  o … essential to the reliability and meaningfulness of study outcomes for patients … safe, ethical conduct … for study participants. Consider whether nonessential activities may be eliminated … to simplify conduct … improve efficiency … target critical areas.
Engaging Stakeholders in Study Design:

- ... best informed by input from a broad range of stakeholders, including patients and treating physicians. It should be open to challenge by subject matter experts and stakeholders from outside, as well as within, the sponsor organisation.

Reviewing Critical to Quality Factors:

- Build on accumulated experience and knowledge with periodic review of critical to quality factors to determine whether adjustments to risk control mechanisms are needed, since new or unanticipated issues may arise once the study has begun.
Involving Stakeholders in ICH GCP Renovation: Two-fold approach

- Stakeholder engagement during the drafting process:
  - Global Workshop on ICH E8 – Oct 2019
  - ICH E6 GCP stakeholder engagement plan
  - Regional Workshops on ICH E6 revision in June 2020
  - Regional Representatives of academic research engage with the ICH E6 GCP Expert Working Group – ongoing since August 2020

- Stakeholder engagement is built into the revised ICH E8 – General Considerations on Clinical Studies guideline:
  - Foresees involvement of patients in study design.
  - Including wide range of stakeholders in the design of the study and identification of what is critical to its quality.

Stakeholder involvement is essential, informative and enriching – it will lead to better guidance and better clinical trial designs, with better implementation of the processes and greatly improved results.
Clinical trials are the cornerstone for evidence generation and ensuring that they are conducted responsibly and effectively is essential.

It is a great responsibility to ensure that clinical trials are designed and conducted in a manner that respects the efforts and contributions of those participating in the trials, and in ways that address their needs.

Clarity and focus on principles are important as innovative clinical trial designs are increasingly explored – decentralized trials and trials conducted in healthcare setting.

Technology can be extremely helpful in making trials more efficient and it may enable those designing and conducting a trial to include relevant patient populations. However, the use of technology should be thoughtful and used to address specific issues. Such use should be customized to fit the purpose and design element of each trial.
• GCP should be flexible to allow for and to encourage innovation, while helping ensure the protection of trial participants and reliability of trial results

• GCP should help focus resources and efforts on what matters most for participant protection and the reliability of trial results – critical to quality factors

• Focus on the intent and goal of GCP, and allow for the many ways these can be achieved
• Comprehensive principles that remain relevant as technology evolve and clinical trial design advances

• Leveraging and facilitating an increasingly digital ecosystem

• Thoughtful process throughout clinical trial conception, design, conduct and analyses
Everyone involved in the conduct of clinical trials should read and understand these guidelines.

Change the way we all work – don’t add more to the status quo.

Change Management is the greatest challenge

– adjusting behaviors, attitudes – away from preconceived ideas and interests – and on to a new, better, way of working.

“Perfection is achieved not when there is nothing more to add but when there is nothing left to take away”  Antoine de Saint-Exupéry

“Everything should be made as simple as possible but not simpler”  Albert Einstein
E6(R3) GCP Expert Working Group
Vision & Engagement:

Lessons Learned from Public Input & Stakeholder Feedback
The aim of this presentation is to share with you:

• ICH E6 Good Clinical Practice (GCP) stakeholder engagement plan and activities

• How the Expert Working Group (EWG) collected and analyzed input from all stakeholders to inform their work
Engagement is Essential to Inform EWG Work

• Acknowledging the wide impact of E6 and the many stakeholders who are affected by this guideline, the ICH Management Committee approved an engagement plan* for the E6(R3) EWG.

• The engagement plan includes:
  o Public engagements, such as today’s web conference, and publishing updates. As a part of the EWG continuous transparency and engagement efforts, the EWG published draft, work-in-progress principles
  o Direct EWG engagement with academic experts during the EWG meetings as the work on the guideline proceeds

## EWG Stakeholder Engagement

Nominated stakeholders that engage directly with the EWG as the work evolves

<table>
<thead>
<tr>
<th>Organization Name</th>
<th>Representative Name</th>
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<tbody>
<tr>
<td>Society of Clinical Trials (USA)</td>
<td>Pamela Tenaerts, MD*</td>
</tr>
<tr>
<td>Network of Networks (Canada)</td>
<td>Lisa Johnston, RN</td>
</tr>
<tr>
<td>Patients’ and Consumers’ and Healthcare Professionals Working Parties (EU)</td>
<td>Martin Landray, PhD</td>
</tr>
<tr>
<td>Brazilian Society of Clinical Research Professionals (Brazil)</td>
<td>Vivienne Castilho, PharmD</td>
</tr>
<tr>
<td>Chinese Pharmaceutical Association (China)</td>
<td>Haiyan Li, MD</td>
</tr>
<tr>
<td>Research Group on ICH GCP Renovation (Japan)</td>
<td>Kenichi Nakamura, MD, PhD</td>
</tr>
</tbody>
</table>

* Pamela Tenaerts has subsequently left this role; a replacement will be announced.
As the EWG worked on developing E6(R3), areas and language were identified for review by stakeholder representatives.

