EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Introduction to ICH E6(R3) and stakeholder engagement plan

ICH E6(R3) Good Clinical Practice workshop with PCWP and HCPWP

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Outline

Overview of E6(R3) Revision

- ICH E6– A Brief History
- Purpose of Revision & Approach
- Stakeholders Outreach
- Progress to Date and Next Steps

ICH E6– 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

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
- Academic stakeholders are not involved in the ICH processes

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

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

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

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.

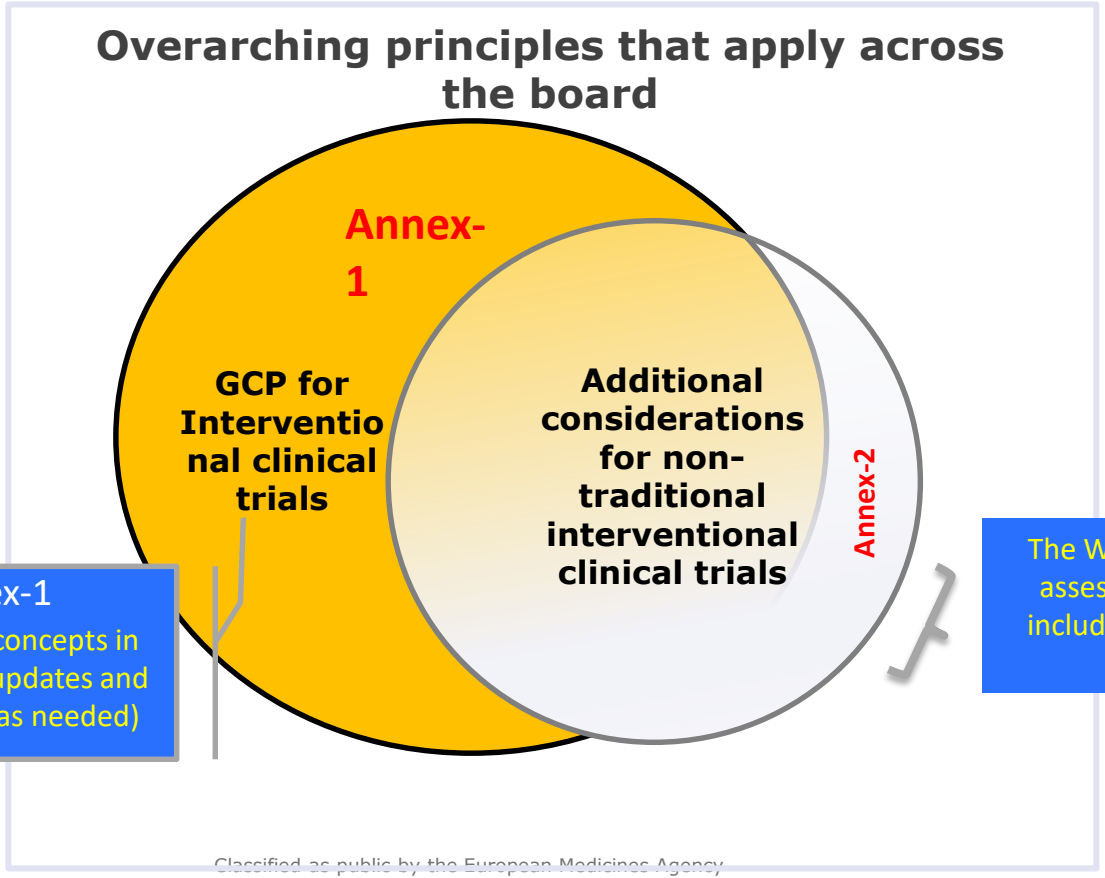
Overview of E6(R3) Revision - Purpose

- 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

Anticipated Approach

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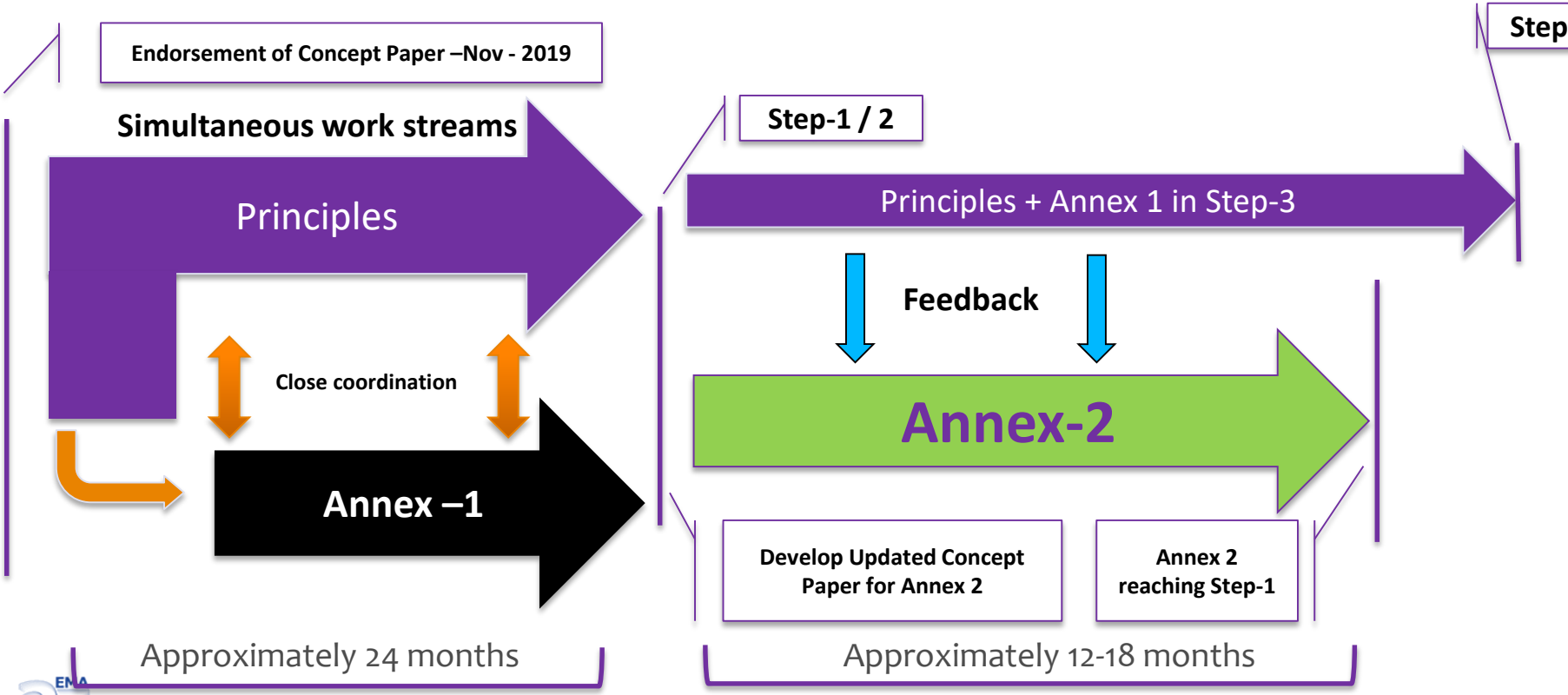
Simultaneous work on the principles ***AND*** Annex-1



External Outreach

- There are many stakeholders impacted by ICH-E6 GCP guidelines
- ICH has committed to stakeholder engagement with academic clinical researchers and patient representatives
- Understanding stakeholder groups' perspectives as the working group develops ICH-E6(R3) will help to ensure that the guidelines are responsive to the needs of those conducting or participating in clinical trials.
- ICH considers the benefits from these engagements to be substantial.
- The knowledge gained by learning from stakeholder experiences and viewpoints will further enrich EWG discussions
- The summary of the E6(3) Stakeholder Engagement Approach can be found on the GCP renovation page: https://admin.ich.org/sites/default/files/2020-05/E6-R3_PublicEngagemenSummary_2020_0421.pdf

External Outreach

These engagements should result in:

