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SCIENCE MEDICINES HEALTH

Renovation of ICH guidelines. What is changing and how is EMA contributing?

PCWP/HCPWP joint meeting

Presented by Fergus Sweeney on 3 March 2020

Key messages of this presentation

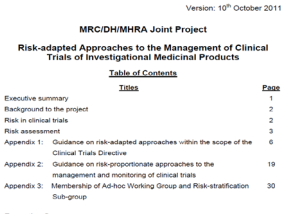
- *ICH E8 and E6 need modernising to prepare for the future – future medicines, future trial designs, future data sources*
- *Emphasise the role of achieving quality by good design*
- *Ensure the involvement of all parties up front in study planning, i.e.: sponsor, patients, trial subjects, investigators, HCPs, regulatory agencies*
- *Set the foundation for new study designs and data sources (RWE, etc.)*

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

Multiple initiatives – Building global consensus – Listening to stakeholders

2009

2011



Version: 10th October 2011

MRC/DH/MHRA Joint Project

Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products

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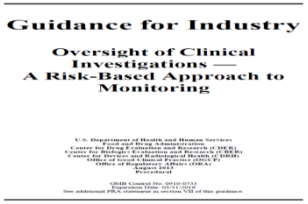
2011

2013



Guidance for Industry

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

2013

2009

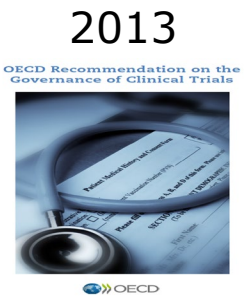
CLINICAL TRIALS ARTICLE Clinical Trials 2009; 6: 585–596

Risk analysis and risk adapted on-site monitoring in noncommercial clinical trials

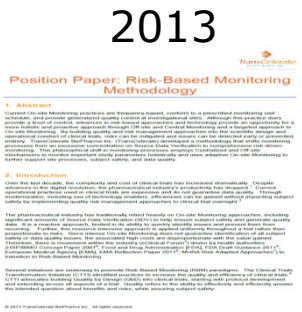
Oana Brosteanu[a], Peggy Houbert[a], Kristina Ihrig[b], Christian Ohmann[c], Ursula Paulus[d], Beate Pfistner[d,e], Gabriele Schwarz[f], Anke Strenge-Hesse[b,h] and Ulrike Zettelmeyer[d]

2011

2013



2013



Stakeholder feedback on ICH E6 (R2) consultation

External Stakeholders' Letter to EMA and ICH 31 Jan/26 Feb 2016

- Academic stakeholders in 22 countries (5 organizations, 119 academic researches)

Concerns

- Need to improve focus on issues most critical for trial quality
- One size fits all approach is not suitable for different types of trials
- External stakeholders are not involved in the ICH processes

- 2016 ICH Meeting in Lisbon
  - External stakeholder representatives invited to meet with Management Committee and ICH E6(R2) EWG representatives to discuss issues raised in their letter

Response to ICH E6 (R2)

- ICH meeting with stakeholders – Lisbon 2016
  - Some additions to ICH E6(R2) addendum to clarify
    - role of E6 in the wider ICH E family of guidelines,
    - status of addendum text as being the definitive view in case of perceived contradiction with pre-existing E6 main text
  - Recognition of the need to manage quality aspects in proportion to risks involved (to trial participants or reliability unitality of data)
- Commitment to involve external stakeholders in future

Outline

Background on ICH

Overview of E6(R3) Revision

- Purpose & Approach
- Stakeholders Outreach
- Progress to Date
- Next Steps

Background on ICH

ICH Guidelines fall into four categories:

- Quality
- Efficacy
- Safety
- Multidisciplinary

ICH-E6 is an efficacy guideline that specifically addresses policies and procedures surrounding good clinical practice (GCP) and the protection of human subjects.

