

**ICH GLOBAL MEETING ON E8(R1)
GUIDELINE ON GENERAL CONSIDERATIONS
FOR CLINICAL STUDIES**

MEETING SUMMARY

Table of Contents

Executive Summary	1
Introduction and Background	3
Summary of Comments.....	4
<i>Challenges with the Interpretation and Application of ICH E8 Guideline</i>	4
<i>Quality by Design</i>	5
<i>Stakeholder Engagement</i>	6
Rethinking stakeholder engagement during the design and conduct of clinical trials.....	6
Involvement in the ICH process	7
<i>Ethical concerns</i>	8
<i>Clinical Trial Complexity Attributed to Guidelines</i>	8
<i>Study Design</i>	9
Selection of Study Population.....	10
Real World Evidence	10
Considerations for Developing Countries.....	11
<i>Data Sources</i>	11
<i>Other comments</i>	11
Conclusion	12
Annex 1: Specific comments	14

Executive Summary

In January 2017, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) announced a strategy to modernize ICH Guidelines related to clinical trial design, planning, management, and conduct. The goal of the proposed plan was to provide updated guidance that is both appropriate and flexible enough to address the increasing diversity of clinical trial designs and data sources that support regulatory and other health policy decisions. As part of this plan, ICH would revise the existing ICH Guidelines: *E8 General Considerations for Clinical Trials* and *E6 Good Clinical Practices*. Additionally, ICH included a provision to engage experts outside of ICH, including in the academic research community and patient groups, to seek their input by holding meetings as key milestones are reached. Following the public consultation period of the revised ICH E8 Guideline, ICH held the first of these meetings at the FDA, United States headquarters, on October 31, 2019. This report provides a summary of the discussion from that meeting.

The meeting participants welcomed the revisions to the Guideline and opportunity to engage with a subset of ICH E8(R1) on the topic of clinical study design. While input was provided that the revisions are a step in the right direction, many highlighted a need for the document to provide more clarity and include additional considerations. Feedback provided at the meeting can be summarized as follows:

- Many perceived that ICH Guidelines related to clinical study design and conduct are being “over-interpreted” as a result of lack of specificity, the risk-adverse nature of the pharmaceutical industry and a tendency to implement requirements that may not be needed to avoid any risk of a negative outcome on a marketing application.
- Quality by design (QbD): While introduction of QbD was welcomed, the majority viewed that more specificity and direction is needed to have the intended outcome of improved study designs. Additionally, examples of anticipated challenges were provided.
- Regarding stakeholder engagement, there was broad agreement that more patient engagement is needed throughout the study design and conduct process as well as with those performing the trials.
- Recommendations from some stakeholders to address ethical issues included a provision to ensure continued patient access to pharmaceuticals found to be beneficial post-trial, even if a patient cannot afford the drug; and revisiting requirements for patient informed consent forms.
- Concern was raised around the complexity of modern clinical trials and cited that simpler guidance is needed.
- Several comments were provided in reference to study design such as the need to account for innovative trial designs, considerations for the selection of a study population to ensure that it is representative of the actual population and use of real-world evidence.
- Considerations for developing countries include the need for very clear and implementable guidelines for non-clinical trialists conducting clinical trials.
- Challenges were also highlighted regarding the use of non-traditional data sources such as from electronic health records, mobile data, registries and secondary data.

ICH values the input received from the diverse group of stakeholders and recognizes many of the challenges with the design and conduct of clinical trials raised during the meeting. The revised E8(R1) Guideline is intended to help address some of the concerns expressed by offering guidance on improved clinical trial design and provisions for patient engagement during the study design process. The comments received will be considered by the ICH E8(R1) working group in their finalisation of the revised Guideline as well as by the ICH Management Committee who is responsible for the operational aspects of the ICH Association.

Introduction and Background

In January 2017, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) endorsed a Reflection Paper titled “[ICH Reflection on “GCP Renovation”: Modernization of ICH E8 and Subsequent Renovation of ICH E6](#)” which outlines an approach to modernize ICH Guidelines related to clinical trial design, planning, management, and conduct. The goal of the proposed plan was to provide updated guidance that is both appropriate and flexible enough to address the increasing diversity of clinical trial designs and data sources that support regulatory and other health policy decisions. The proposal included recommendations to revise the existing ICH Guidelines *E8 General Considerations for Clinical Trials*¹ and *E6 Good Clinical Practice*. In recognition of the considerable stake in clinical trial research and significant Good Clinical Practice (GCP)-expertise of parties outside of ICH in the academic research community and patient groups, the plan also included an enhancement to the public consultation process to seek this stakeholder input by holding meetings as key milestones are reached.

