ICH GCP E6(R2): Changes? Yes Challenges? Not as Difficult as You May Fear

Lorrie D. Divers, President
QRCP Solutions, Inc.

25 October 2017:
University of Rochester
Achieving High Quality Clinical Research Seminar Series
OBJECTIVES

► ICH GCP E6(R2)
  ➢ Who does it impact?
► Regulations versus Guidance
  ➢ What Are Our Obligations?
► Major “Changes”
  ➢ Updated Why and How?
  ➢ What Do They Mean For You?
    ▪ Clinical Investigator / Study Site
    ▪ Sponsor
► What to Remember
ICH GCP E6(R2): What is it?

- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)

“The objective of [the] ICH GCP Guideline is to provide a unified standard for the European Union (EU), Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities.”

“This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities.”
Oh good, this doesn’t apply to me....

It says, “pharmaceuticals” right in the name of the organization (and its definition of a “clinical trial”!)

- I do behavioral intervention trials!
- I am studying an intraocular lens!
ICH GCP E6(R2) also says….

“The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.”
NIH Clinical Trial Definition

A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

1See Common Rule definition of research at 45 CFR 46.102(d).

2See Common Rule definition of human subject at 45 CFR 46.102(f).

3The term "prospectively assigned" refers to a pre-defined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo, or other control) of a clinical trial.

4An intervention is defined as a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints. Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies.

5Health-related biomedical or behavioral outcome is defined as the pre-specified goal(s) or condition(s) that reflect the effect of one or more interventions on human subjects' biomedical or behavioral status or quality of life. Examples include: positive or negative changes to physiological or biological parameters (e.g., improvement of lung capacity, gene expression); positive or negative changes to psychological or neurodevelopmental parameters (e.g., mood management intervention for smokers; reading comprehension and/or information retention); positive or negative changes to disease processes; positive or negative changes to health-related behaviors; and, positive or negative changes to quality of life.

Frequently Asked Questions
NIH Policy on Good Clinical Practice (GCP) Training for
NIH Awardees Involved in NIH-funded Clinical Trials

Question 8: The GCP policy indicates that investigators should be trained in GCP “consistent with the principles of the International Conference on Harmonization (ICH) E6 (R2).” Some of the elements of ICH (E6) seem to pertain specifically to trials of drug and device interventions. How would those elements apply to trials of behavioral interventions?

Answer: The principles of ICH (E6) apply generally to all clinical trials. Some measures, e.g., reporting of adverse drug reactions to regulatory authorities, are pertinent specifically to trials of interventions involving drugs and devices, rather than to trials of behavioral interventions. However, the underlying principle of safety monitoring and reporting is relevant to all clinical trials and can be a guide to behavioral investigators in their monitoring and reporting of safety events to relevant oversight bodies, e.g., the Institutional Review Board.
21 CFR Part 812 (IDE) says....

“*Investigational device* means a device, including a transitional device, that is the object of an investigation.”

“*Investigation* means a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.”
“A clinical trial is defined by NIH as a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.”
But my study will **never** be submitted to the FDA.....

Don’t bet on it.....
It’s *just* guidance, not a regulation!
Regulations vs. Guidance

- Regulations are *minimum* standards
  - You *can* (and most often) should do more
  - You *cannot* do less
  - You are *obligated* to comply with the protocol, IRB approval, and/or contracts which will often state the regulations and guidances
Speaking of Panic.....

More or less?

**Keep records** for 3 years from the date you filed your original return or 2 years from the date you paid the *tax*, whichever is later, if you file a claim for credit or refund after you file your return. **Keep records** for 7 years if you file a claim for a loss from worthless securities or bad debt deduction. Sep 8, 2017

How long should I keep records | Internal Revenue Service

Generally, the **IRS can** include returns filed within the last three *years* in an *audit*. If we identify a substantial error, we may add additional *years*. We usually don't *go back* more than the last six *years*. The **IRS tries to audit** tax returns as soon as possible after *they* are filed.

IRS Audits | Internal Revenue Service
Regulations vs. Guidance

► Exceeding *minimum* requirements:
  ➢ Standardization based on best practices
    ▪ Less challenges now
    ▪ Demonstrates compliance in the future
  ➢ Provides greater protection for research subjects rights, safety and welfare
    ▪ Strengthens data integrity
Regulations vs. Guidance

“Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.”
Guidance documents are not legally binding but they are proven best practices.

