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

January 2017

Introduction

This paper outlines an approach to potential renovation of the ICH Guidelines related to clinical trial design, planning, management, and conduct. The scope of the renovation would include the current *E8 General Considerations for Clinical Trials* and the *E6 Guideline for Good Clinical Practice.* The goal is to provide updated guidance that is both appropriate and flexible enough to address the increasing diversity of clinical trial designs and data sources that are being employed to support regulatory and other health policy decisions. The underlying principles of human subject protection and data quality would remain.

ICH believes that the proposal outlined in this reflection paper would largely address concerns recently expressed by some research organizations and an international consortium of health researchers.[1] In a February 2016 letter to ICH, these stakeholders conveyed concerns that the current ICH E6 guideline fails to sufficiently recognize variations in the level of risk for participants in different types of trials and allow corresponding flexibility in managing the risks. Another major concern was related to E6's limited scope. It was felt that a guideline entitled "good clinical practice" should more holistically address the planning and conduct of clinical trials.

The proposed renovation would address these broad and important concerns through targeted revisions made to two current ICH guidelines.

- First, ICH would propose to address the broader concern about the principles of study design and planning for an appropriate level of data quality through revision to the current *ICH E8 General Considerations for Clinical Trials*. This is based on the recognition that data quality fundamentally depends on the quality of the study that generates the data, and that many aspects of study design affect the reliability of the study conclusions. The proposed revision would include a well-organized and fairly comprehensive review of the issues and questions that are most critical to clinical trial quality. This may include "critical to quality" factors that should be considered by sponsors when planning a study. Among the ICH Efficacy guidelines, the focus of ICH E8 also provides a logical place for an updated comprehensive guide or cross-referencing of all the other relevant ICH guidelines that sponsors should refer to when planning and executing development program-related studies.
- Subsequently, ICH would propose to address the flexibility concern via further renovation of *ICH E6 Good Clinical Practices* to anticipate and address a broader range of study types and data sources, while retaining the current E6 focus on good clinical *investigative site* practices.

This reflection paper begins with a background discussion of the role and value of the current E6 guideline, the range of regulatory and other health research questions that need to be addressed, and data sources in addition to traditional interventional trials that might be used to address them. The paper then outlines how E8 might be revised to enhance its utility in supporting clinical trial design and planning for data

[1] Updated open Letter to EMA & ICH: From 5 research organizations and an international consortium of 119 health researchers in 22 countries, 26th February, 2016: Co-ordinated response to the consultation by the International Council for Harmonisation (ICH) on its proposed E6(R2) "Integrated Addendum" to the ICH E6 Guideline for "Good Clinical Practice".

quality. This is followed by a discussion of the proposed structure for a future "renovated" E6 guideline that might better address the range of possible studies and data sources of interest, applying a risk-based approach to site monitoring. The final section of this paper discusses a proposed plan for how this renovation work could be sequenced and undertaken.

1. Background

The goals and scope of the current E6 include: a) assurance of human subject protection; b) assurance of data quality; c) limited to clinical research performed with regulatory intent; and d) to provide a standard guide so that clinical researchers (drug developers and clinical research staff) know what they need to do both to comply with the regulations and document compliance. E6 is primarily a procedural document that stipulates processes that should be followed both in study conduct and in documentation. E6 has provided critical guidance for both international regulators and clinical researchers who conduct trials to explore the safety and effectiveness of investigational new drugs. Investigational new drugs pose the greatest potential risks to study participants because of the limited safety and effectiveness information available at the time of the study. There is significant cost associated with obtaining the clinical trial data necessary to establish safety and effectiveness for regulatory review. Therefore, the sponsor of this research desires assurance that the planned trial conduct will be acceptable to the regulators. The regulator needs to be able to confirm the veracity of the data because regulatory actions rely upon conclusions drawn from the study results.