Members

Founding Regulatory Members
- EC, Europe
- FDA, US
- MHLW/PMDA, Japan

Founding Industry Members
- EFPIA
- JPMA
- PhRMA

Standing Regulatory Members
- Health Canada, Canada
- Swissmedic, Switzerland

Regulatory Members
- ANVISA, Brazil
- HSA, Singapore
- MFDS, Republic of Korea
- NMPA, China
- TFDA, Chinese Taipei

Industry Members
- BIO
- IGBA
- WSMI

**As of April 2019*

Observers

Standing Observers
- IFPMA
- WHO

Authorities
- CDSCO, India
- CECMED, Cuba
- COFEPRIS, Mexico
- INVIMA, Columbia
- MMDA, Moldova
- National Ctr, Kazakhstan
- NPRA, Malaysia
- NRA, Iran
- Roszdravnadzor, Russia
- SAHPRA, South Africa
- SCDMTE, Armenia
- TFDA, Chinese Taipei
- TGA, Australia
- TITCK, Turkey

Regional Harmonization Initiatives
- APEC
- ASEAN
- EAC
- GHC
- PANDRH
- SADC

Int'l Pharmaceutical Industry Organizations
- APIC

Int'l Orgs regulated by or affected by ICH guidelines
- BMGF
- CIOMS
- EDQM
- IPEC
- PIC/S
- USP

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ICH guideline development steps

Reflection Paper

Guideline Proposal agreed and informal WG established

Concept paper and business plan adopted

Formal EWG established and Step 1 consensus building commences – **E6 GCP is here**

Step 1 sign off by EWG

Step 2a sign off by ICH assembly Step 2b sign off by regulators

Step 3Public consultation launched and post consultation revision – **E8 General Considerations on clinical studies is here**

Step 4 final guideline adopted by ICH

Step 5 final guideline implementation and coming into force in each region

ICH E6 and E8 – A Brief History

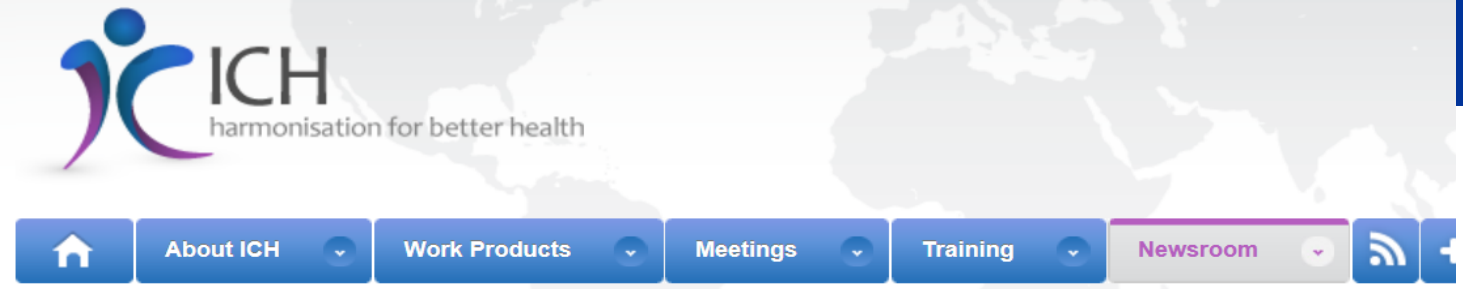
- **E8: General Considerations for Clinical Trials -- finalized in 1997**
  - Sets out general scientific principles for the conduct, performance and control of clinical trials
  - Addresses a wide range of topics in trial design and executions
  - Emphasizes the protection of human subjects in clinical trials

- **E8 (R1) – Draft issued for public comment in May 2019**

ICH E6 and E8 – A Brief History

- **E6: Good Clinical Practice (GCP) – finalized in 1996**
  - Describes the responsibilities and expectations of all stakeholders in the conduct of clinical trials.
  - 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 protections
  - Updated standards for electronic records



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

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.

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ICH E8 & E6

Connected Development

ICH Reflection on GCP Renovation 12 January 2017

*"……recognizing that the **most important tool** for ensuring human subject protection and high-quality data is **a well-designed and well-articulated protocol,** the renovated E6 would also refer to the proposed-to-be-revised E8 guideline for a more comprehensive discussion of study quality considerations and relevant discussion and guidance in other ICH E guidelines……"*

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

ICH Reflection on GCP Renovation

- Step 1: Revision to ICH E8
  - Goal is to address broader concerns about the principles of study design and planning for an appropriate level of data quality
  - Provides comprehensive cross-referencing to the family of ICH guidance documents