Stakeholder representatives were invited to select EWG meetings to provide insight, input, and review.

Stakeholder representatives were also asked to review certain drafts, language, and phrases as a way to test the language for clarity, conciseness, and focus.

Stakeholder representatives provided valuable perspectives from an external reader point of view.
Stakeholder representatives provided valuable insight and input addressing key areas, such as:

- Highlight the importance of well-designed and conducted clinical trials
- Clarity on the scope of E6
- Encourage risk-based approaches across clinical trial processes
- Consider the flexibilities needed for the use of technological tools
- Address the digital data ecosystem
- Consider innovative clinical trial designs, such as decentralised trials, trials in healthcare settings, adaptive trial designs, etc.
E6(R3) development is informed by the results of an extensive analysis of stakeholder input and by consistent engagement with stakeholders.
E6(R3) EWG Analysis
Process for Analyzing Stakeholder Input

• **Goals of this analysis**
  - Identify opportunities for improvement in E6(R3)
  - Provide potential options on how and where to apply the modifications
Analysis is comprised of two approaches:

- An analysis of stakeholder comments on E6(R2)
- An analysis of select ICH guidelines to help align between relevant guidelines whenever appropriate
Stakeholder Comment Analysis

• Academic Responses
  o Open letter & published articles

• CTTI “Informing the Renovations to the ICH E6” Project
  o Stakeholder Survey, In-depth Interviews, Open Comments

• Public Engagement Materials
  o Americas Engagement Meeting
  o Europe Engagement Meeting
  o Japan Engagement Meeting

ICH Guideline Analysis

• All Efficacy Guidelines + M11
• Peer-review publications
What did the analysis of the data tell us?
Public Comments
Sections of Stakeholder Interest

- Investigator Brochure (Section 7)
- Essential Documents (Section 8)
- General
- Sponsor...
- Glossary (Section 1)
- Principles (Section...)
- IRB (Section 3)
- Investigator (Section 4)

~1300 Stakeholder Comments
Comparing ICH Guidelines
Opportunities for Clarity and Consistency

- Investigator Brochure (Section 7)
- Protocol (Section 6)
- Sponsor (Section 5)
- Investigator (Section 4)
- IRB (Section 3)
- Principles (Section 2)
- Glossary (Section 1)
- Essential Documents (Section 8)

>155 Identified Needs
Comparing Areas of Focus

PUBLIC COMMENTS

- General
- Glossary
- Principles
- IRB
- Investigator
- Sponsor
- Protocol
- IB
- ED

COMPARING ICH GUIDELINES
High-level Themes from the Findings

- Scope of E6 guideline could be further clarified
- Stakeholder engagement should inform E6(R3) revisions
- Provide additional discussion of purpose of GCP; difference between research and clinical care
- More emphasis should be placed on critical to quality factors and a proportional approach to clinical trial conduct
- E6 internal consistency and consistency between E6 and E8 should be ensured
• Consider if/how/where participants can take a more active role in GCP process
• Consider including return of trial results to participants
• Clarify/update adverse event reporting recommendations
• ICH E6(R3) should include considerations for new technologies and clinical trial designs
• Some areas lack detail (e.g., data management and the protocol sections)
What did we find after pooling the data?
Missing Key Features in Light of E8 Revisions

• Patient engagement
• Decrease burden for sites and participants
  o E.g., by involving stakeholders and planning trials closer to real life of participants and researchers
• Critical to quality factors
• Proportionality
Considerations for Responsibilities

- Clarifying investigator and sponsor responsibilities in new trial types (e.g., decentralised clinical trial settings)
- Increasing amount of investigator systems
- Contracts and agreements – clarification of requirements in relation to investigator or sponsor responsibilities (complex trial landscape)
- Acknowledgement of the diverse knowledge now required for trials
- Prequalification and performance evaluation of vendors/CROs
Considerations for Data Management

• Systems and Data, missing/lack of details regarding
  o Data Management and Statistical Analysis (5.5)
  o Adding text to bridge between E6 and E9 and include essential documents regarding these processes
  o New technology and data types (e.g., wearables, artificial intelligence)
  o More process and dataflow driven
  o IT security, user management and validation
Considerations for Monitoring

• Clarify some emerging themes and different types of quality control by different sponsor representatives to ensure data quality and sponsor oversight such as:
  o Source data and metadata review versus source data verification
  o Medical monitoring versus centralised monitoring
  o Remote monitoring, use of platforms

• Clarify requirements for review of site systems and for other prequalification activities
Areas Needing Additional Clarification

• **Protocol**
  - New trial designs
  - New systems
  - New data types
  - Additional information in some sections where little or no text

• **Essential Documents**
  - Digital documents and their retention
  - Highlight importance of recordkeeping in an ongoing manner
Areas Needing Additional Clarification

• Safety – clarity required regarding review of potential safety data
• Use of data monitoring/adjudication committee and their processes
• Informed consent
  o Consideration for different patient populations (e.g., assent)
  o Potential for use of data collected outside the trial
Examples of Proposed Minor Updates

Proposed Minor Updates (e.g., additional sentences):

• Documentation of screen failures

• Procedure for rescreening

• Timely review of safety parameters

• Documentation of what can be directly entered into the case report form (or other systems)

• Translation quality of important documents

• Procedure for site termination including informing Health Authorities

• Independence of the monitor from the site

Note: A large number of other areas have been identified
How to Prioritize Those Topics?

