Establishing our Trajectory:
An Overview & Assessment of the Impact of
ICH E6 R2 on Sites and Sponsors

Module 1 of a 4 Part Series

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Special thanks to Crystal Gruetzmacher for helping with the development of this module.
Definition: Odyssey

[od-uh-see] noun
1 : a long wandering journey or voyage usually marked by many changes of fortune
2 : an intellectual or spiritual wandering or quest; an odyssey of self-discovery; a spiritual odyssey from disbelief to faith
Poll Question #1

I understand the impact of ICH E6 R2 for my site as it relates to monitoring:

A. Not at all
B. A little
C. Very much
Addendum to ICH E6 (R2)

Stephanie Shapley (US FDA) - Rapporteur
Dr. Fergus Sweeney (EMA) - Regulatory Chair
Date: December 15, 2015
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: Integrated Addendum: Good Clinical Practice

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

- 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).

- Modernising ICH E6 by supplementing it with additional recommendations will better facilitate broad and consistent international implementation of new methodologies.
Addendum to ICH E6 - Objective

- This guideline has been amended to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording, and reporting while continuing to ensure human subject protection and data integrity.
Which changes impact sites?
4. Investigator

**E6 (R1)**

4.2 Adequate Resources
- 4.1.1 Potential to recruit suitable subjects with agreed period
- 4.2.2 Sufficient time to properly conduct/complete trial within agreed period
- 4.2.3 Adequate number of qualified staff & adequate facilities for the foreseen duration of the trial
- 4.2.4 Ensure all assisting with trial are adequately informed about the protocol, IP, trial related duties & functions

**E6 (R2)**

4.2 Adequate Resources

Addition of new sections 4.2.5 & 4.2.6:
- 4.2.5 Responsible for supervising any individual or party to whom study tasks conducted at the trials site is delegated.
- 4.2.6 If services are retained by any party to perform study tasks, ensures party is qualified to perform tasks & should implement procedures to ensure integrity of the study tasks performed and any data generated

**How can I comply?**
- Demonstration through documentation that this oversight is occurring: SOP’s, notes, delegation logs, etc.
- Make sure you understand how to interpret tasks being delegated for each trial
4. Investigator (cont.)

E6 (R1)

4.9 Records and Reports

• 4.9.1 Accuracy, completeness, legibility, timeliness of data reported to sponsor in CRFs & required reports.
• 4.9.2 CRF Data consistent with source documents; discrepancies explained
• 4.9.3 Changes/Corrections dated, initialed, explained; not obscuring original entry; changes/corrections by sponsor’s designated representatives are necessary, via sponsor SOPs, & endorsed by investigator; audit trail.
• 4.9.4 Maintain Essential Documents per reg requirements. Prevent accidental or premature destruction.
• 4.9.5 Retention of Essential Documents
• 4.9.6 Financial aspects documented in agreement between Sponsor and Investigator/Institution
• 4.9.7 Make all records avail for direct access for monitor, auditor, IRB/IEC, Reg Authority

E6 (R2)

4.9 Records and Reports

Addition of new sections 4.9.0

• 4.9.0 Maintain adequate & accurate source documents/trial records that include all pertinent observations on each of the site’s trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry and should be explained if necessary (e.g., audit trail)

How can I comply?

• Document, document, document!
• Keep doing what you have been doing
ICH E6 R2
Changes Impacting Sponsors
5. Sponsors

In a nutshell:

• Incorporate quality management process (e.g., Risk assessment process)
• Incorporate a risk based monitoring approach (e.g., use centralized monitoring to complement and reduce the extent and or frequency of onsite monitoring)
ICH Recommends Centralized Monitoring

Centralized monitoring is a remote evaluation of accumulating data, performed in a timely manner, supported by appropriately qualified and trained persons (e.g., data managers, biostatisticians). Centralized monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring and help distinguish between reliable data and potentially unreliable data. Review, that may include statistical analyses, of accumulating data from centralized monitoring can be used to:

a) identify missing data, inconsistent data, data outliers, unexpected lack of variability and protocol deviations.

b) examine data trends such as the range, consistency, and variability of data within and across sites.

c) evaluate for systematic or significant errors in data collection and reporting at a site or across sites; or potential data manipulation or data integrity problems.

d) analyze site characteristics and performance metrics.

e) select sites and/or processes for targeted on-site monitoring.

Require reports
Require inclusion in a planning document

How do sites benefit from centralized monitoring?

• Faster identification of errors/issues and trends that MATTER!
• Supports CRA’s in being able to focus on on-site activities that support the site and drive quality and safety of patients
5. Sponsors

ICH E6 R2 5.0 Quality Management Requirements

ICH GCP E6 ADDENDUM FOR RBM

- 5.0.1 Critical Process & Data ID: Identify critical data & processes during protocol development
- 5.0.2 Risk Identification: Identify risks to critical data & processes
- 5.0.3 Risk Evaluation: Evaluation of identified risks (likelihood, impact, detectability)
- 5.0.4 Risk Control: Risk mitigation actions
- 5.0.5 Risk Comm.: Communication of quality management activities to stakeholders
- 5.0.6 Risk Review: Periodic review of risk control measures
- 5.0.7 Risk Reporting: Description of quality management approach & doc. of important deviations
5. Sponsors (cont.)