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.
Regulations vs. Guidance

U.S. Federal GCP regulations can seem like a (frustrating) exercise in the Socratic method

- Often have to consult multiple resources and arrange multiple passages in sequential order then ask a lot of questions
  - ‘What does this one say that this one does not?’
  - ‘Where is this term defined?’
  - ‘When was this regulation revised and why?’
Regulations vs. Guidance

Guidance documents can be extremely helpful for

- Untangling the legalese
- Clarifying the *if-then* and *what-how* debates
- Applying legal (and ethical) principles in practical ways
ICH GCP E6(R2)

Major “Changes”
- Updated Why and How?
- What Do They Mean For You?
ICH GCP E6(R2): Revision History

“Since the development of the ICH GCP Guideline, the scale, complexity, and cost of clinical trials have increased. Evolutions in technology and risk management processes offer new opportunities to increase efficiency and focus on relevant activities. When the original ICH E6(R1) text was prepared, clinical trials were performed in a largely paper-based process. Advances in use of electronic data recording and reporting facilitate implementation of other approaches. For example, centralized monitoring can now offer a greater advantage, to a broader range of trials than is suggested in the original text.”
Therefore, 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 reliability of trial results. Standards regarding electronic records and essential documents intended to increase clinical trial quality and efficiency have also been updated.”
E6(R1)  
Document History

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<th>First Codification</th>
<th>History</th>
<th>Date</th>
<th>New Codification November 2005</th>
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<td>E6</td>
<td>Approval by the Steering Committee under <em>Step 2</em> and release for public consultation.</td>
<td>27 April 1995</td>
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<td>E6</td>
<td>Approval by the Steering Committee under <em>Step 4</em> and recommended for adoption to the three ICH regulatory bodies.</td>
<td>1 May 1996</td>
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**E6(R1) Step 4 version**

<p>| E6                 | Approval by the Steering Committee of <em>Post-Step 4</em> editorial corrections. | 10 June 1996  | E6(R1)                          |</p>
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<tr>
<td>E6(R2)</td>
<td>Adoption by the Regulatory Members of the ICH Assembly under <em>Step 4</em>.</td>
<td>9 November 2016</td>
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<td><strong>Integrated Addendum to ICH E6(R1) document. Changes are integrated directly into the following sections of the parental Guideline:</strong> Introduction, 1.63, 1.64, 1.65, 2.10, 2.13, 4.2.5, 4.2.6, 4.9.0, 5.0, 5.0.1, 5.0.2, 5.0.3, 5.0.4, 5.0.5, 5.0.6, 5.0.7, 5.2.2, 5.5.3 (a), 5.5.3 (b), 5.5.3 (h), 5.18.3, 5.18.6 (e), 5.18.7, 5.20.1, 8.1</td>
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**Good Clinical Practice (GCP)**

**Description**: The first version of the ICH E6 Good Clinical Practice (GCP) Guideline was finalised in 1996 describing 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 of clinical trials and incorporating addenda on the Essential Documents and on the Investigator's Brochure. This harmonised guideline has been amended in 2016 with an integrated Addendum 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 reliability of trial results. Standards regarding electronic records and essential documents intended to increase clinical trial quality and efficiency have also been updated.

**Implementation**: *Step 5*
ICH harmonisation activities fall into 4 categories: Formal ICH Procedure, Q&A Procedure, Revision Procedure and Maintenance Procedure, depending on the activity to be undertaken (see below).

- **New topic for harmonisation of ICH?**
  - Formal ICH Procedure
  - Concept Paper & Business Plan required

- **Clarification needed for an existing ICH Guideline?**
  - Q&A Procedure
  - Concept Paper required (Business Plan may be required in certain cases)

- **Content of an existing ICH Guideline out of date or no longer valid?**
  - Revision Procedure
  - Concept Paper required

- **New information to be added to an existing ICH Guideline?**
  - Revision Procedure

- **Change to be made to either Q3C Guideline or M2 Recommendations?**
  - Maintenance Procedure
  - Proposal/Concept Paper required for Q3C maintenance. No Concept Paper required for M2 Recommendations maintenance

Each harmonisation activity is initiated by a Concept Paper which is a short summary of the proposal. Depending on the category of harmonisation activity a Business Plan may also be required. The Business Plan outlines the costs and benefits of harmonising the topic proposed by the Concept Paper.
The Formal ICH Procedure is a step-wise procedure consisting of 5 steps (see below, click to have information on a particular step). This procedure is followed for the harmonisation of all new ICH topics.

1. **Consensus building - Technical Document**
3. **Regulatory consultation and Discussion**
4. **Adoption of an ICH Harmonised Guideline**
5. **Implementation**

The procedure is initiated with the endorsement by the ICH Assembly of a Concept Paper and Business Plan. An Expert Working Group (EWG) is subsequently established.

