ICH E6 Guideline for Good Clinical Practice (GCP) – Update on Progress

Public Web Conference Report

May 18 & 19, 2021

Introduction

On behalf of the International Council for Harmonisation (ICH), the Expert Working Group (EWG) for ICH E6 Guideline for Good Clinical Practice (GCP) held a public web conference[1] on May 18 and 19, 2021 with more than 5100 attendees across the globe to provide a public update on the progress to revise this guideline. ICH E6 GCP is the international ethical, scientific, and quality standard for the conduct of clinical trials for the development of new drugs and biologics involving human participants intended to support regulatory applications. This guideline establishes globally agreed upon requirements for design and conduct of interventional clinical trials of drugs and biologics.

To enhance transparency and stakeholder engagement beyond the traditional ICH process, ICH published the draft work-in-progress version of principles for ICH E6 on April 19, 2021.[2] The EWG is not taking public comments on the principles at this stage. However, the EWG will invite and consider public consultation once the ICH E6 Guideline achieves Step 3 of the ICH guideline development process which is anticipated in 2022[3]. ICH hosted the May 18-19 web conference to update international parties on the EWG's progress to revise the principles and provide flexibility and applicability to a broad range of clinical trials.

This report highlights key issues from the EWG in the draft work-in-progress principles, and themes raised by stakeholders during the public web conference.

Background

Due to the wide impact of this important guideline, the ICH Management Committee has taken specific steps to keep the public informed on the status of the work by sharing publicly the EWG progress, and engaging academic investigators as well as patients and trial participants in various ways during the guideline development process.[4,5]

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[1] The web conference was convened by the Clinical Trials Transformation Initiative (CTTI), which is a public-private partnership co-founded by FDA, United States and Duke University in 2007.

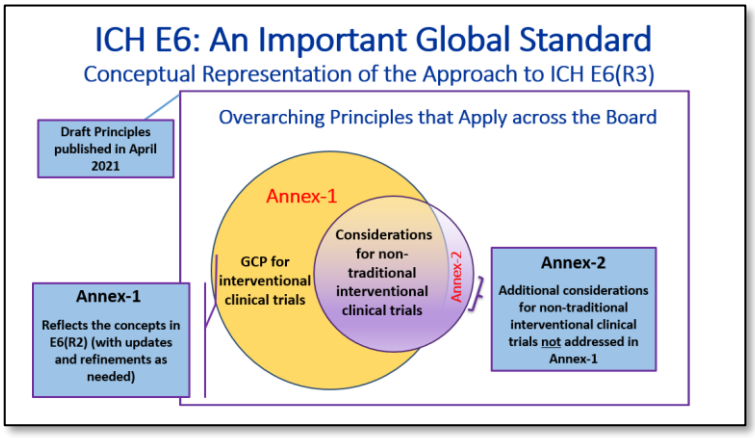
[2] View the principles on the ICH website.

[3] View the work plan on the ICH website.

[4] For further information on the engagement approach, please see the published outline of the ICH E6 engagement proposal.

[5] Other materials on ICH E6(R2), including the current guideline, the business plan, work plan, an expert list, and reports of prior public engagements, are available on the ICH website.

ICH E6(R3) will consist of the overarching principles and two annexes that together are intended to be responsive across clinical trial types and settings, and relevant as clinical research and associated technologies and methodologies advance. The principles and annex 1 will reflect and replace the content and scope of the current ICH E6(R2). Work on annex 2 will proceed after annex 1 is released for public consultation and will provide additional considerations for non-traditional trials. Together, these materials will represent ICH E6(R3) (the third version).



CONFERENCE OVERVIEW

At this international public web conference, EWG members presented the current work to revise the guideline. The first session included a video from the EWG to explain the ICH guideline development process and the ICH E6 guideline revision. During the second session, the EWG shared the vision and goals for the ICH E6 as well as the ICH E8 General Considerations for Clinical Studies. The EWG highlighted the importance of a quality continuum in the design and conduct of clinical trials. EWG members also presented on their extensive review of public comments on ICH E6(R2) and stakeholder input to ensure that they are considering multiple perspectives as they work on revising ICH E6(R2). In the final session, EWG members presented the newly published draft principles, and stakeholders provided their reflections of ICH E6(R2) and their visions and aspirations for future clinical trial design and conduct.

SESSIONS

Vision and Goals for ICH E6(R3) Focus on the Importance of Quality

The EWG shared the vision and goals for ICH E6(R3) and the connections with ICH E8 on General Considerations for Clinical Studies. The EWG highlighted the importance of the quality continuum in the design and conduct of clinical trials.[6] Quality is essential across all aspects of the trial. The quality continuum encourages a focus on factors that are critical to quality – those factors which are most important and provide a clear approach to identifying and implementing critical design aspects and clinical trial practices. The EWG encourages the use of approaches to protocol design and trial processes that are proportionate to the risks to participants and to the importance of the data being generated. The EWG highlighted their approach to revising the guideline in a way that encourages thoughtful design and conduct that takes into consideration the specifics of each trial. The EWG vision is that GCP should be flexible to allow for and encourage innovation and focus efforts and resources on what matters most for ensuring protection of trial participants, and reliability of trial results.

