



# **ICH Public Meeting E8(R1) General Considerations for Clinical Studies**

**October 31, 2019**

International Council for Harmonisation of Technical Requirements  
for Pharmaceuticals for Human Use

# Agenda

- **Opening Remarks**
- **Session I: The role of E8 as part of the ICH GCP Renovation and next steps**
- **Session II: Drug Development Plan**
- **Session III: Components of Study Design**
- **Session IV: Quality by Design/Critical to Quality Factors**
- **Session V: Data Sources**
- **Open Comment**
- **Closing Remarks**



# **ICH Public Meeting E8(R1) General Considerations for Clinical Studies**

*Opening Remarks*

*Dr. Janet Woodcock, Director,  
Center for Drug Evaluation and Research*

**October 31, 2019**

International Council for Harmonisation of Technical Requirements  
for Pharmaceuticals for Human Use



# Session I: The role of E8 as part of the ICH GCP Renovation and next steps

*Chairs:*

*Dr. Lisa LaVange, E8 EWG Rapporteur - FDA, United States*

*Dr. Fergus Sweeney, E8 EWG Regulatory Chair - EC, Europe*

## Overview

- I. Introduction to ICH and its Global Footprint – *Ms. Amanda Roache, ICH Coordinator – FDA, United States***
- II. ICH E8(R1) Role in GCP Renovation – *Dr. Lisa LaVange, E8 EWG Rapporteur, FDA, United States***
- III. Overview of ICH E8(R1) – *Dr. Andreas Kirisits, E8 EWG Representative – EC, Europe***
- IV. Response to public consultations: first impressions and next steps – *Dr. Carole Légaré, EWG Representative, Health Canada, Canada***



# Introduction to ICH and Its Global Footprint

October 31, 2019

**Amanda Roache, MPP**  
**ICH Coordinator, FDA, United States**

International Council for Harmonisation of Technical Requirements  
for Pharmaceuticals for Human Use

# International Council for Harmonisation (ICH)

- Originally founded in 1990, ICH is a unique harmonization initiative for regulatory authorities and pharmaceutical associations
- ICH's mission is to achieve greater harmonization worldwide to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner
- Harmonization is achieved through the development of ICH Guidelines via a process of scientific consensus

## International Harmonization Leads to:

- More efficient regulatory review
- More efficient exchange of information between regulatory authorities
- Reduced time to get a product to the market
- Reduced patient burden through prevention of unnecessary duplication of clinical trials and post market clinical evaluations
- Reduction of unnecessary animal testing without compromising safety and effectiveness

## Reforms of ICH Association

- Reformed as a non-profit legal entity under Swiss Law on October 23, 2015
- The new association aims to focus global pharmaceutical regulatory harmonization work in one venue
- More involvement from regulators and industry around the world is welcomed and expected

# Pathway to Membership

## ELIGIBILITY CRITERIA FOR LEGISLATIVE OR REGULATORY MEMBER

- **Legal personality**
- **Responsible for the regulation of pharmaceutical products for human use**
- **Has participated in at least 3 out of 4 Assembly meetings during the past two years**
- **Has appointed experts in at least two ICH Working Groups**
- **Has implemented the ICH Q1, Q7, and E6 Guidelines**

## INDUSTRY MEMBER CRITERIA

- **Legal Personality**
- **Represents Members from several countries in at least three continents**
- **It or its members are regulated or affected by all or some ICH Guidelines**
- **Has participated in at least 3 out of 4 Assembly meetings during the past two years**
- **Has appointed experts in at least two ICH Working Groups**

# ICH Members

## **Founding Regulatory Members (permanent Management Committee (MC) Members):**

- EC, Europe; FDA, US; MHLW/PMDA, Japan

## **Founding Industry Members (permanent MC Members):**

- EFPIA, JPMA, PhRMA

## **Standing Regulatory Members (permanent MC Members):**

- Swissmedic, Switzerland; Health Canada, Canada

## **Elected MC Members:**

- Regulatory Members: CFDA, China; HSA, Singapore; MFDS, Korea
- Industry Members: BIO, IGBA

## **Regulatory Members:**

- ANVISA, Brazil; TFDA, Chinese Taipei

## **Industry Members:**

- GSCF

**New  
Members  
since ICH  
Reforms**

# ICH Observer Criteria

- **Legislative or administrative authorities and Regional Harmonization Initiatives with the responsibility for regulation of pharmaceuticals for human use**
- **International pharmaceutical industry organizations that are regulated by all of some of ICH guidelines**
- **International organizations represented at the global level who work is regulated or affected by ICH guidelines**

## Standing Observers

- International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) (MC Member)
- World Health Organization (WHO) (MC Member)

## Legislative or Administrative Authorities

- Central Drugs Standard Control Organization (CDSCO, India)
- Centro para el Control Estatal de Medicamentos, Equipos y Dispositivos Médicos (CECMED, Cuba)
- Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS, Mexico)
- Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA, Colombia)
- Medicines and Medical Devices Agency (MMDA, Moldova)
- National Center for the Expertise of Drugs, Medical Devices and Equipment (National Center, Kazakhstan)
- National Pharmaceutical Regulatory Agency (NPRA, Malaysia)
- Roszdravnadzor (Russia)
- South African Healthcare Products Regulatory Authority, (SAHPRA, South Africa)
- The Scientific Center of Drug and Medical Technology Expertise (SCDMTE, Armenia)
- Therapeutic Goods Administration (TGA, Australia)
- Turkish Medicines and Medical Devices Agency

(TITCK, Tukey)

## Regional Harmonization Initiatives

- Asia-Pacific Economic Cooperation (APEC)
- Association of Southeast Asian Nations (ASEAN)
- East African Community (EAC)
- Gulf Cooperation Council (GCC)
- Pan American Network for Drug Regulatory Harmonization (PANDRH)
- Southern African Development Community (SADC)

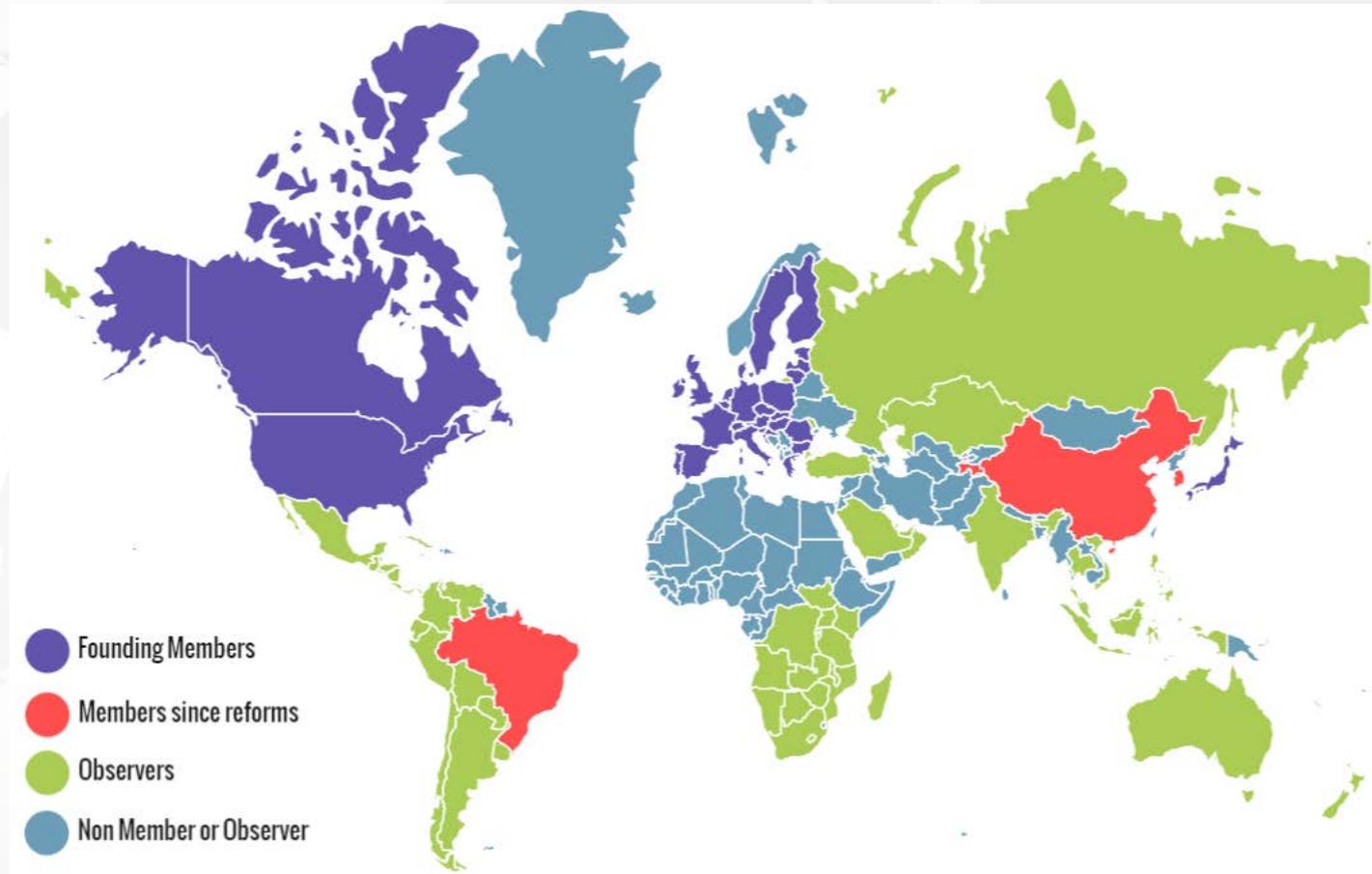
## International Pharmaceutical Industry Organization

- Active Pharmaceutical Ingredients Committee (APIC)

## International Organizations with an Interest in Pharmaceuticals

- Bill & Melinda Gates Foundation
- Council for International Organizations of Medical Sciences (CIOMS)
- European Directorate for the Quality of Medicines & HealthCare (EDQM)
- International Pharmaceutical Excipient Council (IPEC)
- Pharmaceutical Inspection Cooperation Scheme (PIC/S)
- United States Pharmacopeia (USP)