The EWG works to develop a draft Guideline and bring it through the various steps of the procedure which culminate in Step 5 and the implementation in the ICH regions of a Harmonised Guideline.
ICH GCP E6(R2): ICH Status

Published Document: ICH E6(R2) Guideline for Good Clinical Practice

ICH Website: Implementation - Step 5

Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)

Current Step 4 version
dated 9 November 2016
## ICH GCP E6(R2): FDA Status

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<th>FDA Organization</th>
<th>Subject</th>
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<td>09/28/2015</td>
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ICH GCP E6(R2): NIH Status

Sec. 4.1.15.10 NIH Policy on Good Clinical Practice Training for NIH Awardees Involved in NIH-funded Clinical Trials:
Establishes the expectation that all NIH-funded investigators and staff who are involved in the conduct, oversight, or management of clinical trials should be trained in Good Clinical Practice (GCP), consistent with principles of the International Conference on Harmonisation (ICH) E6 (R2). Implements provisions announced in NOT-OD-16-148.
ICH GCP E6(R2): Revisions

- Identified by the word ADDENDUM prior to each added or revised section or text within a section

- “New?” Not really...

  new
  /n(y)oʊ/ (d)
  adjective
  1. not existing before, made, introduced, or discovered recently or now for the first time, “new crop varieties”
  synonyms: recently developed, up to date, latest, current, state-of-the-art, contemporary, advanced, recent, modern, cutting-edge, leading-edge  More
ICH GCP E6(R2): Revisions

Four general areas with the most significant changes:

- Increased clarity in the language regarding investigator oversight - NOT new
- More comprehensive language on sponsor oversight of vendors - NOT new
- Inclusion of risk-based monitoring - NOT new
- Enhanced language on Electronic Systems and Data Handling - Bringing this into the 21st century
1.51 Source Data has always stated: “All information in original records and certified copies of original records...”

1.63 Certified Copy
A copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

1.64 Monitoring Plan
A document that describes the strategy, methods, responsibilities, and requirements for monitoring the trial.

1.65 Validation of Computerized Systems
A process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled from design until decommissioning of the system or transition to a new system. The approach to validation should be based on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results.
Certified Copy - Tips and Techniques

- Whenever the original document cannot (or will not) be retained
  - Process driven or rational reason

- Initial (or sign) and date and simply note ‘Complete Copy of Original’
  - Stamp ‘Certified Copy’ and initial (or sign) and date

- “…or by generation through a validated process…”
  - If source documents will be scanned (e.g., laboratory requisitions), validate the scanning software and procedures
  - If transferring data from one database/software program to another one (i.e., new EHR implementation)
Section 2 - The Principles of ICH GCP

2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

ADDENDUM

This principle applies to all records referenced in this guideline, irrespective of the type of media used.

2.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

ADDENDUM

Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such systems.
Section 4 - INVESTIGATOR

4.2.4 The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

ADDENDUM

*More consistent with U.S. regulatory language*

4.2.5 The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.

4.2.6 If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
Investigator Oversight: How NOT to....

In your November 14, 2016, written response to the Form FDA 483, you indicated that you delegated day-to-day research activities to an independent research company. You noted that you held regular meetings with the independent research company, during which you received updates on recruitment and follow-ups, signed required documents, and reviewed tests. You also noted that the independent research company did not bring any of the above-mentioned violations to your attention during these regular encounters.

We wish to emphasize that as the clinical investigator, it was your ultimate responsibility to ensure that clinical studies were conducted properly and in compliance with FDA regulations, both to protect the rights, safety, and welfare of study subjects and to ensure the validity and integrity of study data. However, your response is inadequate because, although you indicate in your response that you “do not plan to get involved in clinical research again,” you did not provide details about how you personally plan to prevent similar violations if this decision should change and you conduct clinical research in the future. Your explanation, when taken into consideration with the violations described above, suggests systemic failures in your conduct of this clinical investigation.

Your lack of supervision and oversight of the clinical study raises significant concerns about the adequacy of your protection of the study subjects enrolled at your site in the above-mentioned study, and raises concerns about the integrity of the data generated at your site.

https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2017/ucm564172.htm
Investigator Oversight Tips and Techniques

▶ Be involved
  ➢ Actively engage in the informed consent process
  ➢ Assess AEs and SAEs, inclusion/exclusion, study procedure results
  ➢ Document your involvement
    ▪ READ, initial/date IRB and sponsor correspondence
    ▪ Don’t sign ‘blank checks’

▶ Hire qualified personnel
  ➢ Ensure they receive continuous training, support and consistent supervision
Investigator Oversight Tips and Techniques

- If other entities perform trial-related duties and/or functions
  - You must ensure they are qualified to do so and that their performance of the services is compliant
  - Collect/review information to qualify and document review of performance on a regular basis

- May be at the institutional level ("If the investigator/institution retains the services...")
  - Examples: Central IRB or a central clinical trial services group
Section 4 - INVESTIGATOR

4.9 Records and Reports

ADDENDUM

4.9.0 The investigator/institution should maintain adequate and accurate source documents and 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., via an audit trail).

