Stakeholder Engagement on ICH E6 Guideline for Good Clinical Practice

Public Web Conference Report

Introduction

The US Food and Drug Administration (FDA) in collaboration with the Clinical Trials Transformation Initiative (CTTI) held a public web conference entitled, Stakeholder Engagement on ICH E6 Guideline for Good Clinical Practice (GCP).[1] ICH E6 is one of the most impactful guidelines on clinical trial conduct that affects a variety of stakeholders. The web conference described in this report is part of a multifaceted International Council for Harmonisation (ICH) pilot engagement program to capture and consider the experiences of stakeholders that may be affected by ICH E6.

The ICH E6 Expert Working Group (EWG), which is charged with updating the Good Clinical Practice guideline, determined that capturing experiences and perspectives on clinical trial participation, conduct, management, and coordination from a variety of stakeholders would further enrich the discussions of the group, and would enable the EWG to consider these experiences and perspectives in the development of the updated ICH E6(R3) guideline. Ultimately, these engagements will assist the EWG in developing a guideline that is responsive to the needs of all stakeholders. The web conference focused on the Pan American region to complement engagement efforts from EWG members across the globe.

The web conference was held on Thursday, June 4, and Friday, June 5, from 10 am – 1 pm (Eastern Time) each day, with key input from ICH members representing ANVISA (Brazil), Health Canada (Canada), and FDA and the Pharmaceutical Manufacturers of America (PhRMA) (United States). While intending to hold an in-person meeting with experts and stakeholders, the format was changed to a web-only conference due to the COVID-19 global pandemic, declared by the World Health Organization (WHO) in March 2020.

Commitment to Early Engagement with Stakeholders

The ICH E6(R3) EWG is committed to timely engagement with stakeholders in the revision process to obtain input at an early stage to inform the revision, prior to releasing a draft revised guideline for public input as a part of the ICH regular guidance development and harmonisation process.[2] Thus, the EWG invited a diverse group of stakeholders to share their views and experiences at the meeting, obtained comments and questions via email before the

[1] ICH E6 Guideline for Good Clinical Practice is hereinafter referred to as "the guideline" in this report.
[2] ICH Process of Harmonisation is available at https://www.ich.org/page/process-harmonisation.

conference, and obtained further input during the conference through a "chat box" from conference viewers. The conference concluded with public comments from interested stakeholders from academic institutions, as well as industry. Considering that the EWG is rich with representatives from industry and regulatory organizations, the web conference was designed to hear from those who may not necessarily be represented on the EWG. Therefore, the speakers and panelists at the web conference represented academic clinical trialists, ethicists, clinical research managers, representatives from global research and public health organizations, and patients.

This meeting report outlines the meeting format and panels, and highlights specific comments for consideration by the EWG in revising the E6 guideline and other guidelines, where appropriate. This report represents key themes heard from stakeholders, but is not inclusive of all input. Additional meeting details, including the agenda, meeting recording, and presentation slides, are available at the meeting website at: https://www.ctti-clinicaltrials.org/briefing-room/meetings/ich-e6-guideline-good-clinical-practice-stakeholder-engagement.

DAY 1

On the first day, ICH experts provided an overview of the ICH process to revise guidelines. EWG members in attendance[3] then updated the attendees with their approach to revising ICH E6. The updated guideline will start with principles that apply across clinical trial designs and settings. The EWG highlighted that they are working on comprehensive principles that will remain relevant as technologies evolve and clinical trial design advances.

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Along with the principles, the EWG will prepare annexes to address and provide the details relevant to different trial designs. The first annex will be based on the existing language in the current version of E6 with modifications and updates to add clarity when needed and to be responsive to both the community's needs and to advances in design and technology. The second annex will address GCP considerations for nontraditional clinical trials that may not be addressed in the first annex, such as trials with pragmatic elements, decentralized clinical trials, as well as trials utilizing real-world data. The EWG is developing the principles and annex 1 simultaneously. Once the principles and annex 1 reach the development stage where they are made public for comments, the EWG will focus on annex 2 after receiving approval from the ICH management committee on the scope of annex 2. The feedback the EWG receives from the public's review of the principles and annex 1 will also inform the development of annex 2.

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[3] Reference to EWG members includes representatives from Brazil, Canada, and the US, consistent with the regional focus of stakeholder engagement.

On the next panel, CTTI provided a summary of its project to obtain stakeholder experiences with ICH E6(R2) with input from more than 300 stakeholders across the globe. CTTI's findings helped to provide a snapshot of stakeholder concerns and set the tone for the meeting. Although the survey's responses indicated that substantial parts of ICH E6(R2) do not require changes, they pointed to areas within the guideline where improvements and further clarity will be helpful. Following this overview, EWG members from Brazil, Canada, and the US presented their perspectives for the guideline's revision with the objective to make the guideline more responsive to stakeholders who conduct or participate in clinical trials in their areas. The presentation highlighted the alignment between EWG members on the key elements that should be considered in the development of ICH E6(R3) and the importance of engagement throughout the process.