# ICH Footprint



# For more information on Member and Observer eligibility criteria:

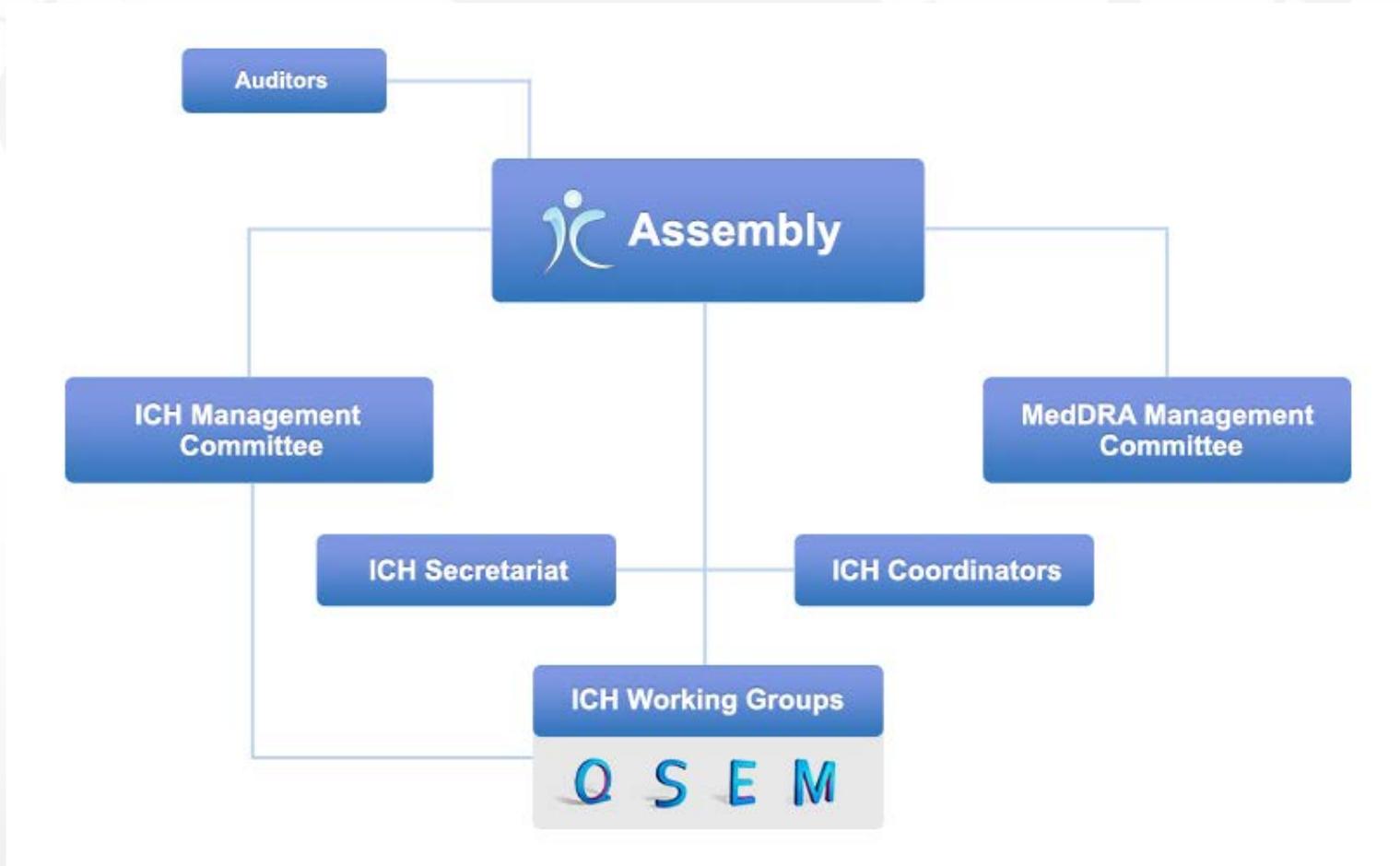
## ICH Assembly Rules of Procedure:

- [https://admin.ich.org/sites/default/files/2019-08/AssemblyRoP\\_Approved\\_v7-0\\_2019\\_0606.pdf](https://admin.ich.org/sites/default/files/2019-08/AssemblyRoP_Approved_v7-0_2019_0606.pdf)

## Articles of Association:

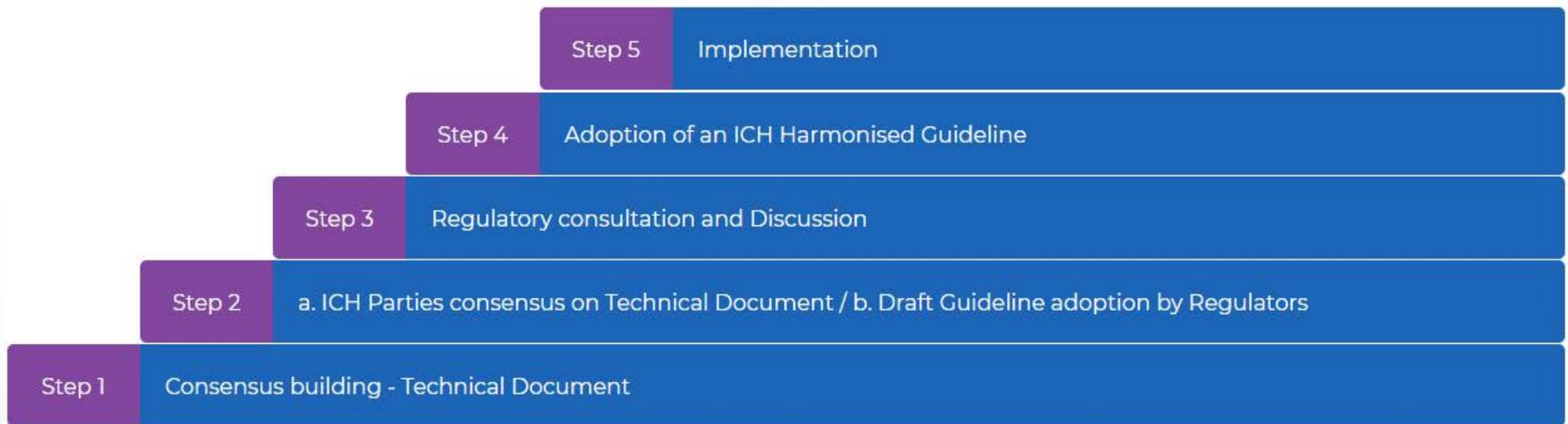
- [https://admin.ich.org/sites/default/files/2019-08/ArticlesOfAssociation\\_Approved\\_v3-0\\_2019\\_0606.pdf](https://admin.ich.org/sites/default/files/2019-08/ArticlesOfAssociation_Approved_v3-0_2019_0606.pdf)

# Governance Structure of ICH Association



# ICH Formal Procedure

- **Harmonisation is achieved through the development of ICH Guidelines via a 5-step process of scientific consensus**



# Following the progress of ICH Guidelines

**E8 General Considerations for Clinical Trials** ^

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> **E8**      **General Considerations for Clinical Trials**

---

v **E8(R1) EWG**      **Revision on General Considerations for Clinical Trials**

ICH is proposing a modernisation 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. The revision would propose to: (1) identify a basic set of critical-to-quality factors that can be adapted to different types of trials to support the meaningfulness and reliability of trial results and to protect human subjects; (2) address a broader range of trial designs and data sources; (3) provide an updated cross-referencing of all other relevant ICH Guidelines that should be referred to when planning clinical studies. The modernisation of ICH E8 is the first step towards the GCP Renovation initiated in 2017.

As part of the GCP renovation plan, an ICH E8(R1) public stakeholder meeting targeted at global stakeholders will be held on October 31, 2019 at 08:30 a.m. to 5:00 p.m. ET in Silver Spring, Maryland, USA, with Webcast option available.

For more information, including how to register to attend either in person or via the webcast, please go to the page on [GCP Renovation](#).

**Rapporteur:** Dr. Lisa M. LaVange (FDA, United States)

**Regulatory Chair:** Dr. Fergus Sweeney (EC, Europe)

Date of *Step 2b*: 8 May 2019

Status: *Step 3*

**Guideline**

 E8(R1) EWG Draft Guideline

**Endorsed Documents**

 E8(R1) EWG Concept Paper

 E8(R1) EWG Business Plan

 E8(R1) EWG Work Plan

**WG Presentations / Trainings**

 E8(R1) EWG Step 2 Presentation

**Expert list**

# Following the progress of ICH Guidelines

## E8 General Considerations for Clinical Trials

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### WG Presentations / Trainings

- E8(R1) EWG Step 2 Presentation

[Expert list](#)

# Follow-up of ICH Guidelines

## E8(R1) EWG Revision on General Considerations for Clinical Trials

### Expert list

<b>E8 Gener</b>	<b>ANVISA, Brazil</b>	<b>BIO</b>
> E8	Ms. Flávia Regina Souza Sobral	Dr. Gregory T. Golm Mr. Matthew Irvin
∨ E8(R1)	<b>EC, Europe</b>	<b>EFPIA</b>
	Mr. Andreas Kirisits Dr. Fergus Sweeney	Dr. Byron Jones Dr. Kerstin Koenig
	<b>FDA, United States</b>	<b>Health Canada, Canada</b>
	Mr. Philip Krause Mr. Mark Levenson	Dr. Carole Legare Mr. Fuhu Wang
	<b>IFPMA</b>	<b>IGBA</b>
	Dr. Angela (Hui) Yan	Dr. Sigrid Balsler Dr. Aletta van Beek
	<b>JPMA</b>	<b>MHLW/PMDA, Japan</b>
	Mr. Osamu Komiyama Mr. Mitsuhiro Kondo	Dr. Yuki Ando Dr. Mitsuhiro Ikuma Mr. Hiroshi Sakaguchi
	<b>NMPA, China</b>	<b>PhRMA</b>
	Dr. Shuang Lu Dr. Tao Wang	Ms. Melissa Mudrick Dr. Joanne Palmisano
	<b>Swissmedic, Switzerland</b>	<b>TFDA, Chinese Taipei</b>
	Dr. Christine Haenggeli	Dr. Hsiao-Yun Chen Ms. Mei-Chen Huang

**Regulatory Chair:** Dr. Fergus Sweeney (EC, Europe)

Date of *Step 2b*: 8 May 2019

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Guideline

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**Expert list**



**Thank you for your attention**

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# ICH E8(R1) Role in GCP Renovation