4.9.1 The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
Section 5 - SPONSOR

- Section with the most significant revisions
- Not imposing new requirements but considerably clarifying sponsor responsibilities for
  - Ensuring quality and compliance in every aspect of the clinical trial
  - Using a risk based approach (which ICH, EMA and FDA have been advocating for many years - at least since 2013)
Section 5 - SPONSOR

As a clinical investigator/study site, you may experience changes in sponsor approach and ‘requirements’

Should be familiar with the revisions to Section 5

- The addition of Section 5.0, Quality Management
- 5.18.3 ADDENDUM on risk-based monitoring
If you are a sponsor-investigator, you are obligated to carry out both sponsor and investigator responsibilities.

A multi-institution trial where you are acting as Program Director, Lead PI or Coordinating Investigator confers the ‘sponsor’ responsibilities on that role.
Section 5 - SPONSOR

5.1 Quality Assurance and Quality Control

5.1.1 The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).
ADDENDUM

5.0 Quality Management

The sponsor should implement a system to manage quality throughout all stages of the trial process.

Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results. Quality management includes the design of efficient clinical trial protocols and tools and procedures for data collection and processing, as well as 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.
Section 5 - SPONSOR Tips and Techniques

➤ You have an excellent resource for assistance:
http://www.rochester.edu/ohsp/quality/qualityManagementPlan.html

➤ Another one that may be helpful:
Quality Management Plan (QMP)

The University of Rochester's Quality Management Plan Guide's central goal is to provide resources that encourage, guide, integrate, and enhance continuous quality improvement for a research site, research program, or department/division. The guide focuses on and is intended to aid investigators and research staff in QMP set-up, implementation, and evaluation and to prioritize areas of potential risk to target.

Quality management within a study protocol includes all of the following: (1) a well-designed study protocol; (2) appropriately trained (and dedicated) study team; (3) Appropriately delegated tasks; (4) Study (and site) feasibility; (5) Sufficient monitoring of subject safety, and (6) adequate data monitoring and management. [1, 2, 4, 5, 6]

Additional information is available through the Clinical Trials Transformation Initiative’s (CTTI) Quality by Design Project[4] and their 'Critical to Quality Factors Principles Document'.[3] Local resources pertaining to study design, protocol development, feasibility assessment, study team training, etc. are available through the Office for Human Subject Protection and the Clinical & Translational Science Institute.
RISK-BASED MONITORING TOOLBOX

Introduction

The Risk-Based Monitoring Toolbox provides information on tools available for risk assessment, monitoring and study conduct, the institutions where they are used, and other relevant details such as links and user feedback. The goal is to enable researchers to create risk-based strategies that are appropriate for their study needs.

Launched end 2015, the Toolbox was created following a systematic literature review on current practices and recommendations as well as a survey of clinical trial units (CTUs). The survey identified existing risk-adapted monitoring tools, risk evaluation methods, and monitoring strategies.

Click on the chapters below to find relevant information:

- Why Risk-Based Monitoring?
- Why a Risk-Based Monitoring Toolbox?
- Key Elements of Monitoring
- Risk Assessment Tools
- Risk-Adapted Monitoring Tools
- References

Related Resources

- Generating evidence on a risk-based monitoring approach in the academic setting – lessons learned
- OECD Recommendation on the Governance of Clinical Trials
Risk Assessment / Risk Management

We all perform risk assessment and risk management on a daily basis.
At the most basic level, risk *assessment* is:

A. Defining the possible unintended occurrences, consequences, outcomes
B. Determining how likely or unlikely it is that these may occur
C. Evaluating what the impact of each could be particularly on study subject rights, safety and welfare and on data integrity
D. Understanding how easy or hard it would be to detect the issues identified

Then ranking these risks from high (critical) to low (minimal)

➤ Tip: There is no such thing as “no risk”!
Risk Management Tips and Techniques

At the most basic level, risk management is:

- Developing and executing actions to maximally control for the impact and occurrence the risks identified in the assessment process → Risk Management Plan

  - Focus greatest effort on the high risks but don’t ignore the others, particularly any with impact on study subject safety, rights, and welfare or data integrity

  - Possible actions? Processes and procedures, standardized work, job aids, quality control, monitoring, quality assurance oversight, etc.
5.18.3 Extent and Nature of Monitoring

The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators’ training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.
Section 5 - SPONSOR

ADDENDUM

The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials. The flexibility in the extent and nature of monitoring described in this section is intended to permit varied approaches that improve the effectiveness and efficiency of monitoring. The sponsor may choose on-site monitoring, a combination of on-site and centralized monitoring, or, where justified, centralized monitoring. The sponsor should document the rationale for the chosen monitoring strategy (e.g., in the monitoring plan).