- Gather Data
- Conduct Analysis
- Data Review and Consolidation
- Establish Small Group (Drafting groups)
- EWG Review and Stakeholder Engagement
Initial Prioritized Sections

- Data Management / Data Governance
- Responsibilities
- Monitoring
- Informed Consent
- Safety
- Protocol
- Essential Documents
First Topics for Drafting

- **Data Management / Data Governance**
  - 233 stakeholder comments
  - E.g., digital data flow

- **Responsibilities**
  - 170 stakeholder comments
  - E.g., responsibilities of the concerned parties in relation to new technology

- **Monitoring**
  - 69 stakeholder comments
  - E.g., different types of monitoring, on-site, central, and remote
• **Small Groups**
  - Subset of full EWG
  - Divided into drafting groups to facilitate topic discussion with full EWG and leads drafting a specific topic / section
  - Regularly meet to ensure that cross-section topics are addressed and considerations applicable throughout the guidelines are aligned
## Draft Overarching Considerations

<table>
<thead>
<tr>
<th>Topic/Issue</th>
<th>Writing Group Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>New technologies, tools, and methodologies</td>
<td>Review and consider updating language in (sub)section to be inclusive of current and future advances in trial technologies, tools, and methodologies. Media neutral to allow for electronic documentation activities.</td>
</tr>
<tr>
<td>Participant engagement</td>
<td>Review (sub)section to identify any areas where participant engagement can or should be sought.</td>
</tr>
<tr>
<td>Risk assessment, critical to quality factors, and proportionality</td>
<td>Review and consider updating each (sub)section to provide additional guidance on topics associated with risk assessment, critical to quality factors, and proportionality.</td>
</tr>
<tr>
<td>Flexibility for new trial designs</td>
<td>Consider if and how language accommodates new types of trials designs (e.g., platform trials, decentralised trials, umbrella trials, trials in healthcare settings).</td>
</tr>
<tr>
<td>Flexibility for trials being conducted in exceptional circumstances</td>
<td>Determine whether (sub)section has any considerations related to trials being conducted in exceptional circumstances (e.g., during public health emergencies).</td>
</tr>
<tr>
<td>ICH Guideline consistency</td>
<td>Review each (sub)section to ensure consistency with other E6 sections and relevant ICH guidelines.</td>
</tr>
<tr>
<td>Paediatrics</td>
<td>Consider issues related to paediatric populations (e.g., assent, age-appropriate lab values and clinical measurements).</td>
</tr>
<tr>
<td>Principles</td>
<td>Ensure that (sub)section is consistent with the spirit and aim of the associated principle.</td>
</tr>
<tr>
<td>Documentation practice</td>
<td>Consider if and how good documentation practice can be applied across all documents relevant to the (sub)section (e.g., version control, signatures are unambiguous). Consider the timeliness of the documentation.</td>
</tr>
<tr>
<td>Minor edit</td>
<td>Consider changing “written” to “documented” throughout (sub)section; Consider changing “human subject/subject” to “participant” throughout (sub)section.</td>
</tr>
</tbody>
</table>
• EWG Review and Stakeholder Engagement
  o Small group will regularly consult the full EWG
  o EWG will provide stakeholder representatives with updates on progress of drafting groups
  o EWG will prioritize opportunities to engage stakeholder representatives
  o EWG will agree on the proposed concepts and draft text
• Information collected from the input analysis will continue to inform the work to develop E6(R3)
• The EWG will continue to engage with stakeholder representatives to maximize clarity and relevance of E6(R3)
• The EWG is committed to the development of E6(R3), which provides a future proofed document while still protecting trial participants and ensuring the reliability of results
Questions / Discussion
ICH E6(R3) Guideline for Good Clinical Practice (GCP)

An Important Global Standard for Clinical Trial Conduct

Draft Principles

E6(R3) Expert Working Group
International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

May 18 & 19, 2021
ICH E6(R3) GCP Principles

Overarching Principles that Apply across the Board

Annex-1

GCP for Interventional clinical trials

Considerations for non-traditional interventional clinical trials

Annex-2

Additional considerations for non-traditional interventional clinical trials not addressed in Annex-1

Draft Principles published in April 2021

Annex-1
Reflects the concepts in E6(R2) (with updates and refinements as needed)
ICH E6(R3) GCP Principles

Overarching Principles* that Apply across the Board

- Comprehensive principles that remain relevant as technology evolves and clinical trial design advances
- Leveraging and facilitating an increasingly digital ecosystem
- Risk-based approach and proportionality
- Thoughtful process throughout clinical trial conception, design, conduct and analyses
Clinical trials are a fundamental part of clinical research that support the development of new medicines or uses of existing medicines.