**Lisa LaVange, PhD**  
**E8 (R1) Rapporteur**  
**FDA, United States**  
**October 31, 2019**

International Council for Harmonisation of Technical Requirements  
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- **Background**
  - ICH E6 and E8
  - External Stakeholders Comments and Meeting
- **ICH Reflection Paper on GCP Renovation**
  - Objectives
  - Proposal for E8 Revision and E6 Renovation
- **Timeline and Next Steps**

# ICH E6 and E8 – A Brief History

- **E6: Good Clinical Practice (GCP) – finalized in 1996**
  - Describes the responsibilities and expectations of all participants in the conduct of clinical trials, including investigators, monitors, sponsors, and IRBs
  - GCP covers aspects of monitoring, reporting, and archiving clinical trials
  - Addenda for essential documents and investigator brochures
- **E6 (R2) – finalized in 2016**
  - Addendum to encourage implementation of improved and more efficient approaches, while continuing to ensure human subject protection
  - Updated standards for electronic records

# ICH E6 and E8 – A Brief History

- **E8: General Considerations for Clinical Trials -- finalized in 1997**
  - Sets out general scientific principles for the conduct, performance and control of clinical trial
  - Addresses a wide range of topics in trial design and executions
  - Emphasizes the protection of human subjects in clinical trials
- **E8 (R1) – Draft issued for public comment in May 2019**

# Response to ICH E6 (R2)

- **External Stakeholders Letter to ICH**
  - From: 5 research organizations, 119 health researchers in 22 countries
  - To: EMA and ICH
  - Submitted 31Jan2016; revised and resubmitted 26Feb2016
  - In response to public consultation on E6 (R2)
- **Stakeholders' concerns**
  - Lack of focus on issues most critical for trial quality
  - Lack of flexibility for different types of trials
  - Lack of involvement of external stakeholders in ICH processes

# Response to ICH E6 (R2)

- **2016 ICH Meeting in Lisbon**
  - Management Committee members met with External Stakeholders to discuss issues outlined in their letter
- **Meeting Discussion**
  - Some concerns cited in the stakeholders letter could be addressed by considering the position of E6 within the broader context of the family of ICH guidelines
  - As an example, consideration of randomization and its impact on the quality of a trial's results is addressed in ICH E9
  - Agreement on the need for flexibility and for emphasizing quality aspects in proportion to risks involved
- **Commitment to involve external stakeholders in future**



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# ICH Reflection on “GCP Renovation”: Modernization of ICH E8 and Subsequent Renovation of ICH E6

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12 January 2017

ICH is inviting public review and comment on a reflection paper on Good Clinical Practice (GCP) "Renovation", which contains the ICH proposal for further modernization of the ICH Guidelines related to clinical trial design, planning, management, and conduct. The scope of the proposed renovation includes the current E8 General Considerations for Clinical Trials and further revision to the E6 Guideline for Good Clinical Practice, which is already undergoing modernization with the recent production of ICH E6(R2).

The reflection paper is available for download via the following link:

- [Reflection paper on GCP Renovation](#)

The goal of the potential renovation 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, as appropriate. The underlying principles of human subject protection and data quality would remain. ICH's decision to invite stakeholder comment on the proposed renovations at this early stage, ahead of guideline development efforts, recognises the considerable stake and relevant expertise in the research community beyond ICH.

The seeking of stakeholder comment on the current reflection paper is seen as a first step in an enhancement of the ICH process with respect to public consultation for the revision of ICH E8 and E6. The GCP Renovation reflection paper outlines additional steps that are also being considered to enhance stakeholder engagement.

# ICH Reflection on GCP Renovation

- **Reflection paper published Jan2017**
  - Modernization of ICH E8 and Subsequent Renovation of ICH E6
- **Goal is to provide updated guidance that:**
  - Is flexible enough to address the increasing diversity of clinical trial designs and data sources
  - Is appropriate for trials that support regulatory and other health policy decisions
  - Adheres to underlying principles of human subject protection and data quality
- **Public comment sought for Reflection Paper, as first step to increase external stakeholder involvement in ICH processes**

# ICH Reflection on GCP Renovation

- **Step 1: Revision to ICH E8 -- rationale**
  - 1997 guidance is a high-level document that serves as a roadmap to other ICH guidance guidelines
  - Focuses on studies to support regulatory decisions
  - Does not address differences in trial designs and conduct required for different types of studies
  - Does not address design or planning considerations for data quality (the quality of the study that generates the data)

# ICH Reflection on GCP Renovation

- **Step 1: Revision to ICH E8 -- proposal**
  - Revise and modernize to address broader concern about the principles of study design and planning for an appropriate level of data quality
  - Include addition of the concept of quality by design as key consideration in study planning, particularly as it relates to non-standard data sources and non-traditional trial designs
  - Update the cross-referencing to the family of ICH guidance documents to facilitate study planning

# ICH Reflection on GCP Renovation

- **Step 2: Renovation of ICH E6 GCP**
  - Preserve a key role for the current focus on traditional interventional trials
  - While also addressing a broader range of study types and data sources
  - Retaining the current focus on good clinical investigative site practices
  - While also referring to E8 (R1) discussion of study quality considerations and other ICH guidance
  - Propose development of a series of annexes with detail on particular study types or data sources

# Timeline and Next Steps

- **ICH E8 (R1)**
  - Expert Working Group (EWG) to review public comments received to date in response to posting in each regulatory region
  - Incorporate discussion from today's public meeting
  - Finalize the guidance document with anticipated completion date of June 2020
- **ICH E6 (R3)**
  - Informal Working Group (IWG) formed to develop work plan for renovation
  - Timeline forthcoming



# Thank you

ICH Secretariat  
Route de Pré-Bois 20  
1215 Geneva  
Switzerland

E-mail: [admin@ich.org](mailto:admin@ich.org)

International Council for Harmonisation of Technical Requirements  
for Pharmaceuticals for Human Use



# Overview of ICH E8(R1)

**Andreas Kirisits**  
**E8 EWG Representative**  
**EC, Europe**  
**Washington, Oct. 31 2019**

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- **E8 (R1) Overview**
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  - Promoting Quality by Design in clinical studies
  - Drug development planning
  - Study design considerations
  - Study conduct & reporting
  - Identifying CtQ factors
  - Annexes
  - Integrative look on the Guideline
- **Today's Meeting**

## E8 (R1) - Goals & Challenges

- Promote **fit-for-purpose clinical trials** by:
  - Introducing ‘Quality by Design’ concept and identifying ‘Critical to Quality’ (CtQ) factors
  - Upfront assessment of risks specific to development programme & study design
  - Proportionate management of these risks and respective controls
  - Facilitating a broad range of study designs and data sources



# General Principles

## Chapter 2

- Protection of Study Participants
  - Health risks and confidentiality
- Scientific Approach
  - On development programme & study level
  - Iterative research process
- Patient Voice
  - On objectives and design realisation
  - To improve feasibility & promote commitment



# Promoting high-quality studies

## Chapter 3

- Introduces ‘Quality by Design’ concept to clinical research
- Suggests devising a specific set of factors critical to the quality of a given study (‘CtQ factors’)
- Outlines approach to identifying and managing risks to these factors

# Critical to Quality Factors

## Chapter 3

- Identifying attributes whose integrity is fundamental to study quality via:
  - Open dialogue, multiple stakeholders
  - Triage and focus on essential activities
  - Proactive implementation in protocol
  - Continuous review and risk-proportionate adaptations
- Flexibility instead of one-size-fits-all strategy

# Drug development planning

## Chapter 4

- Considerations at the development programme level
- From target product profiling through post-approval research
- Main focus on clinical studies, combining step-wise evidence building with flexibility in study planning
- Special populations and study feasibility addressed as additionally important issues

# Types of clinical studies

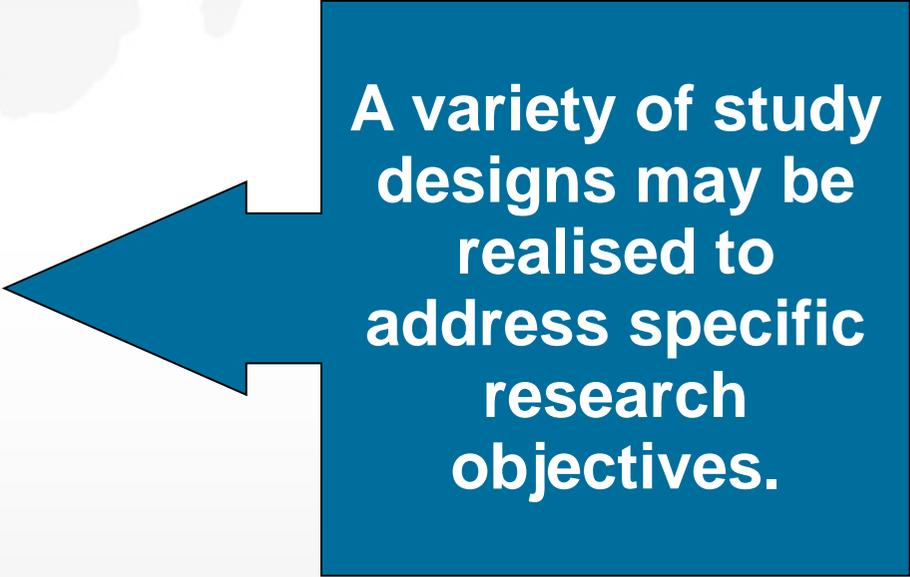
## Chapter 4

Study type	Example study objectives
<b>Human pharmacology</b>	<ul style="list-style-type: none"><li>• Initial Safety &amp; Tolerability</li><li>• Mechanism of action</li><li>• Pharmacokinetics</li><li>• Pharmacodynamics</li></ul>
<b>Exploratory</b>	<ul style="list-style-type: none"><li>• Dose selection</li><li>• Population selection</li><li>• Establish prognostic &amp; predictive factors</li></ul>
<b>Confirmatory</b>	<ul style="list-style-type: none"><li>• Establish efficacy &amp; safety profile in broadly representative population</li></ul>
<b>Post-approval</b>	<ul style="list-style-type: none"><li>• Broaden and refine understanding of efficacy &amp; safety profile</li></ul>

# Elements of study design

## Chapter 5

- Key design aspects include:
  - Study population
  - Intervention
  - Control group
  - Response variable
  - Bias reduction
  - Statistical analysis