- Step 2: Renovation of ICH E6 GCP
  - Goal is to address flexibility concerns with respect to a broader range of study types and data sources
  - Retains the current focus on good clinical investigative site practices

E8 (R1) Overview

General Principles

Quality by Design &
Critical to Quality Factors (CQFs)

Drug development planning

Study design, conduct & reporting

List of Critical to Quality Factor examples

Annex 1 – Study Types & Designs

Annex 2 & 3 – Cross-link to ICH GLs

E8 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)

E8 clinical trial design principles

E6 GCP clinical trial conduct principles

E8 key aspects linking to E6

- *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

2.1 Protection of Clinical Study Subjects

Important principles of **ethical conduct of clinical studies and the protection of subjects,** including special populations, are stated in other ICH guidelines (ICH E6 Good Clinical Practice, ICH E7 Clinical Trials in Geriatric Populations, ICH E11 Clinical Trials in the Pediatric Population, and ICH E18 Genomic Sampling).

These principles have their **origins in the Declaration of Helsinki** and should be observed in the **conduct of all human clinical investigations**. …..

The **confidentiality of information that could identify subjects should be protected** in accordance with the applicable regulatory and legal requirement(s).

….Before initiating a clinical study, sufficient information should be available to ensure that the is acceptably safe for the planned study in humans. Emerging clinical and non-clinical data should be reviewed and evaluated, as they become available, by qualified experts to assess the potential implications for the safety of study subjects…….

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**….. quality of a study is **driven proactively by designing quality into the study protocol and processes.** …."

2.3 Patient Input into Study Design

"…….. **Involving patients at the early stage of study design is likely to increase trust in the study, facilitate recruitment, and promote adherence**, which should continue throughout the duration of the study. **Patients also provide their perspective of living with a condition,** which contributes to the determination of endpoints that are meaningful to patients, selection of the right population, duration of the study, and use of ICH E8(R1) daft Guideline the right comparators. This **ultimately supports the development of medicines that are better tailored to patients' needs**…."

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. "

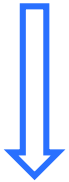
3.3.4 Reviewing Critical to Quality Factors:

- "*….* **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

Section 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

Section 4: Drug Development Planning

Section 5: Design elements for Clinical studies

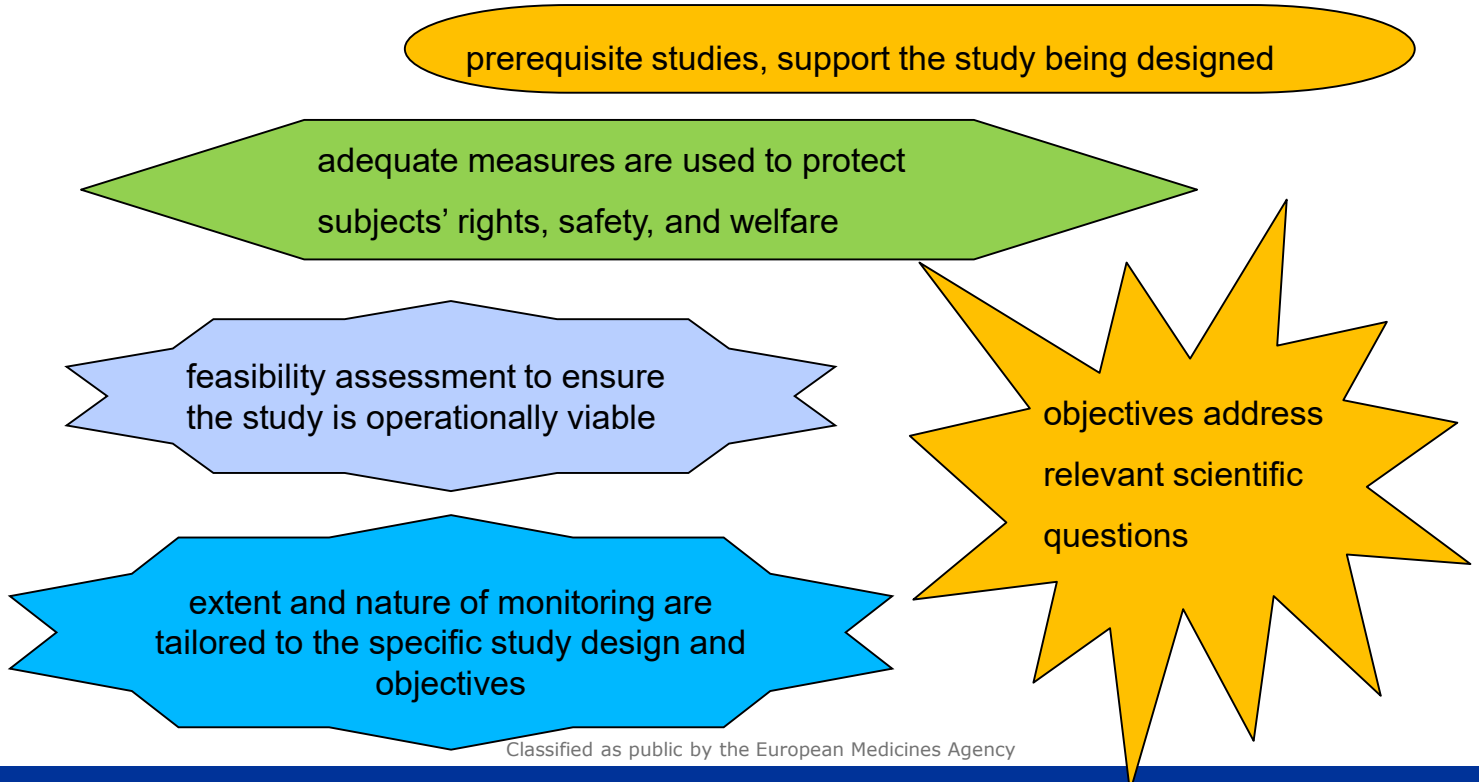
Section 6: Conduct and Reporting

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 Section 7

7 Considerations in Identifying Critical to Quality Factors

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



Conclusion on ICH E8(R1)

- 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 – and on to a new, better, way of working.