E6 was developed in the mid-1990s as the international guideline to be followed when generating clinical data intended to be submitted to regulatory authorities. Moreover, E6 aimed to provide enough specificity so as to minimize potential ambiguity and resulting inconsistency in the interpretation of the guideline across different global regions where approaches to health care delivery and regulatory practice might be expected to vary. The specificity was thus intended to minimize the potential for E6 interpretation to be yet another source of variability across investigational sites in multiregional clinical trials. Over the past twenty years, E6 has played an essential role in enabling the continued growth and success of multiregional clinical trials of investigational new drugs, including critical guidance related to training, responsibilities, and expectations of investigators, sponsors and IRBs. It has thereby supported the earlier submission of new drug applications (with data collected in conformance with the harmonized guidelines adopted by regulators in multiple regions), enabling earlier access to new medicines for patients who need them. E6 is applicable to all clinical trials performed with regulatory intent during the entire life-cycle of product development. In addition to the clinical trials supporting a new drug or biologic marketing application, it includes clinical trials performed to support a new indication of an already approved drug and clinical trials performed to fulfill post-marketing commitments or requirements.

In 2014, ICH endorsed the development of E6(R2) to supplement E6 with "additional recommendations to facilitate innovative approaches to GCP to better ensure data quality and human subject protection in an environment of highly complex multinational trials".[2] E6(R2) is intended "to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure human subject protection and reliability of trial results. Standards regarding

[2] http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2_Concept_Paper_July_2014.pdf

electronic records and essential documents intended to increase clinical trial quality and efficiency have also been updated".[3] E6(R2) reached step 4 in November 2016.

Emerging Data Sources for Drug Regulatory Decisions

In the two decades since E6 was first drafted, the ways in which clinical trials are conducted and the corresponding aspects of good clinical practice have evolved. For example, clinical trials initially were often conducted in only a few clinical sites, often of a single type (e.g., academic medical practices) in a highly controlled setting. Over time, that has evolved to include multiple sites, often including sites from multiple countries. Accordingly, regulatory agencies have embraced a more flexible risk-based approach to the monitoring of clinical trials. This is based in part on the recognition of challenges of the increasing number and complexity of clinical trials and opportunities to use electronic systems with improved statistical assessments for centralized monitoring of clinical sites. A risk-based approach can enable the sponsor to focus oversight activities on preventing or mitigating important and likely risks to data quality and to processes critical to human subject protection and trial integrity.[4] The most recent E6(R2) has made important steps in this direction.

Recently, there has been a further shift to leverage the large amounts of available data from the "real world" (e.g., electronic health records, hospital discharge summaries, claims data, patient/disease registries, etc.), collected and stored for other purposes, that could inform regulatory decision-making. A patient registry has been defined as an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves a predetermined scientific, clinical, or policy purpose(s).[5] Other possible sources of real world data include electronic medical records (EMRs) sometimes referred to as electronic health records (EHRs) generated by ongoing patient care, as well as health care administrative data sources. However, it should be noted that there are no universally accepted standards currently in use for formatting data from these different real-world sources, and this is probably the single biggest impediment to large-scale use of existing health care records in clinical trials. The adoption of standardized electronic formats for health care administrative data, and patient EMRs will greatly improve the ability of researchers to use these data to address health care and policy questions.

There have also been efforts to better integrate clinical studies into regular health care delivery by interfacing the electronic case report form with EMRs to minimize duplicative collection of patient/study participant data. This could facilitate performance of pragmatic clinical trials conducted under everyday clinical conditions and designed to test two or more treatments using more flexible study protocols and local customization, with less strict eligibility criteria, with less collection of data beyond the norm in routine clinical practice.[6]

---

[3] http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Addendum_Step2.pdf

[4] http://www.fda.gov/downloads/Drugs/.../Guidances/UCM269919.pdf

[5] http://www.pcori.org/assets/11-Gliklich-Slides-Registries.pdf

[6] See for example: Use of Electronic Health Record Data in Clinical Investigations Guidance for Industry – May 2016 - http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm501068.pdf