The principles of GCP are designed to be flexible and applicable to a broad range of clinical trials.

This guideline is being developed to encourage thoughtful consideration and planning to address specific and potentially unique aspects of an individual clinical trial.

The principles are intended to support improved and more efficient approaches to trial design and conduct. For example, innovative digital health technologies may expand the possible approaches to trial conduct. Such technologies can be incorporated in existing healthcare infrastructures and enable the use of a variety of relevant data sources in clinical trials.
The use of technology in the conduct of clinical trials should be adapted to fit the participant characteristics and the trial design.

The use of innovative technologies may help enable those designing and conducting a trial to include relevant patient populations.

The process of building quality into the design of the trial may be supported by participation of those directly involved. These may include a broad range of stakeholders, including patients and treating physicians.

This guideline is intended to be media neutral to enable the use of different technologies for the purposes of documentation.
ICH E6(R3) GCP Principles

• Clinical trials should be designed to **protect the rights, safety and well-being** of participants and assure the **reliability of results**.

• Clinical trial designs and processes should be **proportionate to the risks** inherent in the trial and the importance of the data being collected.

• Trial designs and processes should be evaluated to **minimize unnecessary complexity and burden**.
The overarching principles provide a flexible framework for clinical trial conduct.

They are structured to provide guidance throughout the lifecycle of the clinical trial.

These principles are applicable to trials involving human participants, i.e., healthy volunteers or patients.

The principles are interdependent and should be considered in their totality to assure ethical trial conduct and reliable results.
ICH E6(R3) GCP Principle 1

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practice (GCP) and applicable regulatory requirement(s).
2. Clinical trials should be designed and conducted in ways that ensure the rights, safety, and well-being of participants.

• 2.1 The rights, safety, and well-being of the participants are the most important considerations, and should prevail over interests of science and society.

• 2.2 The safety of the participants should be reviewed periodically, as new safety information becomes available which could have an impact on the participant or the conduct of the trial.

• 2.3 Foreseeable risks and inconveniences should be weighed against the anticipated benefits for the individual participants and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
2. Clinical trials should be designed and conducted in ways that ensure the rights, safety, and well-being of participants.

• 2.4 When appropriate, the participant selection process should be representative of the anticipated population who are likely to use the medicinal product in future clinical practice. When designing a clinical trial, the scientific goal and purpose should be carefully considered so as not to unnecessarily exclude particular participant populations.

• 2.5 A qualified physician or, when appropriate, a qualified dentist, should have the overall responsibility for the medical care given to, and medical decisions made on behalf of, participants; however, the practical interactions and the delivery of medical care and decisions can be carried out by appropriately qualified health care professionals in accordance with local regulations.

• 2.6 The confidentiality of information that could identify participants should be protected in accordance with applicable privacy and data protection regulations.
3. Informed consent is an integral feature of the ethical conduct of a trial. Clinical trial participation should be voluntary and based on a consent process that ensures participants are well-informed.

- **3.1** Freely given informed consent should be obtained and documented from every participant prior to clinical trial participation. For participants unable to provide informed consent, their legally authorized representative should provide consent prior to clinical trial participation.

- **3.2** The process and information provided should be designed to achieve the primary objective of enabling trial participants to make an informed decision on whether or not to participate in the trial. The informed consent process should take into consideration relevant aspects of the trial such as characteristics of the participants, the trial design, anticipated benefit and risk of medical intervention(s), setting and context in which the trial will be conducted (e.g., trials in emergency situations), and the potential use of technology to inform participants and obtain informed consent.
4. Clinical trials should be subject to objective review by an institutional review board (IRB)/independent ethics committee (IEC).

- **4.1** A trial should always be conducted in compliance with the protocol that receives prior IRB/IEC approval/favourable opinion.

- **4.2** Periodic review of the trial by the IRB/IEC should also be conducted as appropriate.
5. Clinical trials should be scientifically sound for their intended purpose, and based on robust and current scientific knowledge and approaches.

- **5.1** The available nonclinical and clinical information on an investigational product(s) should be adequate to support the proposed clinical trial.

- **5.2** Clinical trials should be scientifically sound and reflect the state of knowledge and experience with the investigational product(s); including if applicable, the condition to be treated, diagnosed, or prevented; the current understanding of the underlying biological mechanism (of both the condition and the treatment); and the population for which the investigational product is intended.