- Supporting development of a responsive guideline with stakeholders' perspectives and advances in technology and clinical trial design.
- Improving understanding and implementation of ICH-E6(R3) supporting smoother adoption by stakeholders.
- Providing transparency and responsiveness to stakeholders' needs for further involvement during medicines development.

External Outreach

Two types of engagement with stakeholders:

Regional public engagement approach held by ICH member organizations,

- Stakeholder representatives will be selected at the regional level by the Regulatory MC member organisation using, where available, existing mechanisms for public engagement (meetings, surveys etc.)

Meetings with the expert working group (EWG).

- The EWG will engage with academic clinical researchers, and potentially other relevant stakeholders at EWG meetings, face to face and if necessary, by teleconference
- Stakeholders' input will be sought on relevant issues, such as experiences with clinical trials and insights on the most challenging aspects of applying GCP. Stakeholders will provide their individual views and/or the views of their organizations, as appropriate.

External Outreach

- Overall, all engagements should be based on principles of equal opportunity, fairness, transparency, relevant expertise and the stakeholder representative's experience
- This engagement approach will be piloted during the first drafting stage prior to the public consultation of ICH-E6(R3).

Progress and next steps

- Business plan and concept paper finalized and endorsed
  - EWG established November 2019

- Ongoing
  - Drafting of principles of the guidance
  - Drafting of scope and content of the guidance
  - Stakeholder engagement activities being initiated

Any questions?

Further information

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

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