The first panel of stakeholders represented clinical investigators, clinical trial managers, and coordinators who provided their perspectives on the impact of the GCP guideline. Then, two stakeholder panels shared their views. Their comments focused on how the guideline can be at times over-interpreted leading to inflexible criteria that increase the cost of trials, without necessarily aiding trial participant safety or further ensuring the integrity of the trial. The second stakeholder panel consisted of patient advocates who shared their experiences as trial participants and advocates. They emphasized the value that participants bring to the clinical trial enterprise from trial design to conduct, and trial follow-up. Also, they encouraged E6 to continue to consider engagement with participants throughout the guideline development process.

DAY 2

On the second day, the final stakeholder panel represented a clinical investigator from Canada, an institutional review board (IRB) perspective from the US, and stakeholders focused on clinical trials in low and middle income countries as well as Pan American countries. This panel highlighted how the GCP guideline impacts institutional research and facilitates research in other countries. The panel also highlighted the need for effective communications between all parties involved in conducting a clinical trial.

A discussion followed wherein EWG members provided feedback about various themes that stakeholders provided before the meeting. The conference concluded with public comments from stakeholders for further consideration by the EWG. EWG members in attendance noted that although not all input is necessarily within the scope of the guideline, the EWG will consider the perspective and the lessons learned across the board. EWG members expressed their thanks and appreciation for the input received from many stakeholders.

MAIN THEMES

1. Stakeholders suggested that the guideline provide further clarity about the applicability of E6 to various trial designs while still focusing on key concepts, such as risk-based approach, proportionality, and fit-for-purpose. Stakeholders suggested that the guideline include flexibilities to address innovative trial design, new data sources, and

trials conducted during public health emergencies. Also, they suggested that the language used should be drafted to minimize over-interpretation which could burden trials and trialists when applied as one standard approach to all trials. Stakeholders highlighted the need for the guideline to be adaptable to accommodate new trial designs (e.g., decentralized trials, platform, and adaptive trials), and new data sources, such as real world data (e.g., electronic health records or insurance claims).

2. Stakeholders highlighted the need to consider the accelerating trends in utilizing remote technology for data capture and trial monitoring, and the increased use of decentralized trial design. Stakeholders pointed that these trends are now being accelerated due to the COVID public health emergency, adding emphases on the use of telehealth, remote operations, and other clinical trials modalities, such as the use of eConsent and remote training. These tools and advances can contribute to facilitating clinical trials across all phases of design and conduct.
3. The web conference also highlighted the importance of input from many clinical trials stakeholders, including investigators, academic research institutions, as well as trial participants. Stakeholders also urged the EWG to engage participants as partners in protocol design, trial conduct, and other aspects of clinical trials, as appropriate.

KEY COMMENTS

Stakeholders provided many insights for EWG consideration to enable the GCP guideline to zero in on core principles for all trials, and areas for flexibility and adaptability to encompass the current and future clinical trial landscape, including trial designs and data sources.

Scope and Flexibility

- The ICH E6 guideline needs to be applied with flexibility using a risk-based approach and proportionality to different types of research, such as the numerous interventional clinical trial designs, bioequivalence and bioavailability trials, and the multiple settings in which clinical trials are conducted. The revisions to the guideline should consider addressing the flexibility inherent in the guideline, with foundational principles providing an international ethical standard essential for all trials.
- Stakeholders expressed concerns about over-interpretation of the current guideline and how it was applied across many types of trials without regard to proportionality and the risk-based approach. Such a one size fits all approach can be problematic in some situations (e.g., same regulatory requirements for large pharmaceutical trials as well as small academic trials). The input highlighted that clarifying the scope of the guideline and the proportionality needed in its application should be part of the revisions.
- The EWG should consider ways to ensure that the guideline anticipates future technological advances, including digital technology, such as wearables, sensors, advanced analytics, and artificial intelligence.

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- The EWG should consider how to provide best practices to ensure data quality and integrity in an increasingly digital ecosystem where data capture, flow, storage, and

analyses can be done digitally and by utilizing the cloud. Critical issues, such as data completeness and verifiability, should be considered.

- Flexibilities and adaptability to facilitate trials during public health emergencies should be considered.
- The guideline should encourage that trial participants reflect the diversity of patients with the disease, including participation by people from minority communities with the disease.
- The guideline can provide flexibility by allowing stakeholders, such as institutions, to implement efficiencies to ensure investigator qualifications without dictating unnecessary documentation or arbitrary training requirements.
- The guideline could emphasize outcomes as well as participant care and safety in addition to proportionality in documentation, procedures and monitoring, and should provide rationale for requirements.
- Consider that GCP training is not required for health care providers performing same roles in clinical trial that they perform in clinical care and in which they are already qualified and certified to perform and to consider eliminating duplicate or unnecessary GCP training requirements.
- Consider addressing the need to facilitate global research when participant populations are in disparate locations (e.g., trials in pediatrics and rare diseases).
- Consider how the guideline will incorporate quality management, quality by design, critical to quality factors, risk mitigation strategies, and related issues in ICH E8.