ICH issued a draft revision to the E8 Guideline in May 2019 followed by regional public consultations by the ICH Regulatory Members concluding in October 2019. Following the close of the public comment period, ICH conducted a global public meeting, as outlined in the GCP Renovation Plan. The purpose of this meeting was to provide an opportunity for stakeholders not typically involved in the ICH process, including academic researchers and patient groups, to engage in discussion with the ICH E8(R1) working group representatives.

The meeting was held on October 31, 2019 and hosted at the FDA, United States headquarters located in Silver Spring, MD, USA. The meeting was attended in-person by approximately 100 participants and remotely via webcast by approximately 500 participants. A subset of the ICH E8(R1) Expert Working Group representatives presented and chaired five different sessions covering the main content of the Guideline and invited input from 20 panellists representing researchers, clinicians, and the patient population in the Americas, Asia and Europe. Additionally, the public was invited to ask questions and comment on the work during designated sessions of the meeting.

This report provides a summary of the discussion and outcome from the meeting. The feedback and insight provided during the meeting will be considered by the E8(R1) Working Group in its revisions to the draft guideline and by the ICH Management Committee who oversees the operational aspects of the ICH Association.

Additional meeting details including the agenda and a recording of the meeting can be found on the meeting website here: <https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/ich-global-meeting-ich-e8r1-guideline-general-considerations-clinical-studies-10312019-10312019>.

¹ In the revised E8(R1) Guideline, the title has been updated to “General Consideration for Clinical Studies.”

Summary of Comments

Several meeting participants indicated their appreciation to ICH for holding the meeting and for having the opportunity to engage in scientific discussion with the ICH E8(R1) working group representatives on the topic of clinical trial design and conduct. While ICH members may have conducted regional meetings in the past, it was the first time such a meeting was organised by the collective ICH Association.

Many of the meeting participants welcomed the revisions to the Guideline and ICH's approach to the modernization of guidelines related to clinical trial design and conduct and viewed that the changes are an appropriate response to the evolving landscape of clinical research. It was viewed that the efforts to modernize the Guideline will have a meaningful impact in clinical trial design moving forward and that one of the most important aspects is the revision to include the patient's perspective throughout the drug development process. Many expressed that ICH has done a nice job with the revised guideline and that the document has been significantly expanded from the original version and seems well laid out. It was also noted that the examples included throughout the document are beneficial and help to relate to real-world applicability. One panellist expressed appreciation for the flexibility and thoughtfulness put into the revisions and that the risk-proportionate approach is particularly welcome, given the tendency to over-interpret requirements of clinical trial guidelines.

While the meeting participants welcomed the revisions to the guideline and viewed them as a step in the right direction, some also noted that the document needs to take into account additional considerations and provide greater clarity on some issues. This summary is intended to highlight the key input received during the meeting. It should be noted that clinical trial design and conduct is complex and involves diverse stakeholders and while many of the issues and problems cited during the meeting may be valid, they may be beyond the scope of the E8(R1) Guideline. Additional actions from stakeholders both within and outside of ICH would likely be needed to address all the issues raised.

In the following sections, a summary of the general comments received is provided related to: challenges with the interpretation and application of the E8 Guideline, quality by design, stakeholder engagement, ethics, clinical trial complexity, study design and data sources. This report concludes with some considerations for next steps. Specific comments are annexed to this document and will be considered by ICH Working Groups developing this and other related guidance on clinical trials along with the general comments received, as appropriate.

Challenges with the Interpretation and Application of ICH E8 Guideline

Several panellists and public commenters provided input on the risk of over-interpretation of ICH Guidelines related to clinical trials. Over-interpretation is viewed as a result of the risk-averse nature of pharmaceutical developers in circumstances where a guideline is mis-understood or potentially vague leading to developers implementing more requirements than needed to avoid the possibility of having study results rejected by regulatory authorities and receiving a negative decision for a marketing application. There was broad agreement that the E8 and E6 documents have not been interpreted as intended over the years. Many viewed that this has resulted in overly complex clinical trials, excessive

reporting, increased costs for conducting a trial, increased drug prices, decreased pharmaceutical access, inefficiencies in trials, overall decline in clinical research and a deterrence to innovation.