- **5.3** There should be periodic review of current scientific knowledge and approaches to determine whether adjustments to the trial are needed, since new or unanticipated information may arise once the trial has begun.
6. Clinical trials should be designed and conducted by qualified individuals.

- 6.1 Individuals with different expertise and training are needed across all phases of a clinical trial, such as physicians, scientists, ethicists, technology experts, and statisticians. Individuals involved in a trial should be qualified by education, training, and experience to perform their respective task(s).
ICH E6(R3) GCP Principle 7

7. Quality should be built into the scientific and operational design and conduct of clinical trials.

- **7.1** Quality of a clinical trial is considered in this document as fit for purpose. The quality and amount of the information generated during a clinical trial should be sufficient to support good decision making.

- **7.2** Factors critical to the quality of the trial should be identified. These factors are attributes of a trial which are fundamental to the protection of participants, the reliability and interpretability of the trial results, and the decisions made based on those trial results. These quality factors are critical because, if they were to be undermined by errors of design or conduct, the ethical basis of the trial and reliability of results could also be undermined.
7. Quality should be built into the scientific and operational design and conduct of clinical trials.

• 7.3 Quality by design in clinical trial sets out to ensure that the quality of a trial is driven proactively by designing quality into the study protocol and processes. This may involve the use of a prospective, multidisciplinary approach to promote the quality of protocol and process design, and clear communication of how this will be achieved. Quality by design approaches should be applied across the clinical trial and supporting processes.

• 7.4 Strategies should be implemented to avoid, detect, and address serious noncompliance with GCP and prevent recurrence.
8. Clinical trial processes, measures, and approaches should be proportionate to the risks to participants and to the reliability of trial results.

- **8.1** Trial processes should be proportionate to the risks inherent in the trial and the importance of the information collected. Risks in this context include risks to the rights, safety and well-being of trial participants, as well as risks to the reliability of the trial results.

- **8.2** Risks beyond those of standard medical care should be the focus of considerations; however, the risks relating to investigational products which have a marketing authorisation used in the clinical trial context may differ from the usual care of patients and should be taken into consideration.

- **8.3** The quality factors should be prioritized at the time of the trial design to identify those that are critical to the trial.

- **8.4** Risks which have an impact on the quality factors considered critical to the trial should be managed.
9. Clinical trials should be described in a clear, concise, and operationally feasible protocol.

- **9.1** A well-designed trial protocol is a fundamental component for protection of participants and for the generation of reliable results.
- **9.2** The scientific objectives of any trial should be clear and explicitly stated in the protocol.
- **9.3** Trial processes should be operationally feasible and avoid unnecessary complexity, procedures, and data collection. Trial processes should support the study key objectives.
- **9.4** The clinical trial protocol as well as the plans or documents for the protocol execution (e.g., statistical analysis plan, data monitoring plan) should be clear, concise, and operationally feasible.
ICH E6(R3) GCP Principle 10

10. Clinical trials should generate reliable results.

- **10.1** The quality and amount of the information generated in a clinical trial should be sufficient to provide confidence in the trial's results and support good decision making.

- **10.2** Systems and processes that help ensure the quality of the information generated from the clinical trial should be implemented in a way that is proportionate to the risks to participants and the reliability of trial results.

- **10.3** Tools that aid in data capture, management, and analyses should be fit for purpose, should capture the information required by the protocol, and should conform to principles that ensure reliable results.

- **10.4** Digital systems used for clinical trial purposes should consider the factors critical to their quality in their design and be fit for purpose. To this end, validation of systems, data protection, information technology (IT) security and user management are important elements that should be addressed.
ICH E6(R3) GCP Principle 10 (cont.)

10. Clinical trials should generate reliable results.

- **10.5** Clinical trials should incorporate efficient and well-controlled processes for managing information through appropriate management of data integrity, traceability, and protection of personal information, thereby allowing the accurate reporting, interpretation, and verification of the clinical trial-related information.

- **10.6** Clinical trial-related information should be retained securely by sponsors and investigators for the required period of time and should be available to regulatory authorities upon request to enable reconstruction of the trial conduct and results in order to ensure reliability of trial results.

- **10.7** The transparency of clinical trials in drug development includes registration on publicly accessible and recognized databases, and the public posting of clinical trial results.

- **10.8** The principles in this section for trial information and documentation apply irrespective of the type of media used.
ICH E6(R3) GCP Principle 11

11. Roles, tasks and responsibilities in clinical trials should be clear and documented appropriately.

- **11.1** The sponsor and investigator may delegate some or all of their tasks but retain overall responsibility for the quality and integrity of trial conduct and the safety of participants.

- **11.2** Agreements should clearly define the roles, tasks and responsibilities for the clinical trial and be documented appropriately. Where tasks have been delegated or contracted to third parties, the responsibility is retained by the sponsor or investigator who should maintain appropriate oversight of these tasks.
ICH E6(R3) GCP Principle 12

12. Investigational products used in a clinical trial should be manufactured in accordance with applicable Good Manufacturing Practice (GMP) standards and be stored, shipped, and handled in accordance with the product specifications and the trial protocol.

