



# **Informing the Renovations to the ICH E6 GCP Guideline for Good Clinical Practice Executive Summary**

March 16, 2020

The Clinical Trials Transformation Initiative (CTTI)—a public-private partnership between Duke University and the U.S. Food and Drug Administration—independently conducted 1) a global online survey, 2) qualitative, in-depth telephone interviews, and 3) an open comment platform, to provide opportunities for stakeholders affected by ICH E6 GCP to identify areas in ICH E6 GCP that are of greatest need for renovation, to suggest realistic ways for renovation, and to describe their experiences with implementing ICH E6 GCP. All participants reviewed ICH E6 (R2).

In this report, CTTI provides an overview of the project findings. Detailed findings from the survey, in-depth interviews, and open comment opportunity are provided as separate documents

## SURVEY

The survey was completed by 327 stakeholders from 39 countries. Participants represent various research roles and organizations, and have conducted research in 153 countries. Five ICH E6 GCP principles were mentioned most often as needing renovations: 1) implementing systems that assure quality, 2) medical care by qualified physicians/dentists, 3) confidentiality and privacy, 4) informed consent, and 5) information documentation. The sections of ICH E6 GCP identified as needing the most renovation were 1) the Investigator section, and 2) the Sponsor section. The Monitoring topic under the Sponsor section was the topic mentioned most frequently as needing renovation. The Investigator Brochure section was identified as needing the least renovation.

## IN-DEPTH INTERVIEWS

### Aspirations for the ICH E6 GCP guidance

Several main themes emerged from participants' aspirations for the renovation. One of the most commonly mentioned was the desire that **flexibility** be incorporated into future versions of the guidance. While ICH E6 GCP states that the “guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities” it also states that “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.” Many participants described that globally, the guidelines are being strictly applied to many different types of research, including non-regulatory and/or non-drug studies for which the guidance may not be appropriate. The renovation should 1) be very specific about the types of research for which ICH E6 GCP is a requirement, 2) clarify where use of the full ICH E6 GCP is optional and therefore components may be selected as appropriate for the needs of a particular study, and 3) provide a framework for adapting the guidance to other types of research by identifying minimum requirements of GCP necessary for different types of trials and setting quality standards that encompass non-interventional and non-drug studies.

***CTTI determined that while the stated focus of ICH E6 GCP is clinical research that generate data for submission to regulatory authorities, it was important to report on the significant and repeated concerns participants expressed about these issues so that ICH is aware of the reality of the experiences of researchers, and can consider how best to address these concerns as part of the renovation.***

Participants also described that as ICH E6 GCP is a global guideline, it would be helpful to acknowledge in the guidance that flexibility may be required when working in lower and middle-income countries. For example, it may be difficult to implement the full ICH E6 GCP in remote or under-resourced areas or in emergency settings, such as during an Ebola outbreak. Likewise, certain aspects of GCP may need to be adapted to accommodate the needs of vulnerable populations, such as informed consent with orphans with no legal guardian, or indigenous communities.

Participants also described that it would be helpful to **simplify** the guidance to make it more user-friendly, including taking a position on simplifying requirements for GCP refresher training and eliminating duplicative trainings currently required by sponsors. Participants commented that the complexity of the guidelines can serve as a disincentive for investigators to conduct clinical trials and that the burden of trial complexity is viewed as particularly high by potential investigators, and investigators conducting small single-site trials and investigator-initiated studies. Participants further emphasized a desire to move away from a view of ICH E6 GCP as a highly prescriptive “checklist” that must be applied to all studies and that runs the danger of being used as a policing tool for audits and inspections, and towards a document based on the “spirit of GCP” that elucidates organizing principles for guiding research. An introductory preamble to that end, clearly stating that the guidance is not intended to be prescriptive, and reminding end users of the fundamental purposes of research and of GCP—

improving patient outcomes while protecting research participants and ensuring data integrity—would be helpful for arriving at a common understanding of the guidance across users.

Participants also requested that ICH E6 GCP provide templates, examples, scenarios, and best practices throughout its sections and suggested that training materials focused on implementing the guideline be provided.