On-site monitoring is performed at the sites at which the clinical trial is being conducted. 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).
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.
Section 5 - SPONSOR Tips and Techniques

Not New!

IV. RISK-BASED MONITORING

A. Identify Critical Data and Processes to be Monitored

B. Risk Assessment

C. Factors to Consider when Developing a Monitoring Plan

D. Monitoring Plan
   1. Description of Monitoring Approaches
   2. Communication of Monitoring Results
   3. Management of Noncompliance
   4. Ensuring Quality Monitoring
   5. Monitoring Plan Amendments
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.
Section 5 - SPONSOR Tips and Techniques

▶ As an auditor, I see underutilization of regular use of data review techniques
  ➢ Intra-Subject Logic
  ➢ Inter-Site Logic
  ➢ Quality of Documentation
  ➢ Repetitive Errors

▶ Much of this can be done centrally
Section 5 - SPONSOR

5.20 Noncompliance

5.20.1 Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

ADDENDUM

If noncompliance that significantly affects or has the potential to significantly affect human subject protection or reliability of trial results is discovered, the sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions.

5.20.2 If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution’s participation in the trial. When an investigator's/institution’s participation is terminated because of noncompliance, the sponsor should notify promptly the regulatory authority(ies).
Section 5 - SPONSOR Tips and Techniques

“...perform a root cause analysis and implement appropriate corrective and preventive actions.”
Root Cause Analysis and CAPA

Boils down to this:

- Determine the true reason(s) why an unintended consequence occurred
- Evaluate what action(s) directly related to the cause(s) and take the action(s)
- Develop and execute activities to prevent future / similar occurrence
Root Cause Analysis and CAPA

Basic Example: Enrolled a subject who did not meet all the eligibility criteria

- Initial “root” cause: Human error!
Root Cause Analysis and CAPA

Why did the human make the error?

- Used an Eligibility Checklist that was not consistent with the latest protocol amendment.

  Why? Person who received and processed the protocol amendment did not review it against the Checklist.

  Why? Procedure for processing protocol amendments does not include a step to ‘Review amendment to determine if inclusion/exclusion criteria changed and compare to/revise the Eligibility Checklist.’
Root Cause Analysis and CAPA

- What actions can mitigate the ineligible subject’s enrollment?
- What can correct the cause of the problem going forward?
- What similar issues might occur in the future and what can be done?
Root Cause Analysis and CAPA

Don’t find fault, find a remedy.

- Henry Ford

- This is a good reminder that effective root cause analysis needs to identify the reason(s) an issue occurred, not place blame or just default to 'human error'

- The word "remedy" is a great metaphor for developing and implementing effective corrective and preventive actions that 'cure,' not just bandage, those true root cause(s)
ADDENDUM

The sponsor and investigator/institution should maintain a record of the location(s) of their respective essential documents including source documents. The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.

Essential documents for the trial should be supplemented or may be reduced where justified (in advance of trial initiation) based on the importance and relevance of the specific documents to the trial.

The sponsor should ensure that 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.

When a copy is used to replace an original document (e.g., source documents, CRF), the copy should fulfill the requirements for certified copies.

The investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during, and after the trial.
Section 8 - ESSENTIAL DOCUMENTS

This passage seems to be causing Sponsors a lot of stress

- ICH did previously indicate that the Investigator should have a copy of the CRF
- Impact being seen specifically with EDC studies not paper-based CRFs
- **Tip**: As an investigator, make sure you have access to a readable copy of the complete CRFs at the conclusion of the study
ICH GCP E6(R2): What to Remember

► Clarifications and additional information that is helpful to facilitate compliance
  ➢ No “new” requirements per se
► Repeated emphasis on protecting research subject’s rights, safety and welfare
  ➢ Directly equates “quality” to those objectives
► Importance of oversight, risk management, and record-keeping in more contemporary ways
Questions?
References

- ICH E6_R2, INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE, Current Step 4 version dated 9 November 2016
- EMA/269011/2013 [18 November 2013]: Reflection paper on risk based quality management in clinical trials
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