[6] ICH E6 and ICH E8 are being revised as part of GCP renovation.

Lessons Learned from Public Input and Stakeholder Feedback

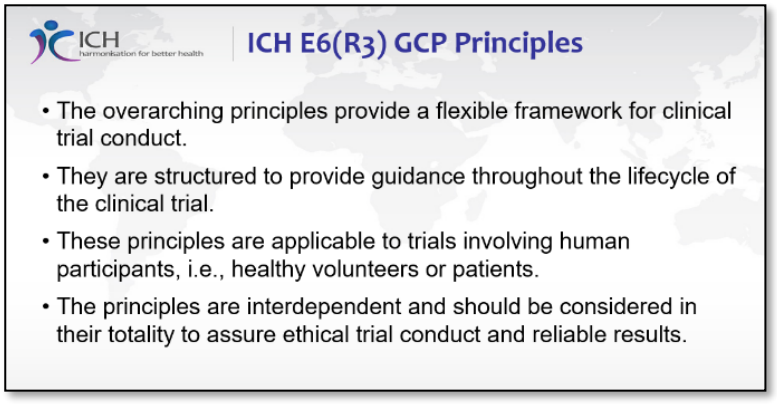
The EWG shared the steps it is taking to increase engagement with stakeholders, including working with investigators, trial participants, and the public at large, to inform the work on ICH E6(R3). The EWG engaged – and continues to involve – academic clinical investigators through meetings to obtain feedback on relevant issues, such as experience with clinical trials and insights on aspects of applying GCP. The EWG reported that engaging with stakeholders was one of the most useful activities that is helping to make ICH E6(R3) a responsive guideline.

As part of considering stakeholder perspectives, the EWG reviewed public comments, conducted analysis of ICH guidelines, and obtained input from experts and from stakeholder engagement meetings. EWG members reviewed hundreds of comments in response to the publication of ICH E6(R2) and identified a number of specific needs for improvement. The comments helped identify areas where modifications, updates, or further clarity can be useful. The input, for example, identified responsibilities of sponsors and investigators as an area where further clarity can be helpful. New technologies and clinical trial designs are continuing to advance rapidly, which was in part catalyzed by the COVID-19 pandemic. Sections on data management and protocols will address the greater use of digital tools and direct data capture, including as the use of data collected outside of trial settings is being explored. Given the increasing breadth of data and the use of multiple systems by investigators, the EWG also will consider exploring the topic of data management to clarify the requirements.

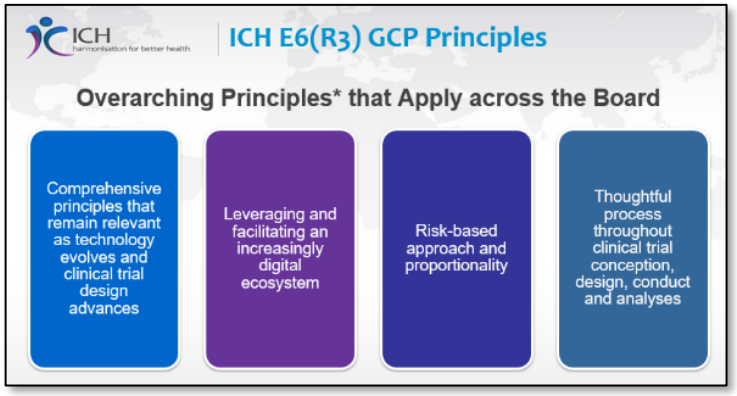
The Principles

The preamble to the principles provides important context and clarity on how to read, understand and utilize the principles. The EWG highlighted that the principles will support improved and more efficient approaches to trial design and conduct. One key element that the preamble highlighted is that trial designs and the processes involved in trial conduct should be proportionate to the risks inherent in the trial and the importance of the data collected. Building quality into the design will enable protocols and processes to minimize unnecessary complexity and burdens.

The EWG prepared and published the draft work-in-progress principles to provide a thoughtful and comprehensive approach to GCP and to emphasize the main elements that are essential for all clinical trials to maintain GCP. The principles are designed to be flexible to encourage innovation and applicable to a broad range of clinical trials while continuing to ensure protection of trial participants and reliability of trial results.



The principles also should: (a) remain relevant as technology, methods, and trial designs evolve and (b) support improved and more efficient approaches to trial design and conduct. They apply to a broad range of trials, including those that incorporate existing health care infrastructures, and enable the use of relevant data sources, such as real-world data.