**A variety of study designs may be realised to address specific research objectives.**

# Data sources

## Chapter 5

- Broadly describes primary & secondary data generation/collection
- Acknowledges different data sources and respective methods and technologies used
- Highlights specific caveats and the importance of data standards



# Study conduct & Reporting

## Chapter 6

- Study Conduct
  - Adequate protocol set-up, adherence and respective training
  - Data Management and (interim) access to study data
- Participant safety
  - Safety monitoring, data collection and stopping rules
  - Role of Data Monitoring Committees
- Study Reporting
  - Reference to ICH E3
  - Promotes transparency and public access to study data

# Identifying CtQ factors

## Chapter 7

- Example list of considerations for identifying CtQ factors at the planning stage
- Non-exhaustive and of varying importance depending on the specific situation
- Evident «usual suspects», but an adaptive approach to devising CtQ factors is the core message



## ‘Living’ Annexes 1-3

- Annex 1:
  - Plots research objectives and respective study examples along drug development process
  - integrates chapters 4 & 5
- Annex 2:
  - ICH E-Guideline family
- Annex 3:
  - Cross-referencing CtQ factors to other ICH documents as applicable

# An integrative look on E8 (R1)

**General Principles**

**Quality by Design &  
Critical to Quality Factors**

**Drug development  
planning**

**Study design,  
conduct & reporting**

**List of CtQ factor examples**

**Annex 1 – Study Types & Designs**

**Annex 2 & 3 – Cross-link to ICH GLs**

## E8 (R1) offers...

- A principal guidance document:
  - promoting internationally agreed principles and practices of clinical research
  - focussed on identifying and safeguarding critical elements in study planning, conduct and reporting
  - applicable to a broad range of development programmes and study types
- An integrative platform for other ICH guidelines ('ICH E0')

# Today's Meeting

- Sessions II-V reflect key content of E8 (R1)
  - Session II: Drug development plan
  - Session III: Study design
  - Session IV: Quality by Design & CtQ factors
  - Session V: Data sources



# Thank you

ICH Secretariat  
Route de Pré-Bois 20  
1215 Geneva  
Switzerland

E-mail: [admin@ich.org](mailto:admin@ich.org)

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# Response to Public Consultations: First impressions and next steps

**Carole Légaré**  
**E8 EWG Representative**  
**Health Canada**  
**Washington, Oct. 31 2019**

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# Table of contents

- Public consultation process
- Preliminary results
- Next steps

## Public consultation process

Once a draft Guideline is ready, it becomes the subject of normal wide-ranging regulatory consultation in each of the Member's regions.

There is also an opportunity for Industry Associations and Regulatory Authorities in other regions to comment on the draft consultation documents, which are published by the ICH Secretariat on the ICH website.

ICH had made a commitment to consult on E8 with those involved in clinical trials outside the pharmaceutical industry

## Preliminary results

As public consultation recently closed, the WG has not collectively reviewed the comments yet.

What follows are some examples of comments received to date from different regions across the world

## General comments

Clear document providing a comprehensive and detailed overview of the challenges raised by current practice in clinical research

Some felt the role of ethics committees should be further emphasized in the different steps of organising and conducting clinical trials.

Others felt the document was written with commercial sponsors in mind

## General comments

Commenters would have liked to see the importance of reproducibility of research results mentioned in the document

Commenters were interested in more discussion regarding benefit-risk

Some thought there was too much focus on efficacy assessment and not enough on safety assessment during the development. Safety assessment may impact the following development plan, pharmacovigilance planning as well as risk management plan.

## General comments

Why not specify “QMS” as the basic concept of E8 as described in E6?

Outcome selection in study and other design features should consider the need for not-individual outcomes (e.g. spread of pathogens resistant to antimicrobials).

The development and uptake of Core Outcome Sets by researchers will ensure that relevant outcomes are included earlier in the research lifecycle

## General comments

Commenters highlighted the need for patient-centred clinical research, in addition to drug-centred research

Why restrict ICH to medicinal products ? Harmonization of the design of clinical studies would also be highly relevant for medical devices

Should clarify how this guideline aligns with the recently revised E9

Please add definitions of key terms into a glossary

## General comments

We recommend lessening the focus on phases 1 - 4 and instead focus on answering the research questions using appropriate methods at the suitable time

The scope of the guideline should be expanded to include discussion of the application of real-world data (RWD) and artificial intelligence (AI)

An opportunity for harmonization of terminology between E8 and E6 arises at the upcoming review of ICH E6 (R3)



## General comments

Please add a second major aim of clinical research, i.e. the development of accurate evidence-based clinical practice guidelines.

We suggest there should be a new section in E8 dedicated to unintentional bias and unblinding

## General principles

This section is written at a too high level

Commenters were very happy about the inclusion of patient engagement in the document

How can one judge if patient input is representative of the patient community?

Patient input may differ between countries

When is it critical to seek patient input? Should consider conflict of interest in those who provide input.

## General principles

Would like more clarity on how patients may influence clinical trial design, given their lack of scientific knowledge

Include examples of how patients' input could be gathered/shared.

The use of Core Outcome Sets is a more robust approach to generating patient-relevant evidence than involving just a few selected patients at the design stage of a trial.

## Designing quality

This section is a welcomed addition to the revised guideline

This section is too academic and would benefit from the addition of best practice guidance

Knowledge of the target patient population and of their characterization through biomarker profiling are also essential when testing ‘personalized’ treatments.

Need to create a culture that is open to identifying errors without blame

## Designing quality

E8 should explain the implementation of QMS in clinical trials and the positioning and the role of QbD in an easy-to-understand manner.

It would be sensible to reference the E6 quality tolerance limits as a mechanism to manage the risks associated with the critical to quality factors

# Drug development

Commenters felt that several additional populations should be considered as special populations (women of childbearing potential, rare diseases, etc.)

Commenters felt that the definition of phases of drug development was not consistent with new guideline concepts or the use of novel designs.

Commenters were interested in more discussion of RWE and RWD, and in particular the use of non-interventional studies in drug development.

# Drug development

What should be considered in cases such as co-development of a drug and medical device? A drug and companion diagnostic test?

A mention should be made regarding drug combinations and trials consisting of standard regimens vs standard + 1 regimens

Sponsors could help stimulate the creation and qualification of new research centers

# Drug development

Add something about trials in small populations: the standard separation between exploratory and confirmatory trial may not be possible and the rules of typical clinical development might not necessarily apply

This section should mention investigator led studies and how this data can be used to support extensions of a licence or future directions for investigation

Expand on the inclusion of nursing mothers in a trial

## Study design

Commenters would like additional discussion of secondary data use

Commenters would like to see more on master protocols

Commenters were interested in more discussion of innovative tools and designs

Would like to see more on the design of observational studies

The document fails to highlight the risks associated with a lack of validity of the systems where secondary data are kept

## Study design

The document still distinguishes between exploratory and confirmatory trials while in practice this transition is more and more fluid these days.

The document is not ready for Orphans and Advanced therapy medicinal products (ATMPs)

Discuss analysis considerations for open label studies

Could reference ICH E20 for adaptive designs

## Study design

The document should emphasize the importance of ensuring that study populations are concordant with the considered ultimate target populations.

It is important to define what the clinically relevant thresholds will be and how they are defined.

There should be a recommendation to stress test data transfer and fidelity between sites and data repository as data cleaning at end of study is much harder.

# Study conduct and reporting

Commenters were concerned that not enough attention was paid to human subjects protections or returning data to study participants

Promote clinical trial data sharing

## Critical to quality factors

The document did not provide enough specifics about critical-to-quality factors and needs examples

Commenters want discussion of the relationship between CtQ factors and quality tolerance limits and E6

## Annexes

Non-commercial trials must be included in Annex 1 as part of the Lifecycle

The post approval box in Annex 1 should include ‘explore treatment regimes in combination with other drugs’

In Annex 3, E6 applies to more critical to quality factor than what is indicated

A caveat would be useful in Annex 3 to encourage the reader to consider what technological and methodological advances in clinical trial conduct have been made

## Annexes

Commenters suggested that E8 provide a more detailed roadmap to the ICH Guidelines.

## Next steps

### ***Discussion of regional consultation comments***

The E8 WG will:

- review and exchange information on the comments they have received from the public in the various regions
- consider what further revisions to the draft Guideline might be needed



# Thank you

ICH Secretariat  
Route de Pré-Bois 20  
1215 Geneva  
Switzerland

E-mail: [admin@ich.org](mailto:admin@ich.org)

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# Session I: The role of E8 as part of the ICH GCP Renovation and next steps

*Comments and Questions*

International Council for Harmonisation of Technical Requirements  
for Pharmaceuticals for Human Use



# Session II: Drug Development Plan

***Chairs:***

***Dr. Joanne Palmisano, EWG Representative – PhRMA***

***Dr. Gregory Golm, EWG Representative – BIO***

International Council for Harmonisation of Technical Requirements  
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# Overview

**Overview presentation – Dr. Joanne Palmisano, EWG  
Representative – PhRMA (10 minutes)**

**Panelist Perspective –**

- **Prof. Louise Bowman, European Society of Cardiology/University of Oxford**
- **Dr. Harumasa Nakamura, Director, Department of Clinical Research Support, National Center of Neurology and Psychiatry, Japan**
- **Dr. John Buse, Division Chief and Director, Diabetes Center, UNC**
- **Mr. John Adams, Best Medicines Coalition of Canada**
- **Dr. Marco Greco, European Patients Forum**



# ICH E8(R1)

## General Considerations for Clinical Studies

### The Drug Development Plan

**Dr. Joanne Palmisano, EWG Representative – PhRMA**

**Dr. Gregory Golm, EWG Representative – BIO**

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# Table of contents

- The Drug Development process
- Ways Drug Development has changed
- Key design principles of clinical studies
- Quality study design and planning
- Patients as Partners in clinical studies
- ICH E family of guidelines as resources