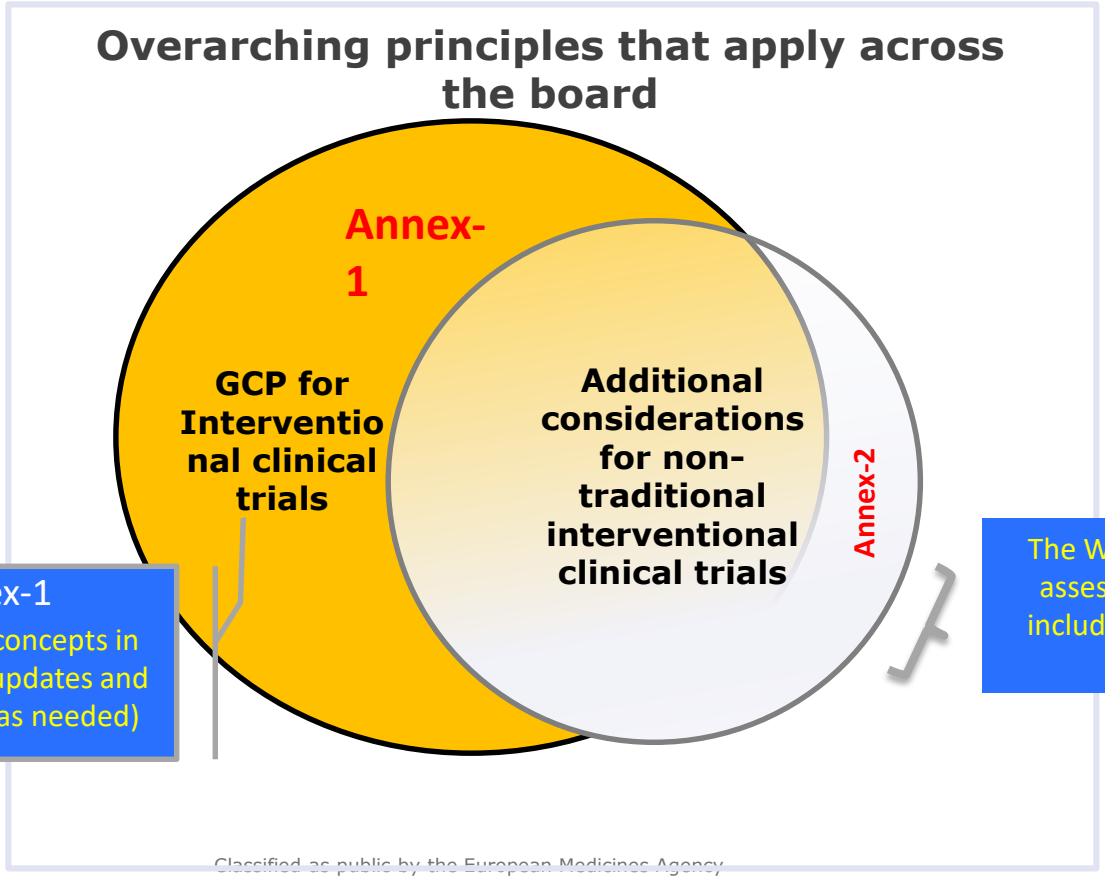
Overview of E6(R3) Revision - Purpose

- To develop a responsive GCP guideline
- Provide flexibility
  - Acknowledge the diversity of trial designs, data sources, and the different contexts in which clinical trials can be conducted
  - Highlight that GCP principles can be satisfied in a variety of ways

Overview of E6(R3) Revision - Approach

- A rewrite and reorganization of ICH-E6(R2)
  - Principles document and Annexes
  - Align with ICH-E8 as appropriate
  - Bridge identified gaps within E6 and between E6 and relevant ICH guidances
- Clear and concise scope
  - Expectations should be fit for purpose
- Focus on key concepts
  - Quality by design and Risk-based approach
  - Proportionality
  - Critical to quality factors
  - Other…

Preliminary Conceptual Representation of the Approach



Annex-1

Reflects the concepts in E6(R2) (with updates and refinements as needed)

The WG will continue to assess what should be included in Annex-1 and Annex-2

Overview of E6(R3) Revisions – Annex 1 and Annex 2

- Annex 1 – Interventional Clinical Trials
  - Considers principles as they relate to the use of unapproved or approved drugs in a controlled setting with prospective allocation of treatment to participants and collection of trial data
- Annex 2 – Non-traditional Interventional Clinical Trials
  - Considers principles as they relate to the use of non-traditional clinical trial designs such as pragmatic clinical trials and decentralized clinical trials, as well as those trials that incorporate real world data sources

Why are observational studies not included?

- Although certain observational studies and data are being utilized to identify safety signals, regulatory organizations are still determining how to best utilize observational studies to support decisions on efficacy.
  - Important issues such as determining appropriate methodologies to establish causal inference and to provide regulatory grade evidence are not fully elucidated for observational studies.
  - Deliberations and planning are still needed to determine best way forward
- Observational studies may have different considerations for the protection of human participants and for data collections compared to interventional trials.
  - Interventional trials prospectively apply an intervention to participants in accordance with the protocol, whereas observational studies are often retrospective in nature and do not involve an intervention.
- Certain elements, such GCP considerations for real-world data sources within the context of interventional clinical trials, are included under annex-2 from the current ICH-E6(R3) concept paper. The scope of Annex-2 will be further defined after Annex-1 has been developed.