While it was viewed that the current revision is going in the right direction, input was provided that the document is still too vague and risks further over-interpretation. The following suggestions were provided to help mitigate this risk:

- Provide more clarity where the guideline is vague
- Consider measures to ensure appropriate implementation of the guideline
- Provide more flexibility in the guideline and make it very clear that options are available
- Soften statements so the reader understands that not everything in the document is a requirement or needs to be done in all circumstances

Further, it was suggested that a study be conducted to better understand problems in designing and conducting a trial that result from over-interpretation of the guideline and understand whether these problems are due to overly burdensome regional regulatory requirements, pharmaceutical developers mis-interpretation of requirements, measures being imposed by drug developers even though not required by regulators, or other causes.

Additionally, some panellists viewed that requirements should be removed from the guideline and that it should be simplified, citing that excessive requirements risk causing more harm than good.

Several panellists and public commenters provided input that the E8 Guideline is too high-level and should provide additional clarity and specificity throughout and that it needs more focus. It was expressed that a lack of detail in the guidance can result in mis-interpretation. Generally, there was a view that many of the ideas presented were conceptual and the guideline needed instead to provide principles around proven practices. Additionally, it was expressed that the Guideline should be written for a one-time read and not be required to be read several times in order to understand the intentions of the document. It was also expressed that ICH should not rely too heavily on training but instead strive to provide the right level of specificity so that content experts will understand how to apply the guideline.

Quality by Design

The quality by design (QbD) approach to clinical research is a new concept introduced in this revision of the E8 Guideline. With this approach, critical to quality factors are identified during the planning phase, and a plan to manage the risk associated with those factors is implemented to ensure the protection of study subjects and the generation of reliable and meaningful results. Many panellists expressed that the QbD concepts and factors that are critical to quality are a welcomed addition to the E8(R1) Guideline and view QbD as an innovative area that could be used to improve study design and conduct. Panellists all highlighted the need to spend time upfront on the planning, development and design of a clinical trial with all stakeholders to ensure a robust study design and to minimize downstream changes. It was also viewed that the factors that are critical to quality could be a helpful tool in understanding which elements of the ICH E6 Guideline on Good Clinical Practice would be applicable and may help to eliminate non-essential data collection and paperwork. While feedback was provided that QbD is a positive addition,

concerns were also expressed around a lack of clarity for how to apply QbD concepts and anticipated challenges, citing that QbD in other areas has not yet been well implemented by the pharmaceutical industry.

Many panellists and commenters viewed that more clarity is needed around how to integrate the concepts of QbD into clinical trial design and that the concepts presented in E8(R1) are too general. One panellist stated that “language should be more forceful in terms of allowing sponsors to adopt QbD concepts, otherwise, there is a risk of introducing additional requirements and a risk of having a whole specialty of quality by design.” Concern was expressed that the introduction of QbD and the need to identify factors that are critical to quality early in study planning could be viewed as additive, when less may actually be needed, and that there is a need to better state the intended outcome of implementing the QbD approach and to be clearer where sponsors can pare down requirements. Regarding the identification and management of factors that are critical to quality, feedback was provided that additional clarity is needed on how to judge which factors may matter for which study types and on whether the factors apply solely for regulatory purposes or also for health policy decision makers and patients. It was suggested that more examples be provided to help clarify how these concepts should be applied.

Examples of anticipated challenges with the implementation of QbD concepts included: the ability to use non-traditional data sources (e.g., registries, electronic medical records, or health care claims), data sharing and standardization, the lack of an oversight committee to provide guidance to sponsors or investigators on factors that are critical to quality and whether quality has been completely thought through, and breaking old habits. One panellist mentioned that many large companies may have a tradition of repeating the same types of trials, whereas the new paradigm encourages innovation and may require use of different types of trials for different objectives and at different stages of development, which could be difficult to adapt to.

Stakeholder Engagement

A common theme throughout the meeting was the view that stakeholder engagement needs a new paradigm in the planning and conduct of clinical trials. Additionally, many panellists and public commenters shared a view that ICH should engage with researchers who conduct clinical trials in the development of Guidelines.

Rethinking stakeholder engagement during the design and conduct of clinical trials

Many panellists, particularly those representing patient advocacy groups, highlighted that patients have not traditionally been involved in clinical study design, often resulting in trials that do not actually fit the needs of the patient. It was noted that in many cases a patient knows more about their disease than most drug developers, and they are very motivated to do whatever it takes to advance the science. Panellists commented that engaging patients early and often throughout the drug development process should be required, including following completion of a trial to evaluate participant experience and identify opportunities for improvement. Many of the patient advocates on the panel repeated the phrase “nothing about us, without us” throughout the meeting. One panellist stated that “patient groups are becoming more organized

and are ready to engage” and that researchers and scientists need to have the ability to explain a trial in lay language to enable these conversations. It was viewed that improved patient engagement and trust would help to facilitate patient participation and thereby increase the likelihood that a trial would meet its objectives.