Other Research Questions for Health Authorities

At the same time that E6 enabled global gains in patients' access to drugs, other technology, policy, and market drivers have been working to expand the set of research questions that health authorities need to address. In addition to the conduct of clinical trials to generate information needed to inform regulatory decision-making for marketing, other potential applications of E6 may include clinical research to assess the value and cost of drugs, comparative effectiveness research (CER), development of clinical practice guidelines, and academic research. Although the principles of human subject protection and data integrity apply in all circumstances, some flexibility in the application of these principles may be appropriate for different trial designs and contexts. For instance, observational studies of two approved therapies used to generate CER may not require the same level of documentation of informed consent, or it may be waived, as compared to a randomized controlled trial (RCT) of an investigational agent. Likewise, the level of resources and costs associated with the processes to document data integrity for an RCT being performed to support drug approval may not be justified for an academic research trial.

The aim of CER is to improve decisions by other players in the health care system and affect medical care at the levels of both policy and the individual. The key elements of CER are (a) head-to-head comparisons of active treatments, (b) study conditions and populations typical of routine clinical practice, and (c) a focus on evidence to inform care tailored to the characteristics of individual patients. Observational studies and randomized trials are often employed in the conduct of CER[7].

Questions concerning the value and cost associated with medical technology are being addressed by health technology assessment (HTA), as well as individual health care payers such as private insurance. HTA refers to the systematic evaluation of properties, effects, and/or impacts of health technology. It is a multidisciplinary process to evaluate the social, economic, organizational and ethical issues of a health intervention or health technology. The main purpose of conducting an assessment is to inform a policy decision making.[8]

The number of other health research questions has grown along with the urgency of need to address them. This is fueled by the rising complexity and cost of health care driven by scientific and medical technology innovation, expansion of health care benefits, and patient needs given significant increases in the number of patients with serious chronic disease, including the elderly with multiple chronic conditions.

The Issue to Address in Future E6 Renovation

As noted previously, the original objective of E6 was "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 [and]…should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities". E6 thus considers clinical trial designs that are typical of such regulatory submissions, namely the RCT in a controlled trial setting where data are collected or acquired prospectively through patient-clinician interactions (e.g., observed, self-reported, measured, or tested), and stipulates procedures for such studies. However, it is recognized that the emerging clinical trial environment may increasingly serve as an important adjunct to traditional interventional trials to support regulatory decisions, and would ideally be addressed more explicitly in ICH guidelines.

[7] Sox HC, Goodman, SN, The methods of comparative effectiveness research*, Ann Rev Public Health.* 2012 Apr; 33:425-45, doi: 10.1146/annurev-publhealth-031811-124610. Epub 2012 Jan 3.

[8] http://www.who.int/medical_devices/assessment/en/

Furthermore, although E6 was not designed with alternative study types or data sources in mind, absent a GCP guideline tailored to the varying human subject risk and data quality considerations posed by these other types of studies and data sources, some researchers, referring to some of the provisions of the current E6, have recently shared concerns about the lack of a good fit.

2. Proposed Structure for a Modernized ICH E8 Guideline and a Future Renovated ICH E6 Guideline

E8 General Considerations for Clinical Trials was finished in 1997 and has not been updated subsequently. E8 is a high level guidance that serves as a general roadmap to other ICH Guidelines concerning clinical trials. For example, it contains a Table classifying clinical studies according to objective, and also an Annex cross-referencing other relevant ICH guidelines. The Table includes examples of large simple trials, comparative effectiveness studies, and pharmacoeconomic studies, but the rest of the guidance is focused on studies intended to support regulatory submissions and does not further address differences in design and conduct that might be encountered in these different types of studies. Section 3.2 of the E8 Guideline, "Considerations for Individual Clinical Trials", has very high level descriptions of trial objectives and design, and does not address design or planning considerations for data quality (i.e., the quality of the study that generates, and determines the quality of, the data). In fact, the 1997 concepts of data quality were more procedural in nature and did not encompass the current goal of "quality by design", that is, explicitly stating the data quality parameters that need to be achieved in the trial, and planning the trial conduct, based on an assessment of risk, in order to achieve these parameters.