Anticipated Approach

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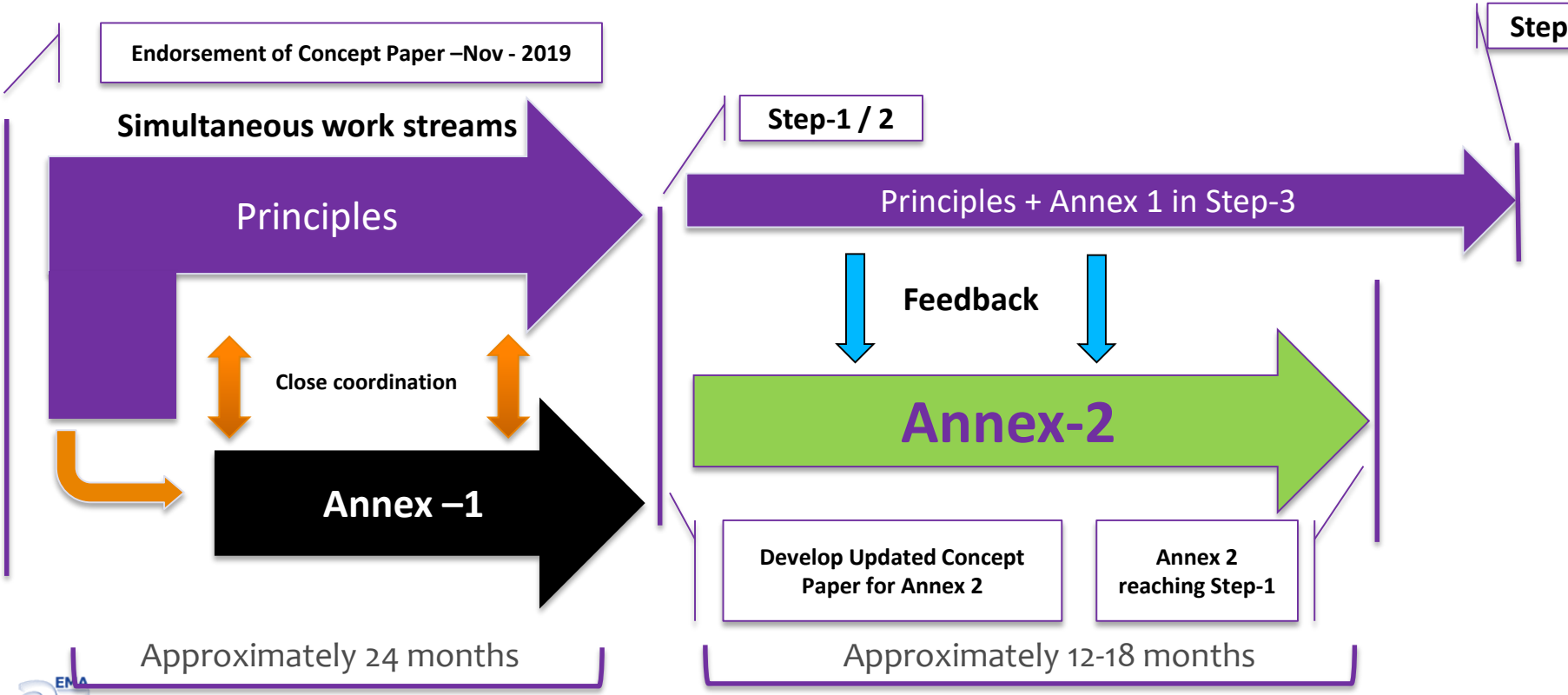
Simultaneous work on the principles ***AND*** Annex-1



External Outreach

- There are many stakeholders impacted by ICH-E6 GCP guidelines
- Stakeholder outreach approaches are being considered by the EWG and ICH member organizations
- The knowledge gained by learning from stakeholder experiences and viewpoints will further enrich EWG discussions

ICH Good Clinical Practice Guidelines (ICH E6)
Open Comment Opportunity

Dear Colleague:

You are invited to provide comments on the ICH Good Clinical Practice (GCP) Guideline (ICH E6). This information is being gathered independently by the Clinical Trials Transformation Initiative (CTTI). Through this open comment opportunity you may suggest specific revisions to GCP. The information collected will be provided to the ICH for their consideration during renovation of GCP. This activity is in follow up to the survey CTTI distributed in August.

PROVIDE COMMENTS HERE

Other important information:

- The open comment opportunity is only available in English.
- Professionals involved in research for regulatory purposes should provide comments.
- You may provide comments as an individual or an organization.
- There is no compensation.
- This activity is not anonymous. Your name and affiliation, together with your comments, will be linked and provided to ICH.

Provide comments no later than Oct. 18, 2019.

We encourage you to forward this email to others who may be interested in providing comments on GCP.

Thank you in advance.

Annemarie Forrest | Director of Projects
Clinical Trials Transformation Initiative
annemarie.forrest@duke.edu
www.ctti-clinicaltrials.org

CTTI Survey

Widely circulated in EU

https://www.ctti-clinicaltrials.org/who-we-are

Progress

- Business plan and concept paper finalized and endorsed
  - EWG established

- EWG discussions
  - Principles of the guidance
  - Scope and content of the guidance
  - Stakeholder engagement activities

Any questions?

Further information

[Insert relevant information sources or contact details as applicable.]

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