Many cited patient advocacy groups as a mechanism to obtain meaningful patient input to clinical study design. One panellist explained that patient advocacy groups gather information from the patient community in a number of ways. They make an effort to represent the average patient and put the patient at the centre of every trial planning decision. It was also suggested that guidance could be offered on this topic in a separate document.

In addition to patient engagement, panellists stated that there is a need for more efficient and effective engagement with other types of stakeholders such as payers, market access teams, clinicians and healthcare providers to ensure appropriate study designs. It was further suggested to have a common discussion with all stakeholders involved rather than sequential discussions with different stakeholders.

One panellist suggested that “the relationships today between Contract Research Organisations (CROs), sponsors and investigators are currently unbalanced in a way that is detrimental to patients and their safety and innovation.” A recommendation was made that there should be a provision for a direct link between the sponsor and medical staff performing the trial and that they should not have to work through a CRO, but this view was not held by other panellists. Additionally, it was highlighted that ICH should consider how guidelines will be implemented by investigators, and that for many guidelines an investigator may not be able to do everything requested by regulators.

In summary, stakeholder engagement was viewed as critical for trial design, recruitment, retention and conduct and that developing and implementing approaches to better engage the various stakeholders should be encouraged among pharmaceutical developers. Panellists agreed on the need to recalibrate the relationship between sponsors and investigators to protect patients and establish a culture of bringing the right stakeholders together with open dialogue. It should be noted that the revised guideline includes a new provision for stakeholder engagement, including with clinicians and the patient population, and that this is intended to assist in addressing many of the issues raised.

Involvement in the ICH process

Historically, only ICH Members, mainly including regional pharmaceutical regulators and international associations representing the regulated pharmaceutical industry, participate in the development of ICH Guidelines. ICH conducts a public consultation following the finalization of draft guidelines to provide the public with an opportunity to provide input; however, many meeting participants viewed that ICH should open the guideline development process for direct, at the table participation by clinicians and patients. A suggestion was made that ICH conduct a nomination and voting process for external stakeholders, who meet designated criteria, to

participate on a panel who would provide input into the development of ICH Guidelines related to clinical trials.

Ethical Concerns

Concerns with clinical trial ethics were raised citing that a clearer course on ethics issues and very clear rules of engagement are needed, particularly around patient access to medications post-trial and the content of patient consent forms.

A suggestion was made that those operating and funding trials, including the patients participating in a clinical trial, should know whether the trial was successful and that patients should have access to their individual results in a clear concise format, not only as aggregated results. Additionally, a question was raised around whether it is ethical to deny continued administration of a drug after a trial if the patient cannot afford it. It was noted that according to a recent revision to the World Medical Association's *Declaration of Helsinki*, provisions should be made to provide post-trial access to clinical trial participants for inventions identified as beneficial. It was suggested that the revised E8 Guideline include a statement on this.

Stakeholders expressed a view that patient consent forms need to be more understandable, clearer, and more concise for patients. One view was expressed that the forms have evolved over time to be upwards of 100 pages with lawyers intended as the primary audience as opposed to patients. A suggestion was made that patients be consulted in the development of informed consent forms and that they are tested with patients to ensure that the forms are comprehensible and useful. A view was also expressed that consideration should be given to the possibility of "implied consent" or having an option to "opt out" of a study, particularly for observational and pragmatic studies.

Clinical Trial Complexity Attributed to Guidelines

Many meeting participants cited that clinical trials have become too expensive and complex and attributed this to the mis-interpretation of regulatory requirements. Concerns were raised that this can lead to smaller trials, trials not being conducted, higher drug prices and a lack of independent research due to costs. Additionally, it was viewed that in many cases, care is not evidence based because a trial was not conducted. Perspective was provided that language in the guidance should be simpler and less complex. Multiple panellists felt that many required activities do not necessarily support development of a medication, and that the "bureaucracy" involved in clinical trials has caused them to be less safe. One example provided was for Investigational New Drug (IND) safety reporting; in some stages, safety reports are needed but as more information is gained less reporting should be required which would allow resources to be used in a more effective way.