- **12.1** Investigational products used in a clinical trial should be manufactured in accordance with applicable GMP.
- **12.2** Measures should be in place to ensure that the investigational product provided to trial participants retains its quality.
- **12.3** Investigational products should be used in accordance with the protocol and relevant study documents.
12. Investigational products used in a clinical trial should be manufactured in accordance with applicable Good Manufacturing Practice (GMP) standards and be stored, shipped, and handled in accordance with the product specifications and the trial protocol.

• 12.4 Manufacturing, handling, and labelling of investigational products should be undertaken in a manner that maintains blinding, and treatment assignment, where applicable.

• 12.5 Investigational product labelling should follow the appropriate regulatory requirements.

• 12.6 Risk-based approaches should be considered when implementing proportionate measures to ensure GMP and the appropriate shipping and handling of the investigational product.
Well designed and conducted clinical trials are essential.

The EWG shares the perspective that trials should be efficient and robust to inform the decisions of many stakeholders.

ICH E6(R3) is being developed as a robust and responsive guideline that facilitates innovation while protecting trial participants.

The EWG is actively working on Annex-1 and will continue to focus on a risk-based approach to GCP that facilitates innovation and protects clinical trial participants.

The EWG will continue to engage with stakeholders to further enrich this discussion.
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Stakeholder Reflections & Vision

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Stakeholder Reflections and Vision for ICH E6

ICH E6-Good Clinical Practice (GCP) - Update on Progress
Public Web Conference
May 18-19, 2021

Janette Panhuis
Chief Operating Officer, PHRI
Reflections on the Quality Objective

Objective
(Pharmacology? / Exploratory? / Confirmatory?)

Design
(Endpoints? / Controls? / Population?)

Conduct
(Site Expertise? / Participant Compliance?)

Analysis
(Data Quality?)

Report

Safety Profile?

Standard of Care?

Multi-Centre?

Population?

Data Types?
Reflection of “E Family” Integration

Sound Design (E4, E8, E9, E10) → Research Methodology (E8, E9) → Quality of Analysis (E6)

Scientific & Ethical Integrity (E2, E3, E9, E10) → Subject Protection/Safety (E2, E3) → Safety of Subjects (E6)

Clinically Relevant (E10, E17) → Quality of Recruitment (E10, E17) → Compliance / Adherence (E6)

Essential Data (E2, E3, E9) → CRF Quality (E9) → Quality of Data (E6)

Quality of Protocol

Quality Results
Vision for E6

CREATE a culture that values and rewards critical thinking about quality risks.

➢ Move away from reliance on checklists and generic standards

Focus on activities that are essential to study outcomes

➢ Prospectively identify and periodically review the critical to quality factors

* CTTI QbD
Vision for E6

- **Less is more**
  - Principles start the journey of “more”
  - Risk Management is key to focusing on “less”
  - Annexes should be the roadmap enabling researchers to achieve this

- **Integration**
  - Integration with other guidelines to establish a clear Risk management path
Vision for Risk Management

- Critical to Quality Factors become the standard for Risk Identification:
  - (draft) E8(R1) step 3 has mapped CtQ factors

- RM starts at study design:
  - Many Risk control strategies can be defined in the protocol (if RM starts early)

- Risk Review and Reporting is built in to study conduct and a natural “by-product”

www.phri.ca
Vision for Annex-2

Beyond non-traditional design
• RM will address design risks

Recognize the type of intervention
• Procedural
• Standard of care

Lessen burden using “Fit for Purpose” principle

Fit for Purpose:
• Qualifications of:
  • Personnel
  • Equipment
  • Systems
• IRB
• Data sources
• Measurements
Vision for Annex-2

ANNEX-1

GCP:
- In-Scope clarity
- Regulatory

Principles
Fit for purpose

ANNEX-2

Considerations:
- Intervention type
- Out-of-Scope clarity
- Downstream Impact

Population Health Research Institute
Hamilton Health Sciences
McMaster University
Innovation and E6

Innovation is about *implementation* of new ideas

- availability of new technology is not enough

**Technologic Innovation:**

- Guidelines should foster integration using Risk Management concepts

**Trial Conduct Innovation:**

- Measures of trial conduct are Principle-based
- Annex 1 and 2 provisions need to state the flexibility
Innovation in Trial Conduct

Principles provide guidance and objectives to meet:

3. **Informed Consent:**
   - In line with trial characteristics
   - On-line, Recording, Authentication

5. **Scientifically Sound**
   - Current knowledge and understanding
   - Adaptive Design, Novel Endpoints, Real-world evidence
Innovation in Trial Conduct

Principles provide guidance and objectives to meet:

9. **Operational feasibility**
   - Explicit, Avoid complexity, support key objectives
   - Fundamental to protections and reliability
     - Qualified personnel (#6), Decentralized trials, Virtual visits