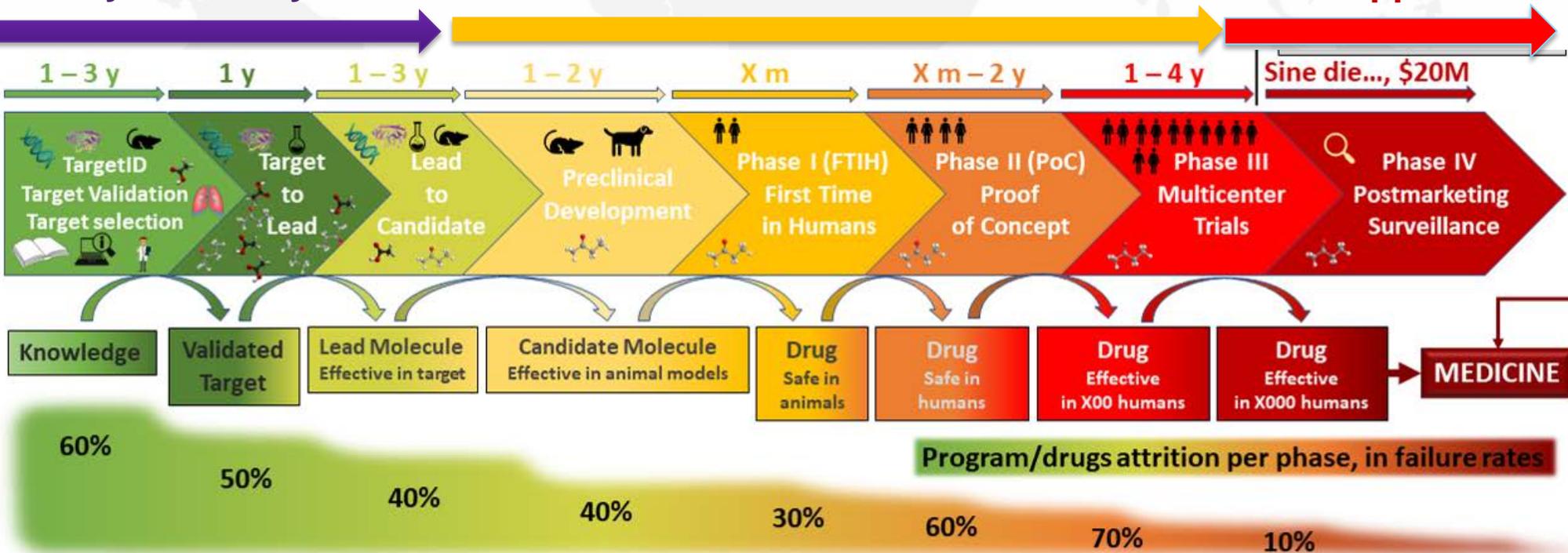
# Advancing stages of knowledge

## The Drug Development Process

### Early discovery

### Development

### Post-approval



- Costs of a medicine's development in 2016 ~ \$2.6 Billion (increase of 145% since 2003)
- Success rate of a drug candidate to approval has decreased to 12% [1 in 8 succeed]
- Estimates of post-approval research in 2016 was \$312 Million

Source: Tufts CCDD R&D Cost Study: DiMasi JA, Grabowski HG, Hansen RA. Innovation in the pharmaceutical industry: new estimates of R&D costs. *Journal of Health Economics* 2016;47:20-33.

## Ways that clinical development has changed

- Globalization/multi-regional studies [E17]
- Innovation and improved efficiency in the design and execution of clinical trials
  - Adaptive designs
  - Pragmatic trials – integrating community practice and clinical trials
  - Master protocols, bucket trials
  - Decentralized clinical trials (DCT)
  - Web-based “virtual” clinical trials
- Precision medicine aspects (e.g., companion diagnostics, biomarkers [E15,16,18])
- Multidimensional data sources
- Technology and digital tools (eConsent, mobile devices, web-based recruitment platforms)

## Key design principles remain the same

- Goal is high-quality evidence to inform decision-making
  - The study addresses an important scientific question
  - Adequate non-clinical data to support human investigation
  - Study design supports the study objective to provide quantitative assessment of treatment effect and safety
  - Selection of subjects/patients assures they are appropriate to address the scientific question (e.g., have the condition or disease)
  - Method of assigning subjects to treatment groups minimizes bias
  - Methods of assessment of outcome measures are well defined/reliable
  - Rights, safety, and welfare of subjects are protected
  - Unique design features in special populations - pediatrics [E11-11A], pregnancy, geriatrics [E7], ethnic factors [E5]

# Quality study design and planning

- Phase/stage of development will inform study design features
  - Subject/patient selection (e.g., inclusion/exclusion criteria –broad or narrow, biomarkers)
  - Treatment assignment (e.g., randomization, balance of treatment groups)
    - control of bias, stratification of prognostic factors
  - Control group (e.g., comparator, placebo, SOC, internal/external) – masking/open [E10]
  - Operational design – e.g., RCT, adaptive, single-arm
  - Outcome assessments – primary and secondary
  - Study size (number of subjects) and power (e.g., exploratory, control of Type 1 error)
  - Statistical approach/methodology and analyses (e.g., frequentist, Bayesian) [E9]
  - Safety data collection [E1, E19]

# Design elements dependent by phase/stage

## Early Stage Clinical Studies

- High uncertainty
- Molecule type/mechanism of action for targeted or non-targeted agents
- Molecularly or clinically-enriched dose escalation and expansion cohorts
- PK/PD [E15]
- Smaller numbers of patients
- Baseline characteristics narrow - Inclusion criteria focused, limited co-morbidities/con-meds
- Limited data sources
- Early tolerability
- Exploratory effectiveness

## Later Stage Clinical Studies

- Less uncertainty
- Recommended doses/regimen
- Confirming PK/PD
- Larger numbers of patients
- Baseline characteristics broad - exclusion criteria limited, more co-morbidities /con-meds
- Expanded data sources
- Expanding/confirming safety
- Confirmation of efficacy

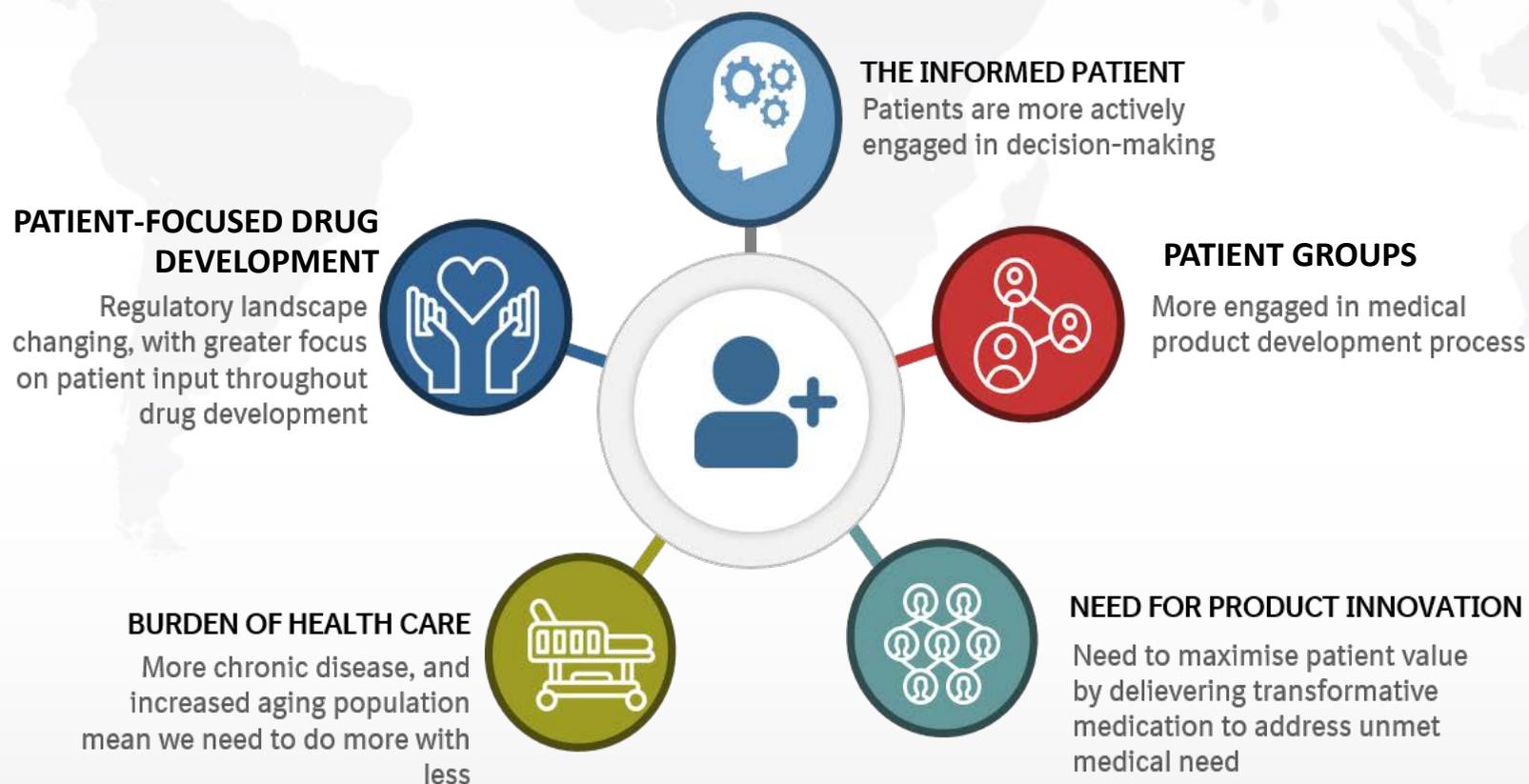
## **Some critical-to-quality factors in clinical studies**

- Study design and planning
- Feasibility and study procedures
- Investigator/site qualification
- Contractual agreements between sponsors/investigators/CROs
- Subject/patient selection and recruitment
- Informed consent, IRB/EC review/approval
- Assignment to treatment/control groups - bias control
- Clinical studies procedures
- Data sources, collection, management and analysis
- Safety reporting
- Communication of results

## Study operational QbD elements

- Clinical study supply management
- Laboratory /biological sample collection/management
- Diagnostic testing
- Digital tools e.g., eDiaries, eConsent
- Use of CROs – almost all global drug development programs utilize one or more CRO for operational support
- Clinical study monitoring [E6]
- Data sources and management
- Clinical study reports [E3]
- Pharmacovigilance [E2A-E2F]

# Patients as Partners in Clinical Studies



# ICH E family of guidelines – need to be read together

## E8 General Considerations for Clinical Trials

### Design and analysis:

- E4 Dose-Response Studies
- E9 Statistical Principles for Clinical Trials
- E10 Choice of Control Group in Clinical Trials
- E17 Multi-Regional Clinical Trials