Participants described several **updates** that should be made to the guidance to accommodate changes in research conduct and technology that have emerged since the guidelines were created (e.g., multi-site and multi-modality trials). For example, the guidance should address different types of informed consent (e.g., delayed consent, waiver of consent, opt-out consent) that may be needed for different types of trials. Participants also requested guidance for working within new research frameworks enabled by advances in technology, such as paperless trials and remote data collection. They expressed confusion about how to adapt ICH E6 GCP guidelines on, for example, investigator oversight, monitoring, and record keeping to these new circumstances.

Participants further described that it will be important to write any revisions at a sufficiently high level that they will continue to be applicable in the future, given that technologies and systems continue to evolve rapidly. The guidance should also be updated to account for new study roles and responsibilities that have arisen since 1996 and/or that have changed substantially since the guidance was created (e.g., monitor, sponsor liaison, study coordinator) and should specifically include patients and communities [i.e., community representatives of research locations] as stakeholders. Further, both investigator and sponsor responsibilities should be more clearly specified and perhaps called out as individual subsections of their respective chapters. Participants requested clarification of terms and concepts such as quality management using a risk-based approach and quality tolerance limits, pointed out inconsistencies of terminology, noted where definitions in the ICH E6 GCP do not match definitions in other commonly accepted documents (e.g., “trial” vs. “study”), and requested that the E6 guidance be more fully integrated with other E documents.

Participants emphasized a desire for **transparency and inclusion** in the process of revising ICH E6 GCP. They stressed that it is important to include a wide variety of stakeholders in the revision process, representing perspectives across a range of trial types, in order to create guidance that is operationally feasible. Patients and

communities should be included in the process of renovating ICH GCP. There should be a balanced representation across geographic regions in the renovation activities. Participants requested transparency surrounding creation of the renovation plan, including the process that will be followed, the rationale behind the decisions that are made, the stakeholders who are involved and how they were selected, the process for soliciting feedback throughout the revision, and what is done with any feedback received.

### Helpful aspects of the ICH E6 GCP guidance

Many participants spoke favorably about the ICH E6 GCP guidance overall, stating that it is helpful, generally clear, and particularly useful for training purposes, while also acknowledging shortcomings and areas that require updating. Participants described that ICH E6 GCP represents the only **globally accepted guidance** and serves as a common standard for research worldwide. It is particularly helpful for establishing a research framework in countries in which existing legal or regulatory requirements for trials are under-developed, or where variation in regulations exists between countries. Participants emphasized that the guidance describes the process for ensuring that the trial data can contribute to supporting marketing organization applications. Further, the information on human subjects protections sets an effective standard for protecting participants' rights, safety, and welfare.

Participants described that certain sections of the ICH E6 GCP guidance were particularly helpful to them. **Section 2**, dealing with the principles of GCP, lays out fundamental concepts that all types of clinical research should strive for and serves as both a standard for research and a checklist of essential elements of GCP. Within **Section 4**, encompassing investigator responsibilities, participants appreciated the clear guidance on investigator oversight and informed consent, noting that the informed consent section can serve as both a reference and a template when building an informed consent document. In **Section 5**, which covers sponsor roles and responsibilities, participants also noted that having clear guidelines for sponsor oversight is useful and described that the shift to quality management using a risk-based approach (e.g., risk-based monitoring) established as part of the R2 revision has been an excellent addition to the guidance. Participants also found much of the information about monitoring, quality assurance, and quality control to be helpful.

Finally, participants noted that within **Section 8**, essential documents for the conduct of a clinical trial, they appreciated having an exhaustive listing of all the documents that could potentially be collected but also valued having the shorter list of core documents that must be obtained during the course of a trial.

### Unhelpful aspects of the ICH E6 GCP guidance

Many general comments on unhelpful aspects of the guidance paralleled those made with respect to aspirations for the renovation; for example, uncertainty about whether or how the guidelines are intended to accommodate non-regulatory and/or non-drug trials.