ICH is proposing that E8 would be revised and modernized to address these critically important aspects of study quality. This would include the need to identify 1) aspects of a trial that are critical to generating reliable data (e.g., relevant critical-to-quality (CTQ) factors) and 2) the strategies and actions that could effectively and efficiently support quality in these critical areas. The document could identify a basic set of CTQ factors generally relevant to the integrity and reliability of study conclusions and patient safety that sponsors should consider, to determine which factors stand out as critical and need to be explicitly addressed in a risk-based management and monitoring plan. Recent literature can provide resources to support development of this revised text, as well as the work by collaborative groups such as the Clinical Trials Transformation Initiative (CTTI)[9]. This type of prospective planning feeds directly into ICH E6, where the procedures implemented and followed should flow from the prospective identification of the desired data quality parameters for various types of data. ICH is proposing a modernization of ICH E8 in order to incorporate the most current concepts achieving fit-for-purpose data quality as one of the essential considerations for all clinical trials.

ICH is proposing a subsequent renovation of the current ICH E6 guideline that would preserve a key role for the current focus on traditional interventional trials conducted in a clinical trial setting while also addressing the other types of data sources or decision contexts. Thus the revised guideline would remain consistent with the assertion in the introduction of the current E6 guideline 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." Following the approach taken in the development of the ICH E6 R2 addendum, the proposed revision to the overarching E6 guideline and the proposed annexes would

[9] E.g., the *CTTI Quality by Design Project Critical To Quality Factors Principles* document https://www.ctti-clinicaltrials.org/files/principles_document_finaldraft_19may15_1.pdf

similarly maintain a focus on essential guidance rather than general, long discussion of topics. Proposed revisions of E6 include the following:

1. The renovated E6 guideline would retain the focus of the current E6 on good clinical site practices and other key considerations in the current document.[10] However, recognizing that the most important tool for ensuring human subject protection and high-quality data[11] is a well-designed and well-articulated protocol, the renovated E6 would also refer to the *proposed-to-be-revised* E8 guideline for a more comprehensive discussion of study quality considerations and relevant discussion and guidance in other ICH E guidelines.

2. It is also being considered that the main body of the renovated E6 guideline would be revised to focus on overarching principles including key elements of human subject protection and data quality, using a risk-based approach to study oversight and monitoring. A number of available reference documents could be used to inform the development of these basic principles and list of candidate CTQ factors including, for example, *FDA Guidance to industry: Oversight of Clinical Investigations—A Risk-Based Approach to Monitoring*[12], the *EMA Reflection paper on risk based quality management in clinical trials*[13], and MHLW administrative notice on Basic Principles of Risk-based Monitoring[14]. The overarching principles document would further recognize that trial design and study objectives will strongly influence the criticality of different factors.

A set of annexes would be developed to be attached to the new E6 guideline. Each annex would address in more detail a particular type of study and/or data source to which E6 could be applied, and provide a more detailed workup of the CTQ factors that should be considered. This approach would allow flexibility to ensure that the principles remained the same regardless of the study's objectives or setting, but the application of those principles would be specific to the type of study and data source. While the scope of these proposed annexes would be further clarified following the renovation work on ICH E8, it is currently envisioned that the initial study types proposed for future development include:

1. <u>Proposed Annex 1: Traditional Interventional Trials of investigational unapproved or approved drugs</u> This would encompass trials of unapproved drugs or of approved drugs for a new indication or use in a controlled setting with prospective collection of trial data. The current E6 document is focused on traditional interventional trials conducted for regulatory purposes in a clinical trial

[10] ICH E6 also includes e.g. a detailed chapter which describe standards for Ethics Committees/ Institutional Review Boards, a chapter describing in detail standards for sponsors when designing, conducting, evaluating and reporting clinical trials, and chapter describing the structure and content of Investigator Brochures and Clinical Trial Protocol. These need revision but should be maintained. Reference to the activities of regulatory authorities for clinical trials should also be included as in many cases these complement the role of the ethics committee, for instance in areas of safety reporting and oversight.