Another example cited was the panellists' perception that the European Medicines Agency requires investigators acknowledge receipt of every report of a serious and unexpected adverse event in a clinical trial, even if the report arises from another clinical site. It was clarified that this is not an EMA requirement but perhaps a requirement of the trial's sponsor or a CRO tasked with safety reporting. It was viewed that these reports are valuable in the context of a phase 2 study, where little is known about the safety of the drug, and there is usually only a handful of those reports. However, for phase 3 studies, as many as 10

safety reports may be received in a day, all of which require the investigator to print, sign, and file, and if there are multiple studies with the same agent, this would have to be done multiple times. While other regulators may not have this same requirement as the EMA, the reporting may still be viewed as required because the studies are intended to support submission in multiple regions. It was viewed that the reports are so broad that it is not possible for an investigator to be able to process them in a meaningful way, and that this occupies hundreds of hours on the part of many people in the conduct of trials across multiple sites.

Guidance that considers requirements more proportional to the risks involved was suggested to enable high-quality assessment of therapeutic products, and that guidance should be based on key scientific and ethical principles, and be clear, concise and consistent.

Study Design

Panellists expressed a view that E8 should be more explicit with respect to innovative trial designs, as pharmaceutical companies are risk adverse and unlikely to change processes and approaches without firm direction. Additionally, a view was expressed that there is a need for the document to cover considerations for rare diseases.

Additional elements that were recommended to be incorporated into components of study design included:

- Establishing an understanding of the science underlying the disease and potential treatments, including understanding the biology of the disease, the appropriate definition of response, disease specific factors, what might happen during and after the trial, and what constitutes success or failure in the trial.
- Sharing of results: make sure the results of a trial are available and can be interpreted to validate whether the study design was appropriate for addressing the study's objectives.
- Anticipating what issues may arise during the post-marketing phase.
- Anticipating the impact of social media – the assumption that people participating in trials are not aware of the other people in the trial and what may be happening to them is no longer a valid assumption.
- Understanding the patient burden of participating in a trial in terms of its financial and resource implications, including consideration of whether a treatment or test is really necessary. Patients may have to travel several hours to an academic centre, stay for several days resulting in high financial and logistical costs, endure multiple biopsies, etc. Consideration should be given to minimizing undue burden to patients.
- Understanding how reimbursement systems differ in various regions.
- Ensuring relevance of questions asked, and that the data collected are necessary.

Additionally, input was provided on considerations for the selection of an appropriate study population, the use of real-world evidence and the implications for developing countries.

Selection of Study Population

Many panellists cited that inclusion and exclusion criteria for selection of study participants are outdated and should be revised. Additionally, it was stated that in many cases, the criteria pose a barrier to patient participation and that these barriers should be removed. One panellist provided an example that the elderly population may be considered a special population and excluded from a study, but in reality, they are not a special population considering that cancer, for example, is primarily a disease of the elderly. Another panellist added that many medications have not been studied in the elderly population, including cancer medications, and are often not available for this population. Another example provided was a computed tomography (CT) or virtual CT colonoscopy procedure, which is not covered by Medicare in the US, due most likely to its not being sufficiently studied in the 65 and older population.

Panellists also highlighted the need to ensure that a study population is representative of real-life patients and to avoid excluding segments of the population that may benefit from the treatment if approved. It was noted that exclusion of patient groups can result in limited patient access in terms of insurance companies denying coverage or clinicians not having the available data to treat a particular patient group with confidence. One panellist provided an example of a drug developed for smoking cessation, after the drug was put on the market, suicide rates increased among mentally ill patients, and it became clear that the drug was not studied in this population. Further it was highlighted that the healthiest population within a disease category is not necessarily representative of the real patient population that would eventually be exposed to the drug, and that many patients may have co-morbidities which should also be studied during development.

While panellists acknowledged that these issues were usually encountered post-trial and may not necessarily be considered by those writing a study protocol, it was viewed that they are very important to consider, especially in countries such as the United States where an absence of study data can result in the drug not being covered by an insurance company.

Real World Evidence

Many panellists felt that real-world evidence (RWE) could play an important role in drug development throughout the entire drug development process, including, for example, pragmatic trials; however, some indicated that more explicit detail is needed in the revised E8 Guideline, with more focus on the methodologic aspects of the trial design and attention to rigor, and to the reproducibility of results. It was also expressed that consideration should be given to questions anticipated to arise during the post-marketing phase and the possible use of pragmatic trials to address these issues earlier in development. Potential benefits of generating RWE with a pragmatic trial that embeds randomization within a health care system and uses electronic health records and claims data as data sources were cited as providing insight into post-market safety issues and potential new indications, informing clinical care practices, providing evidence to support use of a biomarker, allowing for better understanding of adverse events that might occur in a broader population, etc. Panellists cautioned, however, that additional clarity is needed,

particularly regarding how quality by design principles could be applied to these types of studies. One panellist also stated, “in the absence of clear guidance, investigators will continue to rely on outdated approaches simply due to a lack of awareness.” Additionally, it was suggested that clearer expectations are needed for the design features that are known to reduce common sources of systematic bias.