### Conduct and reporting:

- E3 Clinical Study Reports
- E6 Good Clinical Practice

### Safety reporting:

- E1 Clinical Safety for Drugs used in Long-Term Treatment
- E2A - E2F Pharmacovigilance
- E14 Clinical Evaluation of QT
- E19 Safety Data Collection

### Populations:

- E5 Ethnic Factors
- E7 Clinical Trials in Geriatric Population
- E11 - E11A Clinical Trials in Pediatric Population
- E12 Clinical Evaluation by Therapeutic Category

### Genetics/genomics:

- E15 Definitions in Pharmacogenetics / Pharmacogenomics
- E16 Qualification of Genomic Biomarkers
- E18 Genomic Sampling



# Thank you!

ICH Secretariat  
Route Pré-Bois 20  
1215 Geneva  
Switzerland

E-mail: [admin@ich.org](mailto:admin@ich.org)

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## Panelists

- **Prof. Louise Bowman, European Society of Cardiology/University of Oxford**
- **Dr. Harumasa Nakamura, Director, Department of Clinical Research Support, National Center of Neurology and Psychiatry, Japan**
- **Dr. John Buse, Division Chief and Director, Diabetes Center, UNC**
- **Mr. John Adams, Best Medicines Coalition of Canada**
- **Dr. Marco Greco, European Patients Forum**

## Panel Discussion

- **Does Section 4 provide a sufficient description of the types of studies in a drug development program?**
- **Is Annex 1 helpful in summarizing the types of studies in a drug development program?**
- **Do you agree with the manner in which Section 4 moves away from the classic Phase I-II-III-IV nomenclature for clinical studies?**
- **Does Section 4.3 provide a sufficient description of considerations for assessing the feasibility of a study?**
- **Do you agree that Section 4 provides sufficient guidance on gaining input from patients, as important stakeholders in the planning and design of a clinical study?**



# Session II: Drug Development Plan

*Questions and Comments*

International Council for Harmonisation of Technical Requirements  
for Pharmaceuticals for Human Use



**Break**

*The meeting will resume momentarily*



# Session III: Components of Study Design

***Chairs:***

***Dr. Andreas Kirisits, EWG Representative – EC, Europe***

***Dr. Sigrid Balsler, EWG Representative – IGBA***

International Council for Harmonisation of Technical Requirements  
for Pharmaceuticals for Human Use

# Overview

**Overview presentation (10 minutes)- Dr. Sigrid Balser, EWG Representative – IGBA**

**Panelist Perspective -**

- **Ms. Shachi Vyas, Sr. Clinical Trial Manager, JDRF**
- **Dr. Michele Jonsson-Funk, Director, Center for Pharmacoepidemiology, UNC**
- **Ms. Tracy Temple, Associate Director, Clinical Trials, CVC/University of Alberta**
- **Dr. Rosa Giuliani, European Society for Medical Oncology**
- **Dr. Leonard Lichtenfeld, Deputy Chief Medical Officer, American Cancer Society**



# ICH E8(R1)

**General Considerations for Clinical Studies**

## **Components of Study Design Washington, October 2019**

**Andreas Kirisits, EWG Representative – EC, Europe**  
**Sigrid Balser, EWG Representative – IGBA**

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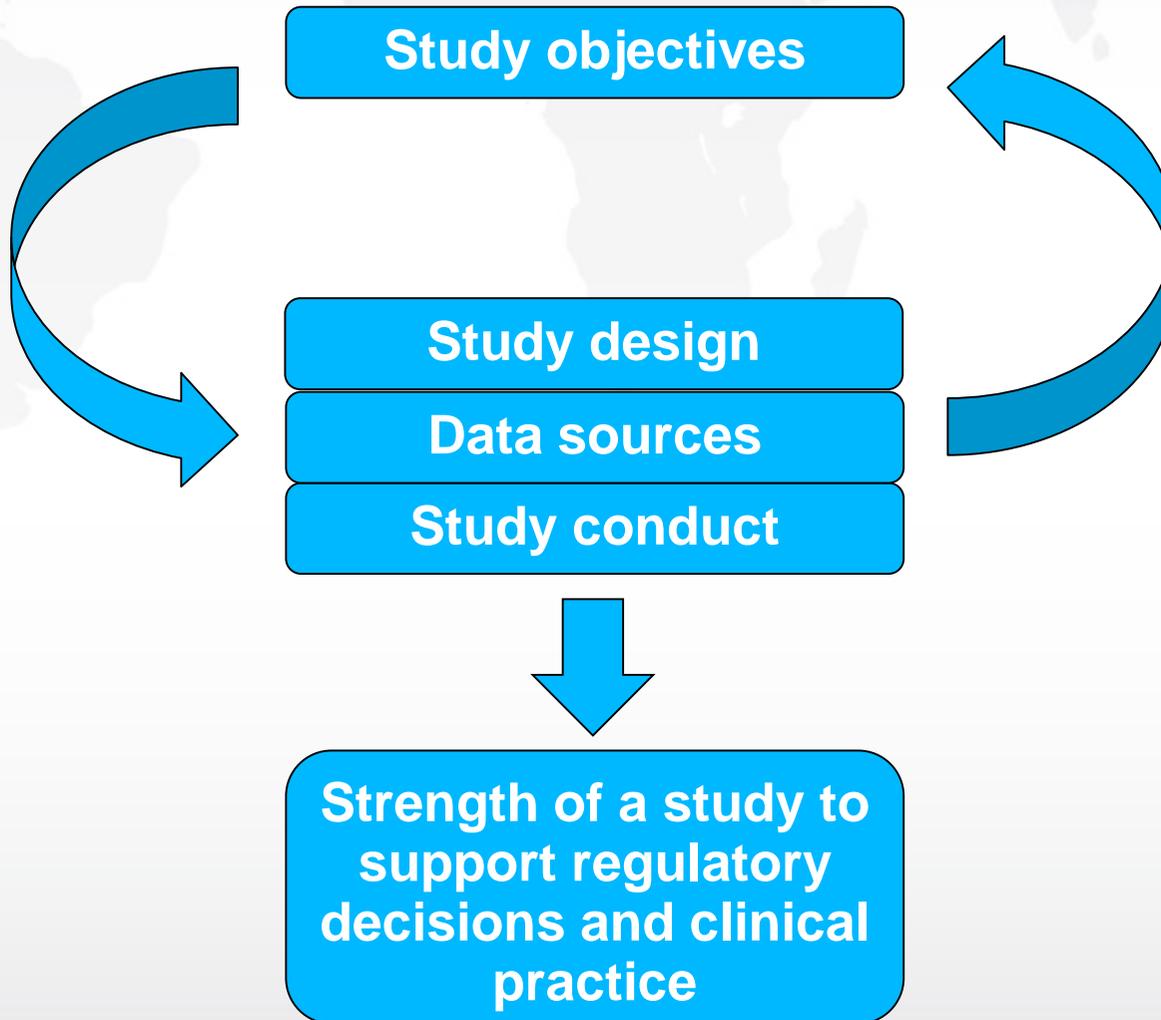
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# Table of contents

- **Design Elements of Clinical Studies**
  - Study population
  - Intervention
  - Control group
  - Response variables
  - Methods to assess and reduce bias
  - Statistical analysis

# Design Elements of Clinical Studies

Clear objectives impact the choice of the study design, data sources, and study conduct



The process of specifying the design may help to further clarify the objectives

## Fundamental design elements

- Study population
- Intervention
- Control group
- Response variable
- Methods to reduce bias
- Statistical analysis

Described in the protocol together with the study objectives, study type, and data sources which should be finalized before start of study (ICH E6)

# Study population

- Chosen to support the study objectives and defined by inclusion/exclusion criteria.
- If part of the objectives, efforts should be made to ensure adequate representation of these subgroups.
- In practice, the study population is limited to subjects available to participate and for whom consent is available (see ICH E6).
- The degree to which a study succeeds in recruiting and enrolling the desired population will impact the ability of the study to meet its objectives.

# Study population

- The study population may be defined
  - Narrow:
    - Maximize the sensitivity of the study
    - E.g., early phase studies tend to be more homogenous
  - Broad:
    - More closely represent the population for whom the drug is intended
    - E.g., later phase or post-approval studies tend to be more heterogeneous
- A sufficient number of subjects needs to be recruited to make statistical conclusions based on the findings (see ICH E9). A larger database may be needed to establish the safety of a drug (see ICH E1).

# Intervention

## Interventional study

- The choice of the study drug and the health management of the subjects are controlled by the study
- Often has the potential to control biases better than observational studies

## Observational study

- The choice of the study drug and the health management of the subjects are merely observed in the study
- Usually conducted in the post-approval period

# Intervention vs. Observation

- Factors for the choice between interventional and observational studies:
  - study objectives
  - feasibility
  - data sources
  - anticipated biases and uncertainty
- Varying overlap between interventional and observational studies, e.g. a pragmatic trial is a mix of the two types (intervention is controlled by the study, health management is controlled to a lesser degree)

## Control group

- Group of subjects, the drug effect is compared to, e.g.
  - Subjects receiving no treatment
  - Subjects receiving other treatments or doses
- Subjects may function as their own control receiving the drug and control at different points in time, e.g.
  - Cross-over design for interventional studies
  - Case-crossover designs for non-interventional studies
- Can also be a target value if no appropriate control data are available, e.g.
  - Response or cure rates

# Control group

- The control group may be internal and/or external to the study
  - Internal:
    - All subjects are selected based on the same process
    - All data are acquired by the same procedure at the same time
    - Differences observed are (only) due to the treatment effect
  - External:
    - Subjects are selected from an external source
    - Subjects may have been treated at an earlier time (historical controls) or at the same time, but in a different setting
    - Subjects may differ with respect to follow-up treatment, outcome measures, demographics, background characteristics, etc.
    - Complexity needs to be taken into account in the design and analysis of the study
- For further considerations refer to ICH E10

## Response variables

- Subject-level attribute of interest that may be affected by the drug
- May relate to the pharmacokinetics, pharmacodynamics, efficacy, safety, or post-approval use including compliance with risk minimization measures
- Study endpoints = response variables that are chosen to assess drug effects
- The knowledge of the drug, the clinical context, and the purpose of a given study affect what response variables should be collected