[11] Including electronic health records (EHRs)

[12] http://www.fda.gov/downloads/Drugs/.../Guidances/UCM269919.pdf

[13] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/11/WC500155491.pdf

[14] http://www.pmda.go.jp/files/000215858.pdf

setting, with data collected primarily through traditional case report forms and trial monitoring requirements consistent with the regulatory requirements for studies of investigational products. This document would become the first annex to the new overarching principles document, with revisions, as needed to reflect current risk-based approaches and practices and remove any inconsistencies. It is anticipated that this annex would include the updates and risk-based approaches addressed in the current E6(R2).

2. Proposed Annex 2: Non-Traditional Interventional Trials and/or data sources. Trial designs such as pragmatic clinical trials would be included in this annex, as would real world data sources to supplement or possibly replace new data collection within the trial itself. The study objectives could include evidence generation for regulatory review of approved products as well as for broader research questions, as appropriate. Principles for protocol compliance and trial monitoring would reflect the fact that approved, marketed products with better-documented and better-known safety profiles are being studied.

3. Proposed Annex 3: Non-Traditional Trial Designs. This annex would include designs other than RCTs and may include observational studies, patient registries, and other non-traditional trial designs that rely heavily on alternative data sources (e.g., EHRs, claims data, etc.). The studies may be designed to generate findings for important research objectives regarding health care practice and policy but could also be used to address regulatory questions (e.g., concerning product safety post-marketing). Principles for protocol compliance and trial monitoring laid out in this annex would be consistent with the data source and also, as in proposed annex 2, reflect the fact that marketed products with better-known safety profiles are being studied.

ICH anticipates that ICH EWGs would lead and undertake first the development of the revised E8, next the new E6 overarching principles document, and later undertake the development of the proposed annexes. In view of the inter-relationship of issues and considerations that will be addressed in E8 and E6, with ICH *E9 Statistical Principles for Clinical Trials*, including concepts of randomization, power and data/safety monitoring committees, plans would be made for cross-consultation and coordination of any parallel ongoing work of WG experts for these guidelines. Recognizing the broader application of the types of studies included in the third proposed annex ICH would also anticipate engaging others with expertise in the conduct of such studies, which may include government health researchers as well as academic researchers, perhaps working in collaboration in development of the proposed guideline annex for these types of studies.

3. Proposed Plan for "Renovation" Work

ICH proposes that the renovation work would be organized into a series of guideline efforts conducted by EWGs.

A. ICH proposes that the first effort would focus on modernization of E8 per the approach described above. This revision would include the addition of quality by design as a key consideration in the planning and design of clinical trials. The revision could also include an updating of the current E8 cross-referencing of the other ICH guidelines that should be referred to when planning clinical studies. The cross-referencing could be provided, for example, in a table or chart that lists the CTQ factors identified in the revised E8 guideline and shows where the CTQ factors included in this list may be addressed in other ICH E guidelines. Such an updated reference chart, with an appropriate level of explanation could be quite helpful to prospective users of the ICH guidelines. For the E8 renovation

work, the EWGs could be comprised of experts from a mix of relevant disciplines including clinical, statistical, data science, patient-reported outcome/clinical outcome assessment experts, and potentially others. This work might proceed as follows:

I. **Guideline effort 1**: Develop a revised ICH E8 guideline – potentially starting in the late 2017 or in 2018.

B. For the E6 renovation work, the EWGs would be comprised of experts in clinical trial conduct and GCP compliance, and for the development of a particular annex, experts in the study types identified for that annex. The work might proceed as follows:

I. **Guideline effort 2**: Develop new ICH E6 Overarching Principles guideline. This work might start after the proposed Guideline effort 1 work on ICH E8 reaches at least Step 2b. An appropriate subset of the elements for study quality and CTQ factors identified in the revised E8, that would be relevant to E6, could then be carried over and referenced in the overarching principles of a revised E6.