- **Section 5.18 Monitoring**

  The sponsor should implement a systematic, prioritized **RISK BASED** approach to monitoring clinical trials.

  Centralized Monitoring processes provide additional monitoring capability that can complement & reduce the extent and or frequency of on site monitoring by such methods as:

  5.18.3 Extent and Nature of Monitoring

  - Using statistical analyses to identify data trends
  - Analyzing site characteristics and performance metrics
  - Selection of sites or processes for targeting monitoring
5. Sponsors (cont.)

5.18.6

(e) 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.

5.18.7

The sponsor should develop a monitoring plan tailored to the specific subject protection and data integrity risks of the trial. Describe the monitoring strategy, responsibilities of all the parties involved, various monitoring methods to be used and the rationale for use. Emphasize monitoring of critical data and processes. Give particular attention to those non routine clinical practice aspects and those that require additional training. Reference applicable policies and procedures.
5. Sponsors (cont.)

5.20 Non Compliance

Adding To:

5.20.1

When significant noncompliance is discovered, the sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions.

If required by applicable law or regulation the sponsor should inform the regulatory authority(ies) when the noncompliance is a serious breach of the trial protocol or GCP.
8. Essential Documents for the Conduct of a Clinical Trial

8.1 Investigator & Sponsor maintains a record of the location(s) of their respective essential documents

The storage system (irrespective of media) should provide for document identification, search and retrieval

Individual trials may require additional documents not specifically mentioned in the essential document list and be included as part of the TMF

Sponsor ensures the investigator has control of and continuous access to the CRF data reported to the sponsor.

The sponsor should not have exclusive control of those data
 Copies used to replace an original document should be certified copies.

The investigator/institution should have control of all essential documents and records generated by them
Poll Question #2

I understand the impact of ICH E6 R2 for my site as it relates to monitoring:
A. Not at all,
B. A little,
C. Very much
Examples of ICH E6 R2 in Practice?
Poll Question #3

I see the value in replacing/supplementing on site monitoring with centralized monitoring

A. Not at all,
B. A little,
C. Very much
Primary endpoint in a trial is improvement in cognitive rating scales, so critical data is cognitive rating scale values and critical process is collection/conduct of cognitive rating scales.

Risks to cognitive rating scales (what could go wrong?): site not using certified rater, not using same rater within a subject, subject not having eaten prior to scale, incomplete scales, scales completed out of order.

Per Medical Monitor and statisticians, any deviation in requirements for cognitive scales could have significant impact to data.

- Add instruction in protocol to set expectations around cognitive scale conduct/collection, include training at Inv meeting for raters
- Ensure data management plan has edits for scales out of range or missing data
- Ensure monitoring plan has expectations for CRAs to look for continuity in raters and protocol deviations
- Ensure centralized monitoring plan has trending of cognitive rating scales scores to identify anomalies that could signal potential transcription errors or protocol deviations
Centralized Monitoring Example: Cognitive Rating Scale Anomalies
Example: Rating Scale Anomalies
Example: Rating Scale Anomalies
Centralized Monitoring Investigations

Findings tracked for CRA to investigate

• Transcription error?
  – Yes = Query
  – No = Look for potential process failure/deviation

• Protocol deviation?
  – Yes = Document in CTMS as deviation, report to IRB, evaluate significance, assess root cause, modify process, retrain, evaluate effectiveness of changes/training
  – No = Evaluate for trends in future analyses
ICH GCP E6 ADDENDUM FOR RBM

5.0.5 Risk Communication

Maintain a risk register, train sites on risks of noncompliance with protocol specifications on conduct of cognitive scales

5.0.2 Risk Identification

CRO and sponsor meet monthly to review queries, deviations and centralized monitoring findings/trends and determine if new mitigations should be added to plans or additional site training or protocol clarifications are needed

5.0.7 Risk Reporting

Provides a monthly report on decisions and actions to sponsor
Poll Question #4

I see the value in supplementing on site monitoring with centralized monitoring

A. Not at all,
B. A little,
C. Very much
Key Takeaways
Expected Benefits of Taking this Path

▪ Fewer critical findings in audits than traditionally monitored studies
▪ More timely review of data using remote and centralized review allow for faster identification of issues and remediation before the mistakes are repeated = BETTER PATIENT SAFETY
▪ Creates more time for CRAs to work with sites on root cause and process improvement = CRA’S GET TO SPEND QUALITY TIME WITH SITE PERSONNEL WORKING ON THINGS THAT MATTER VS. DEALING WITH INCONSEQUENTIAL TRANSCRIPTION ERRORS
▪ Allows sites to spend more time on the things that matter: patient care and process improvement = GREATER PATIENT CENTRICITY
## Upcoming Modules

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<td>Module #2 What Could Go Wrong? ICH E6 R2, Investigative Sites and Risk Assessment</td>
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<td>Module #3 Centralized Monitoring</td>
<td>5 April 2018</td>
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<td>Module #4 Operationalizing, Change &amp; Site Management</td>
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Faculty Disclosure

In compliance with ANCC Guidelines, I hereby declare:

I do not have financial or other relationships with the manufacturer(s) of any commercial service(s) discussed in this educational activity.

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Kristin Mauri  
Global Head, Risk-Based Monitoring, Bioclinica
Thank you!

SCRS members can visit http://myscrs.org/insite/ to view InSite, the global journal for clinical research sites.
Thank you!
Questions?

CROForum