Considerations for Developing Countries

One panellist provided a perspective from a developing country. A view was expressed that the Guideline should take into consideration unique circumstances that are encountered in developing countries and that it may not be feasible to implement some of the elements contained within the Guideline. Stated examples of challenges that may be unique to the conduct of clinical trials in developing countries included:

- A patient may not be aware that they are participating in a clinical trial; all they know is that they are getting the drug free of cost.
- There may be a lack of availability of electronic health records.
- The majority of clinical data may be controlled by private entities; ensuring that these data are taken into consideration when planning a clinical trial will be important.
- Negative public perception around clinical trials may impact patients’ participation.
- The patient voice may be lacking. In many cases the doctor decides on the course of care the patient will take, and the patients does not always have a say.
- Bigger hospitals typically conduct clinical trials, and the site investigator may not have expertise in the disease area of the trial.
- Ethical committees may lack knowledge of a condition, or the members of the committee may be closely tied to the institution conducting the trial.

Data Sources

Many panellists cited challenges with the use of innovative data sources in clinical trials, and while it was acknowledged that the E8(R1) document signals an openness to work with different kinds of data, more is needed to help progress the ability to leverage more modern technology. Additionally, it was highlighted that there is a need to leverage the large amounts of data generated from electronic health records, mobile data, registries, and secondary data as much as possible. It was also acknowledged that there is a need to look for ways to avoid undue risk or bias and to validate electronic data which could be accomplished using modern technology and possibly tailoring for each study. It was also emphasized that data standardization is needed to facilitate sharing and the reuse of data from sources such as patient registries. Many panellists expressed the view that use of these types of data could help drive study design, facilitate enrolment and improve data quality.

Other comments

Other general comments provided pertained to the use of the ICH E8 Guideline as a roadmap to other ICH Guidelines, the desire for it to provide insight on “what not to do,” and the need to have flexible guidance to accommodate technology advances.

It was noted that the E8 Guideline is intended to inform the reader of which guidelines to reference for various aspects of clinical trial design, conduct, and reporting. While the panellists acknowledged this, a view was expressed that the Guideline should provide additional clarity in terms of what the expectations are for a clinical trial, if the recommendations in the Guidelines are followed. It was indicated that the Guideline should be strengthened as the backbone for the efficacy family of Guidelines. It was also highlighted that the application of these Guidelines be focused on the important issues for a given clinical trial, and it was suggested that the references to other Guidelines be reviewed and updated.

Panellists also suggested that ICH Guidelines provide insight into “what not to do” as opposed to solely “what to do” such as providing examples of what is not considered good clinical practice.

Several stakeholders raised concern that ICH Guidelines take many years to finalize and are not revised frequently; therefore, the Guideline should allow for enough flexibility to accommodate potential future innovations and scientific advances and to ensure that it is still relevant many years following its finalisation. Additionally, it was noted that there are some circumstances where more flexibility is needed. For example, cancer science is very rapidly evolving and there is a need to find the right balance between flexibility and the reliability of a trial’s results.

Conclusion

The E8 Guideline was first finalized in 1997, and the science of clinical trial design has advanced and new technologies have become available since. The current revision is intended to modernize guidance related to clinical trial design, planning, management and conduct. The goal 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.

The ICH E8(R1) global meeting was planned as part of ICH’s “GCP Renovation” and in recognition of the considerable stake in clinical trial research, GCP expertise, and clinical trial experience of parties outside of ICH, particularly those in the academic research community and patient groups. Feedback was provided that the revisions to the Guideline are welcomed and are viewed as a step in the right direction; however, many indicated that more specificity throughout the document is needed. Key comment areas included:

- Challenges with interpretation and application of the ICH E8 Guideline in clinical trial practice
- Aspects related to the implementation of a quality by design approach and a need for more targeted stakeholder engagement that is more inclusive of the patient population
- Ethics of clinical trials including with informed consent and continued drug access post-trial
- Complexity of guidance on clinical study design
- Selection of an appropriate study population
- Generation and use of real-world evidence
- Considerations for developing countries
- Use of non-traditional data sources

ICH appreciates the participation of all stakeholders involved in the meeting and their insights. The feedback received will be reviewed by the E8(R1) Expert Working Group in their finalization of the revised Guideline as well as the ICH Management Committee. ICH will also consider additional options for the continued engagement of clinical researchers and the patient population in subsequent revision of ICH Guidelines related to clinical trial design and conduct.