10. **Reliable Results**
    - Data Sources, Central Data Monitoring
    - Remote Site Monitoring
Conclusion

ICH E6 R3
- Must reflect an understanding nascent quality attributes in study design
- Application of scientific principles in risk assessment
- Systematic approach
- Integration of E Guidelines – via ICH (draft) E8(R1) step 3
  - an integral part of core concepts for risk management and quality
Thank you
Stakeholder reflections and vision
- a Japanese investigator’s perspective on GCP

Kenichi NAKAMURA MD PhD
National Cancer Center Hospital JAPAN
Japanese investigators’ interests on E6(R3)

- **Scope of ICH-GCP**
  - Will non-drug interventional studies be incorporated?
  - Can all drug interventional studies be utilized for pharmaceutical application?

- **Utilization of registry data/real world data**
Confusion about the scope of E6(R2)

INTRODUCTION

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The objective of this ICH GCP Guideline is to provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

The guideline was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO).

This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities.

The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.

ICH-GCP should be applied only to clinical trials aiming at New Drug Application (NDA)

ALL clinical trials including medical device, radiotherapy and surgery should be compliant with ICH-GCP
Interventional study

Do you intend to use the trial result for pharmaceutical approval?

- NO
  - Do you intend to clarify the efficacy or safety of pharmaceuticals* by the use of such pharmaceuticals in humans?
    - YES
      - Do you use unapproved or off-label pharmaceuticals?
        - YES
          - Do you receive research funds or other benefits provided by a manufacturer with marketing approval for pharmaceuticals?
            - Either is YES
            - Both are NO
          - Clinical Trials under the Ethical Guidelines
            - Ethical Guidelines
              - Clinical Trials Act
                - Clinical Trials under the Ethical Guidelines
                  - Advanced Medical Care System (add on)
                    - Concept of ICH-E6 is incorporated, but not comprehensively.
                      (e.g., essential documents are not fully required)
    - NO
      - Investigator-initiated registration directed trials
        - Pharmaceutical Affairs Law, Japanese-GCP
          - ICH-E6 is directly applied to this category
          - Concept of ICH-E6 is incorporated, but not comprehensively.
            (e.g., essential documents are not fully required)

* Either pharmaceuticals, medical devices or regenerative medicine products

(Nakamura K, Shibata T. Jpn J Clin Oncol 2020)
Current Japanese situation

- Descriptive difference between J-GCP and ICH-GCP has decreased, but the required quality level for NDA is still strict in Japan.
- Basically, only clinical trials under strict J-GCP can be utilized for NDA.
- Even for expanding drug indication for rare diseases or pediatric patients, investigator-initiated registration-directed trials under strict J-GCP should be conducted using more than one million USD.
- Although many clinical trials under the Clinical Trials Act do not primarily intend NDA, it is unclear whether clinical trials under the Act can be used for NDA.
No matter what the purpose of trial is, we should strive for clinical trials of a quality that helps answer the questions sufficiently.

Required quality level and the clinical trial cost should be proportionate to the risks in each trial and the importance of the information collected.

Some clinical trials under Clinical Trials Act do not originally intend NDA and their data quality is various; however, if some trials fulfill required regulatory grade, they should be utilized for NDA as a secondary purpose.
Japanese investigators’ interests on E6(R3)

- Scope of ICH-GCP
  - Will non-drug interventional studies be incorporated?
  - Can all drug interventional studies be utilized for pharmaceutical application?

- Utilization of registry data/real world data
MASTER KEY project

Molecular Diagnostic testing (NGS, IHC, etc)

- Rare cancer
- Rare histological subtype
- Carcinoma of unknown primary
- Pediatric cancers
- Hematologic malignancies

Follow-up of all pts
[A large scale reliable database]

Registry part

>1800 patients

I.C. Registration

Review biomarker status

Treatment assigned by physician

MK Clinical trial part

Biomarker A
Drug A Clinical trial

Biomarker B
Drug B Clinical trial

Biomarker negative
Drug X Clinical trial
Drug Y Clinical trial

14 ongoing trials

Other treatment

Other clinical trial
Drug XX

Routine practice treatment
Reimbursed treatment

Follow-up of all pts
[A large scale reliable database]
Adaptive monitoring for the MK registry

- Current data management in MK registry
  - Central monitoring by data managers
  - Sampling routine on-site monitoring to assure the quality of process management

- Do we need intensive on-site monitoring for the registry part?
  - It is difficult and inefficient to perform 100% source data verification
    - Data used as a historical control for one product would usually be less than 5%
  - Data quality should be "fit-for-purpose", but we cannot determine the purpose or required quality of the registry in advance
  - After the purpose and the required data quality of each product is determined, we perform “add-on monitoring” to fulfill the required quality level of each project
Potential regulatory usage of registry data