## Response variables

- The choice of endpoints is critical to the quality of the study
- The primary endpoint should be capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the study (ICH E9)
- Secondary variables are either supportive measurements related to the primary objective or measurements of effects related to the secondary objectives.
- The choice of endpoints should be meaningful for the intended population and take into account the views of patients and feasibility considerations

## Response variables

- The definition of each study endpoint should be specific, including information about how and when it is ascertained and the duration of follow-up.
- The methods used to ascertain endpoints should be of sufficient accuracy, precision, responsiveness (sensitivity to change), reproducibility, reliability, and validity.
- Examples:
  - Proof-of-concept studies may employ short-term surrogates rather than clinical outcomes
  - Clinical outcomes would then be used to confirm a clinically meaningful effect in a large scale confirmatory study

# Methods to reduce and assess bias

- The study design should address sources of bias that can undermine the reliability of results
- Different study types are subject to different sources of bias
- Randomization and blinding are the most effective approaches to reduce bias
- Randomization addresses differences between the groups at the time of randomization, but does not prevent differences arising thereafter (intercurrent events)
- Observational studies pose unique challenges to the control of bias and multiple design elements are often necessary to address these challenges

# Statistical analysis

- The statistical analysis needs to be pre-specified in the
  - Study protocol:
    - Should include a statistical methods section that is appropriate for the objectives and study design (ICH E6 and E9)
    - Should be finalized before the conduct of the study
  - Statistical analysis plan:
    - May be used to provide the necessary details for implementation
    - Describes all aspects of the analysis, incl. sensitivity analyses, handling of intercurrent events
    - Should be finalized before unblinding of study data, or in the case of an open-label study, before the conduct of the study
- Pre-specification increases confidence that important aspects of analysis planning were not based on accumulating study data or inappropriate use of external data.



# Thank you!

ICH Secretariat  
Route Pré-Bois 20  
1215 Geneva  
Switzerland

E-mail: [admin@ich.org](mailto:admin@ich.org)

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## Session III – Panel discussion

- Dr. Rosa Giuliani, European Society for Medical Oncology
- Dr. Michele Jonsson-Funk, Director Center for Pharmacoepidemiology, University of North Carolina
- Dr. Leonard Lichtenfeld, Deputy Chief Medical Officer, American Cancer Society
- Ms. Tracy Temple, Associate Director Clinical Trials, Canadian VIGOUR Centre/University of Alberta
- Ms. Shachi Vyas, Sr. Clinical Trial Manager, JDRF

## **Session III – Panel discussion**

Does the study design framework provided in section 5.1 strike a good balance between general applicability across different study types and level of detail?

## Session III – Panel discussion

E8 (R1) intends to facilitate a broad variety of study designs. From your professional experience, do you see conflicts between the principles laid down in section 5.1 and study planning & conduct?

## Session III – Panel discussion

How can we best obtain the views of the medical community and patients for study planning, e.g., regarding the most meaningful response variables but also about the feasibility of the study more generally?

## Session III – Panel discussion

If you had to make one statement about E8(R1), what would you say?



# Session III: Components of Study Design

*Comments and Questions*

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# Lunch Break

*The meeting will resume at 13:15*

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# Session IV: Quality by Design/ Critical to Quality Factors

***Chairs:***

***Dr. Kerstin Koenig, EWG Representative – EFPIA***

***Dr. Mutsuhiro Ikuma, EWG Representative – MHLW/PMDA, Japan***

International Council for Harmonisation of Technical Requirements  
for Pharmaceuticals for Human Use

# Overview

**Overview presentation (10 minutes)- Dr. Fergus Sweeney, E8 EWG  
Regulatory Chair - EC, Europe**

**Stakeholder Panelist Perspective -**

- **Dr. Christine Kubiak, European Clinical Research Infrastructure Network**
- **Mr. Francois Houyez, European Organisation for Rare Diseases (Eurordis)**
- **Ms. Janette Panhuis, Chief Operating Officer, Population Health Research Institute**
- **Dr. Janet Wittes, Statistics Collaborative Inc.**
- **Dr. Victoria Manax, Pancreatic Cancer Action Network**



# Public Meeting on ICH E8 (R1): Quality by Design/ Critical to Quality Factors

**Fergus Sweeney**  
**EWG Regulatory Chair – EC, Europe**  
**31 October, 2019**

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# Multiple initiatives – building global consensus – Listening to stakeholders

2009



2009

CLINICAL TRIALS ARTICLE  
Clinical Trials 2009, 6: 585-596  
**Risk analysis and risk adapted on-site monitoring in noncommercial clinical trials**  
Oana Brosteanu<sup>1</sup>, Peggy Houbert<sup>2</sup>, Kristina Irlitz<sup>3</sup>, Christian Ohmann<sup>4</sup>, Ursula Paulus<sup>5</sup>, Beate Pfister<sup>6</sup>, Gabriele Schwarz<sup>7</sup>, Anke Stränge-Hessen<sup>8</sup> and Ulrike Zettelmeyer<sup>9</sup>

2011

Version: 10<sup>th</sup> October 2011  
MRC/DH/MHRA Joint Project  
**Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products**

**Table of Contents**

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Executive summary	1
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Risk assessment	6
Appendix 1: Guidance on risk-adapted approaches within the scope of the Clinical Trials Directive	6
Appendix 2: Guidance on risk-proportionate approaches to the management and monitoring of clinical trials	19
Appendix 3: Membership of Ad-hoc Working Group and Risk-stratification Sub-group	30

2011



**Safer, Faster, Cheaper**  
Improving Clinical Trials and Regulatory Pathways to Fight Neglected Diseases

Report of the Center for Global Development's Working Group on Clinical Trials and Regulatory Pathways  
October 2011

2011



Validation of a risk-assessment scale and a risk-adapted monitoring plan for on-site clinical research studies - The Pre-Exploratory study  
Suzanne Powell<sup>1</sup>, Guy-Pierre Dreyer<sup>2</sup>, Steve Cooper<sup>3</sup>, Wolfgang Hoyer<sup>4</sup>, Bruce Ripstein<sup>5</sup>, Robert H. Threlkeld<sup>6</sup>, Marianne M. G. van den Broek<sup>7</sup>, Michael S. Gorman<sup>8</sup>, Caroline Taylor<sup>9</sup>, and the staff of the System Collaborative Group  
MRC/DH/MHRA Joint Project  
Version 10<sup>th</sup> October 2011

2013

OECD Recommendation on the Governance of Clinical Trials



OECD

2013

Guidance for Industry

**Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring**

U.S. Department of Health and Human Services  
Center for Drug Evaluation and Research, U.S. Food and Drug Administration  
Center for Biologics Evaluation and Research, U.S. Food and Drug Administration  
Center for Devices and Radiological Health, U.S. Food and Drug Administration  
Center for Veterinary Medicine, U.S. Food and Drug Administration  
FDA-2013-0012  
Date of original PDUFA submission to the public: 02/12/13  
For additional PDUFA information on this PDUFA, visit the public page.

2013

Position Paper: Risk-Based Monitoring Methodology

**1. Abstract**  
Current drug development practices are frequently based, customarily to a pre-specified monitoring and safety plan, and present operational issues across an international site. Although this practice may ensure a high level of product quality, it may not be the most efficient or the most cost-effective. A risk-based approach, based on the ability to identify safety issues and present them to regulatory authorities, may be a more efficient and cost-effective approach. This paper discusses the current practice and the challenges associated with the current practice. It also discusses the challenges associated with the current practice and the challenges associated with the current practice. This paper discusses the current practice and the challenges associated with the current practice. This paper discusses the current practice and the challenges associated with the current practice.

**2. Introduction**  
Over the last decade, the complexity and cost of clinical trials has increased dramatically. Complex objectives in the clinical trial, the international nature of the trial, and the increasing number of clinical trial sites, have led to a growing need for a more efficient and cost-effective approach. This paper discusses the current practice and the challenges associated with the current practice. This paper discusses the current practice and the challenges associated with the current practice.

2013



Reflection paper on risk-based quality management in clinical trials  
EMA  
EMA-2013-0012  
Date of original PDUFA submission to the public: 02/12/13  
For additional PDUFA information on this PDUFA, visit the public page.



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- ***Principles***
  - *Quality*
  - *Quality by Design*
- ***Designing quality into clinical trials***
  - Quality by design of clinical studies
  - Critical to Quality Factors
  - Risk proportionate approach
  - Involvement of wide range of stakeholders in clinical trial design
  - Examples of critical to quality factors

This is about doing things differently – change – don't just add more to the status quo.

## 2.2 Scientific Approach in Clinical Study Design, Conduct, and Analysis

- Quality of a clinical study is considered in this document as fitness for purpose.  

- The purpose of a clinical study is to generate reliable information to answer key questions and support decision making while protecting study subjects.
- The quality of the information generated should therefore be sufficient to support good decision making.



Reliable  
information



Decision  
making

## 2.2 Scientific Approach in Clinical Study Design, Conduct, and Analysis

- Quality by design in clinical research sets out to ensure that the quality of a study is driven proactively by designing quality into the study protocol and processes.
- This involves the use of a prospective, multidisciplinary approach to promote the quality of protocol and process design, and clear communication of how this will be achieved.



Quality  
by Design

### 3 Designing Quality into Clinical Studies

- The quality by design approach to clinical research involves focusing on critical to quality factors to ensure the protection of study subjects, the generation of reliable and meaningful results, and the management of risks to those factors.



## 3.1 Quality by Design of Clinical Studies

- *The **likelihood** that a clinical study will **answer** the research **questions posed in a reliable manner**, meaningful for decision makers and patients, while preventing important errors, can be **dramatically improved through prospective attention to the design....of the .... protocol, procedures and associated operational plans.***
- ***Quality should rely on good design and its execution rather than overreliance on retrospective document checking, monitoring, auditing or inspection.** These activities are an important part of a quality assurance process but are not sufficient to ensure quality of a clinical study.*

## 3.2 Critical to Quality Factors

- ***A basic set of factors relevant to ensuring study quality should be identified for each study. Emphasis should be given to those factors that stand out as critical to study quality.***
- ***..critical because, if their integrity were to be undermined ...the reliability or ethics of decision-making would also be undermined.***
- ***..determine the risks that threaten their integrity, the probability and impact of those risks and to decide whether they can be accepted or should be mitigated.***
- ***Perfection in every aspect ..is rarely achievable or .. only .. achieved by use of resources ..out of proportion to the benefit obtained. ...study procedures should be proportionate to the risks inherent in the study and the importance of the information collected.”***

## 3.3 Approach to Identifying the Critical to Quality Factors

### ***3.3.1 Establishing a Culture that Supports Open Dialogue:***

- Create a culture that **values and rewards critical thinking and open dialogue** about quality and that goes **beyond sole reliance on tools and checklists**.