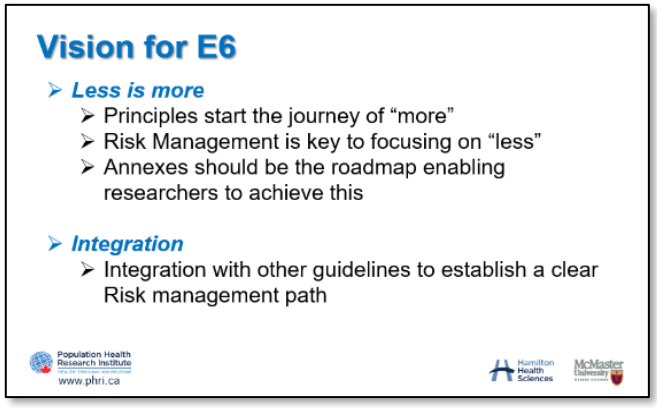
The principles will enable investigators and sponsors to build quality into trial design with support of many stakeholders, including patients and physicians.

View the published principles on the ICH website.

Stakeholder Reflections and Vision

Several stakeholder representatives shared their reflections on GCP and their vision and aspirations for clinical trials.

Ms. Janette Panhuis, from the Population Health Research Institute in Canada, highlighted the benefits of building quality into clinical trial design by incorporating critical thinking to help re-envision clinical trial processes. GCP requires the assessment of factors that define quality in order to manage quality at each stage, as quality is progressive and impactful in clinical trials. Patient safety starts with scientific integrity and quality of the trial. As Ms. Panhuis explained, creating a culture that values and rewards thinking about quality issues is needed to move away from checklists and generic standards. Less is more; using risk management approaches to trial design and conduct is the key to identifying and addressing critical risks that may affect trial quality or participant safety. By reading and utilizing ICH E6 in conjunction with other relevant ICH guidelines, a risk management path can be envisioned – starting with trial design. Further, risk evaluation and management can be built into trial conduct. Trial processes and quality safeguards need to be fit for purpose – designed to be commensurate with the trial characteristics to lessen unnecessary burden. Quality design that is fit for purpose would also allow for subsequent modifications to adapt to the changing clinical trial landscape.



Dr. Kenichi Nakamura, National Cancer Center Hospital in Japan, discussed how ICH E6 applies to clinical trials in Japan and the interaction between ICH GCP and GCP principles from Japanese regulatory authorities. He encouraged the use of new processes and measures to enable the use of new data sources in trials, such as real-world data and registry data, while maintaining GCP. He mentioned that it is difficult to determine in advance how data quality should be fit for purpose, when the purpose of data collection is not always known up front. In addition, data are collected for different purposes and have variable quality. He urged that requirements for data quality should be determined proportionately based on the intended purpose of using any particular data source.

Dr. Marco Greco of the European Patients Forum emphasized that the patient should be at the center of clinical trials. Patients can always offer unique and valuable insights and should be involved, including as collaborators. Patient involvement and awareness of participant needs for trial design, implementation, and research evaluation can improve outcome measures and recruitment strategies, increase retention, and aid in dissemination of findings as well as increase public confidence in trials. The role of patient representatives should always be encouraged as the benefits may have untold value, including reducing trial timelines, which results in more efficient trials.

KEY THEMES FROM Q&A

The attendees of the web conference provided multiple comments and questions for EWG consideration. Key themes included:

- Informed consent – Consider addressing and facilitating the electronic consent process, including the use of digital technology to facilitate the consent process (e.g., remote consent options).
- Changing trial design and data sources – Consider the potential uses of noninterventional study designs, and the use of new data sources, such as real-world data including data from electronic health records, wearable devices, and the use of predictive algorithms and artificial intelligence.
- Quality and critical thinking – Consider demonstrating how to use critical thinking and critical to quality factors for good design and conduct, as well as discussing the culture of quality.
- Data management – Consider addressing remote source data verification and systems validation.
- Patient engagement – Consider providing suggestions and best practices on ways to involve patients in clinical trials from study design to conduct.
- Responsibilities – Consider addressing oversight of decentralized trials with management of mobile health care providers, home patient visits, delegations of authority, and definition of sites.
- Monitoring – Consider providing information on how to distinguish critical and non-critical data for risk-based monitoring; discuss central monitoring.
- Inspections – Consider the use of remote GCP inspections developed during COVID.
- Essential documents – Consider the retention of essential information instead of essential documents.

CLOSING

The EWG appreciates the excellent discussion and will take the comments and questions into consideration as it continues to revise ICH E6. The EWG will strive to be forward thinking to accommodate the many ongoing developments and innovations in clinical trials, so that ICH E6 can remain relevant for future clinical trial designs and innovations. The EWG is committed to continuing its work to advance efficient and innovative clinical trials that help address public health needs.

LIST OF SPEAKERS

ICH E6 Expert Working Group Representatives

Nitin Bagul, TGA, Australia
M. Khair ElZarrad, FDA, United States
Gail Francis, PIC/S
Kanako Ito, PMDA, Japan
Carole Légaré, Health Canada, Canada
Miriam Onishi, ANVISA, Brazil
Sumitra Sachidanandan, HSA, Singapore
Rebecca Stanbrook, EFPIA
Fergus Sweeney, EC, Europe
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Speakers

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Dr. Marco Greco, European Patients Forum, Europe
Dr. Kenichi Nakamura, National Cancer Center Hospital, Japan
Ms. Janette Panhuis, Population Health Research Institute, Canada
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