Annex 1: Specific comments

Informed consent

- In reference to the statement, “In practice, the study population is limited to subjects available to participate and for whom consent is available.” Given this document is not meant to only address clinical studies that will facilitate acceptance of data and results by regulatory authorities, there may need to be some additional flexibility in this statement, since these guidelines are also used by those conducting observational and pragmatic studies including registries, retrospective chart reviews and linkage of data from different sources including health system records. In these circumstances consent could be implied as part of institutional change in practice, utilization of an opt out consent approach or be absent if data sources or retrospective chart reviews are being utilized. Ensuring flexibility and consistency with regard to consent will be important to not limit these opportunities where alternatives to consent would be considered.

RWE

- We should be trying to incorporate real-world data under a certain set of assumptions and when appropriate.
- Some view pragmatic trials as a way to avoid certain things, as a way to speed things up and reduce costs; however, one should decide on the question first and then determine if RWE is the best approach. It’s important to be precise about the question.

Stakeholder Engagement

- The choice of language is important - patients are not subjects.
- ICH should consider building capacity for effective patient engagement.
- In terms of study reporting, the patient participants in the research enterprise are entitled to feedback as to what the results were from the study and whether it was successful or not. This should be put into the guideline for general considerations.

E8 References

- The references in E8 to other sections of ICH Efficacy Guidelines which offer more detail on the elements of study design, should be reviewed and updated to align and bring consistency overall in the guidance.

Regulatory burden

- If you look at Annex 3, nine different guidelines would need to be referenced to understand everything about eligibility or randomization. It is viewed that this adds complexity and could be simplified. The upside of that is an enormous bureaucracy and a whole new industry that exists of CROs and has an impact on where the majority of research is and the impact of those processes

spill over into the research and that has a very negative consequence in terms of what is happening.

QbD

- It was suggested that annex 3 could be used as a tool to provide more clarity on quality by design and identifying the risk within the study and creating a framework for the relevant study.
- Would like to see the factors listed in section 7 more structured. Three types of threats to quality – internal and external validity, threats stemming from bias and threats stemming from lack of precision. The one related to external validity are threats related to generalizability. It would be very helpful if those were separated.
- Would be helpful to have some examples of the use of critical to quality factors in sections 3 and 4 but particularly section 4.
- Quality by design is essential. There is so much that investigators and trialists do that's a total waste of time and effort based on the impression of regulators working with sponsors who believe that we need to do certain things to avoid criticism further down the line.
- It should be clarified how important Annex 3 is in terms of navigating CtQ factors
- Section 3.3 has some good reminders in terms of trust, culture and communication but to avoid too much it will be valuable to integrate those concepts into one of the other sections 3.1 and 3.2. (Integrate section 3.3 into 3.1. and 3.2).
- More direct references to Annex 1 and Annex 3 are suggested to improve understanding and application of QbD and CTQ principles (E8) (move from concept to implementation).
- There is a need to clarify what is meant by quality –this is defined as fitness for purpose, but what does that mean? It should relate to clear clinical useful results whether they are positive or negative but not ambiguous.
- Linking the principles in the E Guidelines to the QbD framework and CtQ factors is essential for any impact.
- Reference to QbD concepts needs greater clarity e.g. each bullet point (lines 105 – 113) can reference specific E Guidelines
- CTQ must be related to the study objectives, currently the document is too general, although good concepts are presented, they are not unique to clinical studies (i.e, performance indicators aligned with CtQ factors (not other short-term financial objectives), critical thought rewarded, open dialogue with all stakeholders).
- Data sharing plan is something that should be one element of the QbD approach because this will help to improve the quality.
- Research on personalized medicine - where you test various treatments after stratification of a patient's population in homogeneous groups and again the validity of the stratification is crucial aspect for multi-arm trials and for the trial to be ran after the stratification. So this is an aspect that could be integrated in this quality by design approach and critical to quality factors.

- Some challenges are anticipated relevant to the quality by design approach including with secondary use of data, data sharing, and personalized medicine. Challenges associated with secondary use of data include:
 - Use of data from the registry - this a huge opportunity to contain costs
 - Reliability of the control and tractability of the data
 - Compatibility with the clinical trial database management system
 Use of the data from the electronic health record includes some of the same issues in terms of quality format and trust-ability. Additionally, sometimes the data is not structured so there is a need to raise an additional phase of digitalization and also interoperability between the system and the clinical trial standards and also between electronic health record. Standardization is also critical for quality and sharing patient data. Data sharing plan is something that should be one element of the QbD approach because this will help to improve the quality.
- If the outcomes are intended to be part of the RCT, it is important to consider quality by design from the beginning.
- The CtQ factors used will depend on the type of study being employed. For example, a small sample size will require high precision whereas a larger sample will require less precision.
- Some tools by CTTI might be useful in referencing in the annexes.