- New drug application: “Evaluation data”
  - Safety and efficacy information of off-label use
  - Comparator of single arm clinical trial

- New drug application: “Reference data”
  - Safety and efficacy information of off-label use

- New drug application: supplementary/related information
  - Post market commitment required for conditional early approval
  - Surveillance sometimes required for the public knowledge-based application
  - Clarification for the borderline of indication
  - Platform for clinical trials

- Reexamination drug application
  - Post-marketing surveillance
Registry data under E6(R3)

- The purpose of registry data utilization should be well-considered and the required regulatory grade be determined proportionately
  - Purposes to use registry data/RWD would be different in each project/product

- Some additional procedures such as adaptive monitoring may be a solution to fulfill regulatory grade
  - Original purposes of most existing registries or real-world data are not NDA
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  - Yoshiyuki MAJIMA Rare Cancers Japan (RCJ)
  - Nobuhiro UMESAWA Ethics Committee member of National Cancer Center
  - Kiyo MATSUZAWA Ethics Committee member of National Cancer Center
The patient at the centre of clinical research – and how ICH guidelines can support this vision

Marco Greco, President, European Patients’ Forum
Patient-driven research is an imperative

• From a moral point of view – because patients are the end-users of therapies and have a right to participate in research as partners

• From an instrumental point of view – because patients and society (payers) want innovation that brings added value – and this is only possible when patient perspective is fully integrated in research from the start

• One of the main reasons for “waste” in clinical research is when trials focus on research questions or measure outcomes that are not prioritised by patients (Chalmers et al, 2014)
Patient involvement in trial design adds value

Patients bring unique knowledge and practical insights from experience

- Patients “always” offer unique, invaluable insights → their advice when designing, implementing and evaluating research “invariably” makes studies more effective, more credible, and often more cost-efficient (INVOLVE, 2009)
- Patient involvement improves outcome measures, recruitment (better recruitment strategy), retention (managing expectations), response rates, dissemination of findings (PatientPartner project, 2007)
- Increasing public confidence in clinical trials and appreciation of volunteers who participate in trials (EPF, 2011)
- Patient Focussed Drug Development Reflection Paper of ICH;
  - ICH E8 includes Patient Engagement as a key principle in that (section 2.3)

“HCPs see non-compliance, but patients can perceive poor communication, insufficient information or unhelpful attitude”

“In degenerative disease, not getting any worse may be equally valuable to getting better”
Knowledge and practical value → economic value

Partnership with patients makes also economic sense

- Impact of a patient engagement activity that avoids one protocol amendment and improves enrolment, adherence, and retention is cumulative → increase in net present value of $62-65m, increase in expected net present value of $35-75m [1]

- NPV and ENPV [2] increase can exceed 500 x the investment in patient engagement → equivalent to accelerating product launch by 1.5-2.5 years (Levitan et al., 2017)

- Drugs developed using patient-centric designs recruit participants more quickly, and are more likely to be launched (87%) compared to other trials (68%) (Economist Intelligence Unit)

[1] depending on whether trial is phase 2 or 3
[2] ENPV integrates key business drivers (cost, time, revenue, risk) into a summary metric for project strategy and portfolio decisions
How to increase participation

What makes a clinical trial attractive to patients?

- Patient-centric co-design and management
- Participation as convenient as possible and for patients (extra burden)
- Ethical conduct
- Relevant inclusion & exclusion criteria
- Research question and endpoints – clinical, QoL – are both relevant and meaningful to patients
- Quality data at the end + transparency of the results and data (publication)
Some reflections on the ICH draft principles

• Representativeness
  – Point 2.4. “When appropriate, the participant selection process should be representative of the anticipated population who are likely to use the medicinal product in future clinical practice.” Should this not be always, unless otherwise justified?
  – EU Clinical Trial Regulation mandates representativeness - exceptions must be justified in protocol (recital 14, Annex 1.D.17.y)
  – The principles do recognise that digital technology may help outreach towards communities of people

• Informed consent
  – Point 3: mention importance of co-design → informed consent that is “fit for purpose”
  – More details regarding potential of digital technologies would be useful (in annex?)
Some reflections on the ICH draft principles

• Patient involvement
  – Current draft principles do not mention patient involvement
  – Calls have been made for recognition of co-production a separate section on this (EMA workshop report)
  – Patient roles can range from advisory to co-researcher – increasingly patient advocates are trained → evolution in the patient role should be recognised in ICH guidance
  – Resources exist that can be used to shape best-practice principles
  – Many patient organisations would like to be involved – capacity limitations → need to be enabled
Involvement across the life-cycle

This requires co-operation between all actors

THANK YOU FOR YOUR ATTENTION!

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“A STRONG PATIENTS’ VOICE TO DRIVE BETTER HEALTH IN EUROPE”
ICH E6(R3) Guideline for Good Clinical Practice (GCP)

Update on Progress

THANK YOU!

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May 18 & 19, 2021