II. **Guideline effort 3**: Develop E6 Annex 1 focused on *traditional interventional* trials of investigational unapproved or approved drugs (i.e., trials of unapproved drugs or of approved drugs for a new indication or use) in a controlled setting with prospective collection of trial data. This work would start after the proposed Guideline effort 2 work on the ICH E6 Overarching Principles has reached at least Step 2b.

III. **Guideline effort 4**: Develop ICH E6 Annex 2 focused on *non-traditional interventional* trials and/or data sources. This work would be expected to start after the proposed Guideline effort 3 had reached at least Step 2b.

IV. **Guideline effort 5**: Develop ICH E6 Annex 3 focused on *non-traditional* trial designs. This work would be expected to start after the proposed Guideline effort 4 had reached at least Step 2b. It is also being proposed that ICH incorporate a process of engagement taking the approach outlined below.

ICH Step Process Enhancement for the GCP Renovation

In recognition of the considerable stake and significant GCP expertise of parties outside ICH in the academic research community, ICH also proposes specific enhancements to the public consultation process for the revision of ICH E8 and E6.

As a first component of expanded consultation, ICH is seeking stakeholder comment on the overall GCP Renovation proposal herein. To begin obtaining stakeholder input, ICH is therefore posting this proposal on its website, in conjunction with issuance of a press release to provide public notice of our interest in hearing the views of public stakeholders. A 60-day comment period is being provided to enable time for the stakeholder review and response, while still allowing time following the close of the comment period for ICH analysis of the input received, to determine if major revisions should be considered to the current proposal based on the public input. The aim is to proceed with initiating needed renovation work as soon as practical, for example, within the next year.

Additional components of the proposed enhancements include the following recommendations for information sharing, consultation and interaction:

1. Seek outside stakeholder comment on the Concept Paper and Business Plan associated with the Guideline efforts outlined above. These work products are developed prior to the initiation of Step 1 of the five-step Formal ICH Procedure, at the time when work on those documents is being planned and scoped in preparation for getting Working Group efforts under way. ICH is considering providing a 30-day public comment period to receive timely comments at this early and formative stage while avoiding delays in the start of work.
2. Hold meetings with outside stakeholders at key guideline development milestones. ICH is proposing to hold a meeting with public stakeholders to present, get input, and discuss work to date and planned next steps at one or more points in the proposed guideline development. ICH is considering holding these meetings at the following key points in the process:
    a. Before the completion of Step1 – to get input on the Step 1 draft before completion.
    b. At Step 3 to have a face-to-face meeting and in-depth discussion and consultation on the Step 3 document.
    c. After Step 4 to review and discuss the final resulting version and get input on design of training materials for guideline implementation.

Conclusion

Over the past twenty years, the ICH E6 and E8 guidelines, ICH E6 in particular, have played an essential role in enabling the continued growth and success of multiregional clinical trials of investigational new drugs, including critical guidance related to training, responsibilities, and expectations of investigators, sponsors and IRBs. ICH believes that the proposed approach to renovation of the ICH Guidelines related to clinical trial design, planning, management, and conduct of studies outlined in this paper would address important concerns recently expressed by some of our external stakeholders, but also bring critical modernization to these foundational guidelines. The proposed renovation work will build on the important work of ICH E6 R2 and expand it, and bring even greater cohesiveness to the critical interplay of factors addressed in various E guidelines including but not limited to the topics of quality by design and related study quality considerations, statistical principles, and good clinical practices.