Study Design

- The guidelines may need to think about how studying new treatments that could improve quality of life but potentially shorten it may be considered acceptable in select circumstances
- Need to use modern electronic systems or artificial intelligence to collect data by someone who understands this data.
- Need to filter signals by someone who understands the results to avoid unnecessary reporting – in many cases, those collecting the data and sending it back to the clinicians do not understand what they are doing and report everything
- We need more innovative smarter design trials so we can deliver in a quicker fashion – facilitate clinical trial design, want to look at the disease in its entirety.
- Three principles should be considered for development of modern observational pharmacoepidemiologic study design:

1) Use of active treatment for comparator - this can balance the treatment groups on major drivers of the outcomes such as the indication for treatment and disease severity, health care seeking and frailty. For example: patients with gestational diabetes who are initially treated with metformin are substantially similar to those who receive insulin; and adults who receive glargine are much like those who receive NPH insulin. In contrast, non-user comparison groups include an unhelpful mix of patients who are 'too healthy' by virtue of not being sick enough to require treatment and those who are 'too frail' to tolerate treatment despite being indicated for it.

Focusing on the patients who are receiving active treatment greatly reduces this bias by design

2) Anchoring the start of follow-up at the time of treatment initiation - Identification of new users, or treatment initiation, effectively anchors the start of follow-up at a common point. Like in a randomized trial, this design feature ensure that the capture of outcomes includes similar windows of time for both treatment groups. This is particularly important when those patients who are vulnerable to an adverse outcome or who fail to have sufficient therapeutic response discontinue the medication early on. The pool of prevalent users has already eliminated both of these groups and therefore no longer represents the risks and benefits of treatment for all those who initiated it but rather is enriched with those who receive benefit and did not experience any harms. Anchoring time at treatment initiation also ensures that confounders measured at baseline have not already been affected by the treatment itself.

3) Avoiding looking into the future to select patients - We need to recognize that we cannot use omniscient powers derived from access to secondary healthcare data to select patients. Physicians are not able to selectively treat patients based on events that will occur months or years in the future, and therefore neither can we. Eliminating patients from treatment groups up front based on failure to adhere to the treatment or failure to survive for some time into the future introduces bias, just as it would in a randomized trial.

- 4.4.3 post-approval studies, also the duty of pharmaceutical companies, short comment would be helpful that this is the case for other healthcare providers, because this is the most efficient way to incorporate quality. Post-approval studies need to be easy to do, modern technologies can be leveraged such as electronic health records, etc. there are missed opportunities due to overly complicated guidance.
- Three types of studies are conflated in the document, sometimes they were separate and sometimes they were together, randomized interventional trials, nonrandomized interventional trials and observational studies. When those concepts get conflated as they did later on in the document, not in the beginning, one would think that what is being said applies to them all, but they are different. The three types of studies yield very different types of results and the CtQ factors will have to differ for them.

Study population

- Structural bias is being created in the studies in terms of the ability of the study meet the objectives. The Guideline states, “the study has to be designed with the people in mind who can help the study meet the objectives,” sometimes you can make a study structured in such a way that you define the population of people you're going to study, and the people in the study become very homogeneous and not reflective of the population the drug is intended to be used in, this can be referred to as structural bias. You can ask for people who are exceptionally healthy within a disease focus or you can require a test has to be done that can't be done anywhere expect for a few cancer centres that may not have relevance to the intended population. This can result in a population being excluding.
- Regarding missing data, if the doctor didn't capture something, it was never meant to be there.
- Need to consider other special groups in addition to pregnant women, elderly, etc.

- Placebo or standard of care arm is a barrier to entry – considering the length of time for enrolment and conducting the trial and then the patient finds out they were receiving placebos - that five or six years of loss of function that can mean forfeiting the ability to be in the trial.
- Additionally, many companies may simply reuse criteria for previous studies whether or not the criteria are still relevant.

Drug development plan

- The type of data collected will matter at which state of the trial you are.
- Regarding safety issues, there should be an effort to try and get a majority of the answer from the regional trials as opposed to post-approval trial, sometimes it is not ethical to run a post approval trial, need to try to find a way to get the answer from the original trial

Data sources:

- Document should include considerations for data generated through new technologies.
- It's important to emphasize economy of data and focus.