Embracing Innovative Trial Designs

- The GCP guideline should not be viewed as a regulatory checklist with standard requirements for all trial types.
- Stakeholders urged clarity on the applicability and scope of E6 to studies that are exempt from regulatory oversight.
- Consider whether expectations would differ based on risk level in trials, such as trials using an approved product for a new indication or a different population. This could facilitate the investigator and local institution when conducting those trials to collect more data for health care providers and the public, e.g., more knowledge of pediatric products.
- The current guideline's approach seems to be burdensome for adaptive and platform trials as well as trials with master protocols.
- The current guideline may stifle some research, especially in settings with limited resources and research for treatments with potentially limited markets. Consider flexibilities for trials on rare diseases, pediatrics, and underserved populations.

Lessons from Clinical Trials During Public Health Emergencies

- The work on revising the guideline should recognize and incorporate lessons from the COVID-19 public health emergency. Even prior to the public health emergency, clinical trials were trending towards the use of more remote technology. Changes necessitated by the public health emergency may accelerate existing trends and usher in new ways of doing clinical trials. This may include decentralized clinical trials, the use of digital tools for documentation and to manage data-related processes, the use of electronic consent,

electronic signatures, telehealth visits, mobile technology/wearable devices, remote monitoring, remote auditing, and remote investigator meetings. More information on new approaches that need to be addressed include the need for direct distribution of drug to participants, ensuring participant privacy and confidentiality, and guaranteeing patient safety and data integrity.

- During public health emergencies, the revisions should be guided by good risk assessment processes and focused on study data and processes when addressing remote monitoring, including remote source data verification and source data review.
- Address how inadequate data management could threaten validity of overall conclusion or accuracy of treatment estimates.
- Address adaptability of regulatory standards and frameworks for ongoing research during public health emergencies.
- Consider defining more broadly the language regarding medical oversight of participants to allow for independent practitioners who may not be physicians or dentists to be part of the oversight. This oversight can still be performed ultimately under the supervision of a physician or a dentist.

Applicability to Low and Middle Income Countries

- Stakeholders recognized the importance of ICH E6 in establishing an ethical standard that can serve as a framework for low and middle income countries to participate in research and innovation, and reminded the EWG of important considerations and challenges for global research. ICH E6 can assist in enabling more countries and participants to be engaged in critical research, such as studies evaluating treatments and vaccines for COVID-19.
- Stakeholders highlighted that, as an international regulatory document, the guideline should consider the variable cultural and economic contexts in which research is conducted. This includes considerations of the specific characteristics of the patient populations, such as variable comorbidities, potential limited availability of health care access and clinical research, and even more basic needs, such as electricity – an issue of great importance when considering the use of digital tools.
- Stakeholders mentioned that there are efforts to explore the possibility for joint assessments of medical products in several Latin American countries, with the development of a new assessment/benchmarking tool by the World Health Organization (WHO) and the Pan-American Health Organization (PAHO) to help build regulatory capacity. Such efforts can benefit greatly from the presence of a robust and responsive GCP guideline.
- Stakeholders also recommended the guideline address the need for cultural awareness, and community consultation for issues, such as consent for research participation, and local jurisdictional impact on legal age for consent. They also stressed the need to provide local research benefits to avoid unethical exploitation of communities.

Increasing Participant Communication

- Stakeholders emphasized the need for sponsors and investigators to communicate with participants throughout the trial, including considering when updating informed consent

is appropriate. Overall, stakeholders highlighted that increased communications with participants will aid retention and compliance in the clinical trials.

- Stakeholders suggested that the EWG reenvision trial participants as partners and recognize participants' need to be informed before, during, and after a trial, including receipt of information about trial results and publications.
- Consider tools to facilitate the process of consent, such as the use of electronic consent, which could enable researchers to consider enrolling participants located farther from the trial site.

Encouraging Stakeholder Engagement

- Recognize the importance of participants as key partners in clinical trials, including changing terminology from "subjects" to "participants." Participants can improve support of clinical research overall, including early involvement in protocol design. Also, continue to engage participants throughout trials. As one stakeholder for trial participants stated, "nothing about us without us."
- Consider that effective engagement and partnership with patients can make a huge difference in how well trials are performed, including: 1) increased participant retention, 2) identifying the right questions to ask, 3) helping to inform trial design and conduct, 4) participating in data monitoring committees, and 5) aiding assessment of risk to participants with trial interruption or suspension.
- Another consideration from stakeholders was to evaluate and encourage communicating results (even in aggregate form) to participants and communities in meaningful and understandable ways.
- Consider the use of digital technologies to bring trials to participants, and the identification and use of other participant-centric approaches. This may help to maximize participation while also lowering the burden on patients.

CLOSING

FDA and CTTI appreciate the input received from all presenters and public stakeholders in providing helpful feedback for EWG consideration as the EWG continues the deliberations to revise the ICH E6 guideline. Engagement is at the heart of the E6 revision process. This meeting underscored the importance of communication between stakeholders and ICH EWG members. Additional stakeholder engagement meetings are being planned. For further information on the ICH engagement approach and related activities, please see the ICH website at https://www.ich.org/page/reflection-papers#4-1.

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