### ***3.3.2 Focusing on Activities Essential to the Study:***

- **Focus effort** on activities .. **essential to the reliability and meaningfulness of study outcomes for patients, and the safe, ethical conduct of the study for study subjects**. Consider whether **nonessential activities may be eliminated** from the study to simplify conduct, improve study efficiency, and target resources to critical areas.

## 3.3 Approach to Identifying Critical to Quality Factors

### 3.3.3 *Engaging Stakeholders in Study Design:*

- **“Clinical study design is best informed by input from a broad range of stakeholders, including patients and treating physicians. It should be open to challenge by subject matter experts and stakeholders from outside, as well as within, the sponsor organisation. “**

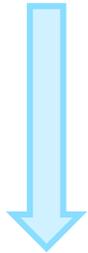
### 3.3.4 *Reviewing Critical to Quality Factors:*

- **“.... Build on accumulated experience and knowledge with periodic review of critical to quality factors to determine whether adjustments to risk control mechanisms are needed, since new or unanticipated issues may arise once the study has begun.**

# 7 Considerations in Identifying Critical to Quality Factors

## Discussion of critical to quality factors in this guideline

### Sec.3: Designing Quality into Clinical Studies



The identification of critical to quality factors should be supported by proactive, cross-functional discussions and decision making at the time of study planning

### Sec.4: Drug Development Planning

### Sec.5: Design elements for Clinical studies

### Sec.6: Conduct and Reporting

Different factors will stand out as critical for different types of studies

In designing a study, applicable aspects such as the following should be considered to support the identification of critical to quality factors, as shown in Sec.7

## 7 Considerations in Identifying Critical to Quality Factors

Think about **what is critical** for the **specific** study. Examples:

**prerequisite studies, support the study being designed**

**adequate measures are used to protect  
subjects' rights, safety, and welfare**

**feasibility assessment to ensure  
the study is operationally viable**

**extent and nature of monitoring are  
tailored to the specific study design  
and objectives**

**objectives  
address relevant  
scientific  
questions**

## Annex3: Selected Examples of Critical to Quality Factors

Selected Examples of Critical to Quality Factors	E1	E2A -E2F	E3	E4	E5	E6	E7	E8	E9	E10	E11	E12	E14	E15	E16	E17	E18
<b>Protocol Design</b>																	
Eligibility Criteria						✓	✓	✓	✓		✓	✓	✓			✓	
Randomisation				✓		✓		✓	✓	✓		✓	✓			✓	
Blinding/Masking						✓		✓	✓	✓							
Types of Controls	✓			✓				✓		✓			✓			✓	
Data Quality	✓						✓	✓	✓								
Endpoints				✓	✓			✓	✓	✓	✓	✓				✓	
Procedures Supporting Study Endpoints and Data Integrity					✓	✓		✓	✓	✓	✓	✓				✓	
Investigational Product (IP) Handling and Administration						✓							✓				
<b>Feasibility</b>																	
Study and Site Feasibility																✓	✓
Accrual									✓		✓		✓				

## Annex3: Selected Examples of Critical to Quality Factors

Selected Examples of Critical to Quality Factors	E1	E2A -E2F	E3	E4	E5	E6	E7	E8	E9	E10	E11	E12	E14	E15	E16	E17	E18
<b>Patient Safety</b>																	
Informed Consent						✓					✓						✓
Withdrawal Criteria and Trial Participant Retention			✓			✓					✓		✓				
Signal Detection and Safety Reporting		✓ B	✓			✓						✓	✓				
Data Monitoring Committee (DMC) /Stopping Rules						✓			✓	✓			✓				
<b>Study Conduct</b>																	
Training						✓							✓			✓	✓
Data Recording and Reporting		✓ B,C,F	✓	✓					✓		✓		✓		✓	✓	✓
Data Monitoring and Management		✓ A,B,D	✓						✓						✓	✓	✓
Statistical Analysis			✓	✓	✓				✓				✓			✓	
<b>Study Reporting</b>																	
Dissemination of Study Results		✓ D,F															✓
<b>Third-Party Engagement</b>																	
Delegation of Sponsor Responsibilities						✓											
Collaborations						✓											

## Conclusion

- ❑ This document focuses on designing quality into clinical studies, considering the diversity of clinical study designs and data sources used to support regulatory and other health policy decisions.
- ❑ The principles and approaches set out in this guideline, including those of quality by design, should inform the approach taken to the design, conduct, and reporting of clinical studies and the proportionality of control measures employed to ensure the integrity of the critical to quality factors.

Everyone involved in the conduct of clinical trials should read and understand this guideline.

Change the way we all work – don't add more to the status quo.

Change Management is the greatest challenge

– adjusting behaviors, attitudes – away from preconceived ideas and interests.



# Thank you

ICH Secretariat  
Route de Pré-Bois 20  
1215 Geneva  
Switzerland

E-mail: [admin@ich.org](mailto:admin@ich.org)

International Council for Harmonisation of Technical Requirements  
for Pharmaceuticals for Human Use

## Stakeholder Panelist Perspective

- **Dr. Christine Kubiak, European Clinical Research Infrastructure Network**
- **Mr. Francois Houyez, European Organisation for Rare Diseases (Eurordis)**
- **Ms. Janette Panhuis, Chief Operating Officer, Population Health Research Institute**
- **Dr. Janet Wittes, Statistics Collaborative Inc.**
- **Dr. Victoria Manax, Pancreatic Cancer Action Network**

# Panelist Questions

- 1. Does E8(R1) adequately address the critically important aspects of (the) quality in the clinical study?**
- 2. Does E8(R1) provide sufficient guidance on strategies and actions that could effectively and efficiently support the quality in these critical areas?**
- 3. Is E8(R1) helpful for identifying Critical-to-Quality factors generally relevant to the integrity and reliability of study conclusions and patient safety?**
- 4. Does E8(R1) give the reader sufficient guidance on what is Quality-by-Design in clinical study?**
- 5. Does E8(R1) give the reader enough guidance on how one could find out CtQ factors?**
- 6. Where do you see your role in driving the adoption of Quality by Design and Critical to Quality Factors?**
- 7. What do you consider as the most important challenges / barriers regarding the adoption of QbD and CtQs?**



# Session IV: Quality by Design/ Critical to Quality Factors

## *Comments and Questions*

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**Break**

*The meeting will resume shortly*

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# Session V: Data sources

## ***Chairs:***

***Dr. Byron Jones, EWG Representative – EFPIA***

***Dr. Osamu Komiyama, EWG Representative – JPMA***

# Overview

**Overview Presentation - *Dr. Byron Jones, EWG Representative – EFPIA***

**Stakeholder Panel Perspective –**

- **Mr. Prasanna Shirol, Parent and Co founder, Organisation for Rare Diseases, India**
- **Ms. Abby Bronson, Parent Project Muscular Dystrophy**
- **Dr. Frank Rockhold, Professor of Biostatistics and Bioinformatics, Duke Clinical Research Institute**
- **Dr. PJ Devereaux, Director of the Division of Perioperative Care, McMaster University**
- **Prof. Steven Le Gouill, European Hematology Association**



# Public Meeting on ICH E8 (R1): Data Sources

**Byron Jones**  
**EWG Representative – EFPIA**  
**October 31, 2019**

International Council for Harmonisation of Technical Requirements  
for Pharmaceuticals for Human Use

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# Table of contents

- **Study Data**
- **Types of Data**
- **Secondary Data Use**
- **Other Considerations**

## Study Data (1)

- The study data should reliably contain the necessary information to **conduct, monitor, and analyse** the study.
- The study data may be **acquired through a variety of methods**, including paper-based and electronic capture.
- **Data from the use of technologies** (e.g., digital health tools), **electronic health record databases** and **patient registries may contribute** to the development of a new investigational drug or for further evaluation of an approved drug.

## Study Data (2)

- Data **generated specifically** for the present study.
- Data **obtained from sources external** to the present study.
- Data from **both types of data sources** comprise the clinical database.

# Types of Data

- o Primary Data
  - Data **collected for the study purposes**, using processes that ensure a sufficient level of quality.
- o Secondary Data
  - These data may have careful quality control processes, but these processes were **not designed with the objectives of the present study in mind.**
  - The **appropriateness** of the available data **should be considered.**

## Secondary Data Use, Cont'd

- For example, when using **existing electronic health record data** to ascertain the study endpoint rather than through primary data collection, information in the health record about outcomes would need to be converted to the study endpoint.
- The **sensitivity, specificity, and timing** of the outcomes in the record should be considered.
- In some cases, secondary data use **may not be sufficient** for all aspects of the study and may need to be supplemented with primary data.

# Additional Considerations When Using Secondary Data

- **Concealing the drug name** in the measurement and recording of data is typically not present in secondary data use.
- **Absence of affirmative information** on a condition or event does not necessarily mean the condition is not present.
  - For example, absence of smoking status in a medical record may not mean the patient is not a smoker.
- There also may be a **delay between events** and their presence in existing data sources.

# Additional Considerations When Using Secondary Data, Cont'd

- The **use of data standards** for the terminology, storage, exchange, and access of study data promotes the reliability and the proper interpretation of the data.
- Data standards also **facilitate the ease and correctness** of the data analysis.
  - International data standards exist for many sources of study data.
  - Data standards should be developed for emerging sources of study data.

## Other considerations

- For all data sources, procedures to ensure the **confidentiality of personal data** should be implemented.
- The study design should explicitly address the **protection of personal data**.
- **Local regulations** related to privacy of participants' data should be followed.



# Thank you

ICH Secretariat  
Route de Pré-Bois 20  
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Switzerland

E-mail: [admin@ich.org](mailto:admin@ich.org)

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# Session V: Data sources

## *Questions and Comments*

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# **ICH Public Meeting E8(R1) General Considerations for Clinical Trials**

*Open Comment*

**October 31, 2019**

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# ICH Public Meeting E8(R1) General Considerations for Clinical Trials

*Closing Remarks*

**October 31, 2019**

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