With regard to specific sections, while a number of individual comments were made about various aspects of the guidance, the majority dealt with the **investigator and sponsor sections**. Participants pointed out that the allocation of responsibilities could be more clearly detailed in both of these sections and requested clarification of terms and alignment of ICH E6 GCP processes with other current regulations (e.g., SAE reporting responsibility has shifted from investigators to sponsors since the guidance was produced). Some expansion of the **investigator** guidance was also requested; for example, within the section on adequate resources, to incorporate more flexibility in staff member roles and to address the consequences of having inadequate resources.

Within the **sponsor** section, multiple issues were raised, including concerns about monitoring, quality management using a risk-based approach, and trial management, data handling, and record keeping. Here, participants reported a lack of clarity across multiple fronts, including on best practices for implementation of the guidelines in these areas. Participants described that individual sponsors' interpretation of ICH E6 GCP varies, generally leading to over-resourcing both low- and high-impact risks, to ensure GCP compliance. This results in sponsors' implementation of increasingly complex quality control, quality management, and documentation requirements. Participants further expressed concern that inspections are not yet being conducted in accordance with R2 but are still based on the 1996 criteria; thus, sponsors implementing the risk-based approach do not yet know if they are interpreting the revised ICH E6 GCP correctly. ICH should strongly encourage regulatory authorities responsible for conducting inspections to base these on the current version of the guidelines.

Lack of clarity was also an issue for **Section 6** of the guidance, which deals with clinical trial protocols. Participants expressed that the guidance on protocol development is too vague and would benefit from additional direction on how to make protocols simpler and more feasible, as well as expansion of this section to include templates, definitions, and guidance on version changes. Expansion was also recommended for **Section 7**, investigator's brochure, which was perceived as being quite brief. Finally, clarification of requirements was also seen as playing a role for **Section 8** on essential documents, as participants noted that interpretation of GCP impacts the types of essential documents collected.

## OPEN COMMENT OPPORTUNITY

The Open Comment Opportunity was completed by 36 stakeholders from 13 countries. The majority of comments were made on the Principles of ICH E6 GCP, including suggestions for principles missing from the current guideline version (R2). Respondents suggested revisions to all of the sections of ICH E6 GCP. Most comments were made on the IRB/IEC, Investigator, and Sponsor sections. Fewer comments were made on the Clinical Trial Protocol and Protocol Amendments, Investigator's Brochure, and Essential Documents sections. Additional overarching comments on the guidance and associated renovation were also provided.

## STUDY TEAMS

### Survey and In-Depth Interviews

- ▶ **Principal Investigator:** Amy Corneli, PhD, MPH. CTTI Lead Social Scientist. Associate Professor, Duke University Departments of Population Health Sciences and Medicine.
- ▶ **Team Leads:**
  - ▶ Annemarie Forrest, RN, MS, MPH, CTTI Director of Projects.
  - ▶ Pamela Tenaerts, MD, MBA, CTTI Executive Director.

- ▶ Teri Swezey, PhD, MA. CTTI Assistant Social Scientist. Clinical Trials Project Leader, Duke Department of Population Health Sciences.
- ▶ **Interviewer:** Teri Swezey, PhD, MA.
- ▶ **Qualitative Data Analysts:**
  - ▶ Teri Swezey, PhD, MA
  - ▶ Carrie Dombeck, MA. CTTI Research Associate. Research Program Leader, Duke Department of Population Health Sciences.
- ▶ **Statistician:** Li Lin, MS. Senior Biostatistician. Duke University Department of Population Health Sciences.
- ▶ **Research Assistant:** Adora Nsonwu, Clinical Research Specialist, Duke University Department of Population Health Sciences.

### Open Comment Opportunity

- ▶ **Team Leads:**
  - ▶ Annemarie Forrest, RN, MS, MPH, CTTI Director of Projects.
  - ▶ Pamela Tenaerts, MD, MBA, CTTI Executive Director.
- ▶ **Research Assistant:** Adora Nsonwu, Clinical Research Specialist, Duke University Department of Population Health Sciences.