EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ICH E6 Addendum on Good Clinical Practice

PCWP/HCPWP on 9 March 2016

Presented by Fergus Sweeney on 9 March 2015
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Background – how has the discussion evolved?

Multiple regional initiatives at regulatory, academic or international organisation level

For example

OECD Global Science Forum

Facilitating International Cooperation in Non-Commercial Clinical Trials

OCTOBER 2011

OECD

Final Version Agreed and published:

RECOMMENDATION SCIENTIFIC AND TECHNOLOGICAL POLICY

OECD **Recommendation of the Council on the Governance of Clinical Trials**

10 December 2012 - C(2012)167

Guidance for Industry

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

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Good Clinical Practice (OGCP)
Office of Regulatory Affairs (ORA)
August 2013
Procedural

OMB Control No. 0910-0733
Expiration Date: 03/31/2016
See additional PRA statement in section VII of this guidance.

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18 November 2013
EMA/269011/2013
Compliance and Inspection

Reflection paper on risk based quality management in clinical trials

Draft Agreed by the Clinical Trial Facilitation Group (CTFG) for release for consultation	31 May 2011
Draft Adopted by the Good Clinical Practice (GCP) Inspectors Working Group for consultation	14 June 20111
Start of public consultation	5 August 2011
End of consultation (deadline for comments)	15 February 2012
Agreed by the Clinical Trial Facilitation Group (CTFG) for publication	13 September 2013
Adopted by GCP Inspectors Working Group	12 September 2013

Keywords	Quality Management, Risk Management, Quality Tolerance Limit, Risk Control, Clinical Trial

Changing attitudes and concepts

Need to facilitate the development of a more:

- systematic,
- prioritised,
- risk-based approach to quality management of clinical trials,
- to support the principles of GCP and to complement existing quality practices, requirements and standards.

Problem can be summarised:

- current practices are not proportionate
- nor well adapted to achieving the desired goals
- generally very costly,
- resulting either in success at an unnecessarily high cost or failure which is also very costly.

The origins of the problem are multifactorial.

- Building **quality into the design and operation of clinical trials** to gain more efficient and effective monitoring and data verification systems
- Utilise limited resources to address the most important issues and priorities, especially those associated with predictable or identifiable risks to the **wellbeing of trial subjects and the quality of trial data**
- Encourage interaction and discussion of the risk based approaches taken between the **sponsor and the regulators**

ICH Minneapolis June 2014

ICH
harmonisation for better health

Final Concept Paper
Addendum for ICH E6: Guideline for Good Clinical Practice
dated 2 June 2014
Endorsed by the ICH Steering Committee on 5 June 2014

Type of Harmonization Action Proposed

Addition of an addendum to an existing Guideline, ICH E6, *Good Clinical Practice (GCP)*: Consolidated Guideline

Statement of the Perceived Problem

Harmonisation of Standards
The current ICH E6 Expert Working Group includes:

- 14 representatives from the six ICH founding members (4 from US, 4 from EMA/EU, 6 from Japan)
- 2 experts/ one each from the two new ICH members Canada and Switzerland (Health Canada and Swissmedic joined the ICH Steering Committee in June 2014)
- 4 observers/one each from ANVISA (DRA of Brazil), DoH of Chinese Taipei, MFDS (DRA of Korea) and WSMI

Statement of the perceived problem– why do we need an addendum to ICH E6?

Since 1996 adoption of ICH E6 GCP, clinical trials have evolved substantially,

- increases in globalisation, study complexity, and technological capabilities.
- approach to GCP needs modernisation to keep pace with the scale and complexity of clinical trials and to ensure appropriate use of technology

ICH E6 gave sponsors flexibility to implement innovative approaches – But has been misinterpreted and implemented in ways that impede innovation

e.g. emphasising less important aspects of trials (e.g., focusing on the completeness and accuracy of every piece of data) at the expense of critical aspects (e.g., carefully managing risks to the integrity of key outcome data).

Statement of the perceived problem– why do we need an addendum to ICH E6?

Modernising ICH E6 by supplementing it with additional recommendations will better facilitate broad and consistent international implementation of new methodologies. Topics to be discussed by EWG:

Facilitate innovative approaches to clinical trials including:

- quality risk management
- quality-by-design processes
- emphasize upfront assessment of risks specific to a study design and protocol.
- risk- based monitoring, focusing on critical study elements,
- use of technological tools to ensure robust conduct, oversight, and reporting.

Workplan timelines

1. Anticipated Milestones *(A high-level summary of the main deliverable(s) & timeframe(s) should be provided in the table below)*

Completion Date	Deliverable
June/2015	*Step 1 Technical Document*
June/2015	*Step 2a Technical Document*
July/2015	*Step 2b Draft Guideline*
June/2016	*Step 3 Expert draft Guideline*
November/2016	***Step 4 Final Guideline***

What is an addendum?

- An addendum involves the preparation of new text, of equal regulatory value to the original text.
- It does not replace the original text but adds to it.

- Novel approach for ICH introduced with the GCP addendum – the new text is inserted in the right places next to the original text, rather than as a separate document that would have been confusing.

5. Sponsor

ADDENDUM

5.0. Quality management

The sponsor should implement a system to manage quality throughout the design, conduct, recording, evaluation, reporting and archiving of clinical trials.

Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results. Quality management includes the efficient design of clinical trial protocols, data collection tools and procedures, and the collection of information that is essential to decision making.

The methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected. The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures and data collection. Protocols, case report forms, and other operational documents should be clear, concise and consistent.

The quality management system should use a risk-based approach as described below.

5.0.1. Critical process and data identification

During protocol development, the sponsor should identify those processes and data that are critical to assure human subject protection and the reliability of study results.

or to be taken and/or actions recommended to secure compliance.

- The review and follow-up of the monitoring report with the sponsor should be documented by the sponsor's designated representative.

ADDENDUM

- Monitoring results should be provided to the sponsor (including appropriate management and staff responsible for trial and site oversight) in a timely manner for review and follow up as indicated. Results of monitoring activities should be documented in sufficient detail to allow verification of compliance with the monitoring plan.

ADDENDUM

5.18.7. Monitoring plan

The sponsor should develop a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial. The plan should describe the monitoring strategy, the monitoring responsibilities of all the parties involved, the various monitoring methods to be used and the rationale for their use. The plan should also emphasize the monitoring of critical data and processes. Particular attention should be given to those aspects that are not routine clinical practice and that require additional training. The monitoring plan should reference the applicable policies and procedures.

5.19. Audit

If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

5.19.1. Purpose

The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs,

Addendum Content

- Introduction
- Glossary
  - certified copy,
  - monitoring plan,
  - monitoring report,
  - validation of computerized systems
- GCP Principles
  - applicability of GCP standards when using electronic media

Addendum Content

- Investigator responsibilities:
  - Supervision of tasks delegated
  - Ensure qualification and implement procedures to ensure integrity
  - Source documents and trial records for each trial subject
- Attributable, legible, contemporaneous, original, accurate, and complete

Addendum Content

- Sponsor responsibilities
  - Quality Management
    - Sponsor should implement a system to manage quality throughout the design, conduct, recording, evaluation, reporting, and archiving of clinical trials
    - Sponsors should focus on essential trial activities
    - Methods used to assure and control quality of trial should be proportionate to risks
    - Avoid unnecessary complexity, procedures and data collected

Addendum Content

- Sponsor responsibilities
  - Quality Management
    - risk-based approach to quality management,
      - Critical process & data identification
      - Risk Identification
      - Risk Evaluation
      - Risk Control
      - Risk Communication
      - Risk Review
      - Risk Reporting

Addendum Content

- Sponsor responsibilities
  - oversight,
  - subcontracting by contract research organizations (CROs),
  - use of computerized systems,
  - follow-up of non-compliance

Addendum Content

- Sponsor responsibilities
  - Monitoring- including risk based, centralised and on-site monitoring approaches,
    - Sponsor should develop a systematic, prioritised, risk-based approach
    - Permission of varied approaches e.g combination of on-site and centralised monitoring to improve effectiveness & efficiency
    - Rationale for chosen strategy should be documented
    - Documentation of monitoring results
    - Sponsor should develop monitoring plan tailored to the human subject protection and data integrity risks of the trial

Addendum Content

- Essential Documents/(e)TMF
  - Sponsor and investigator should maintain record of location(s) of their respective essential documents. Storage system should provide for document identification, search and retrieval
  - Individual trials may require additional documents not mentioned in essential document list. Sponsor and/or investigator should include these as part of trial master file (TMF)
  - Investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during and after the trial
  - When copy used to replace original document, it should fulfil requirements for certified copies

Addendum Content

- Sponsor should not have exclusive control of CRF data
  - Sponsor should ensure that investigator has control of and access to CRF data reported to sponsor

1 23 July 2015
2 EMA/CHMP/ICH/135/1995
3 Committee for Human Medicinal Products

4 Guideline for good clinical practice E6(R2)

5 Step 2b

Adopted by CHMP for release for consultation	23 July 2015
Start of public consultation	4 August 2015
End of consultation (deadline for comments)	3 February 2016

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Comments should be provided using this template. The completed comments form should be sent to ich@ema.europa.eu

Mailed to 140 EU research organisations and learned societies, 10 EU pharmaceutical industry and CRO associations.

52 responses received, 300 pages:

- 15 Academia/research organisations
- 15 Pharmaceutical industry
- 9 CRO associations/individual CROs
- 6 Professional associations (industry linked)
- 3 Regulator/public health
- 4 Other (mainly individuals of varying background)

Workplan timelines – next steps

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Conclusion

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- The need to modernise GCP is clear
- Proportionate, risk based approaches are required
- Not one size fits all
- Need to take greater advantage of new tools and approaches (mixes of on-site and central monitoring, data driven activity – the role and tools of monitoring change)
- Greater use of electronically available data to understand and monitor sources of variability and to anticipate, identify and act on problems before during and after the trial
- The greatest challenge is in Change Management – adjusting behaviours, attitudes – moving away from preconceived ideas
- The greatest achievements will be by those who embrace new approaches and seek to make them work – there is no regulatory impediment per se.

Thank you for your attention

I am available at the EMA booth exhibition hall number 3.D03 to answer questions on 13 April at 15:00-16:00

Further information

Contact me at fergus.sweeney@ema.europa.eu

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