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Keeping up with Regs: Good Clinical Practice ICH E6(R2) Feb 2018 Integrated Addendum

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- MWA Consulting, Inc. was formerly Marion Weinreb & Associates, Inc. and was sold in 2016 to Bill Daniels.
- MWA offers a full range of consulting services in GMP, GLP, and GCP compliance from development through commercialization.
- Contributed to the approval of over 50 new drugs and devices over the last two decades.
- Associates are highly trained with over 20 years industry experience on average.
- Several hundred associates in our network to help provide client services.
- Work for large and small companies world-wide.
- Flexibility and access to extensive experience without increasing head count.
- Establish infrastructure and operations more quickly and cost effectively.
- Over 75% repeat business.

AGENDA

- Why do we need an addendum to ICH E6?
- Additions to the glossary of terms
- Changes to Investigator responsibilities
- Sponsor responsibilities for quality management
- A risk-based approach
- Computer Systems Validation
- New requirements related to Essential Documents

WHY DO WE NEED AN ADDENDUM TO ICH E6?

- Since the 1996 adoption of ICH E6 GCP, clinical trials have evolved substantially.
- Increases in globalization, study complexity, and technological capabilities.
- Approach to Good Clinical Practice (GCP) needs modernization 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.

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WHY DO WE NEED AN ADDENDUM TO ICH E6

- Modernizing ICH E6 by supplementing it with additional recommendations will **better facilitate broad and consistent international implementation of new methodologies**.
- ICH E6(R1) 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**.

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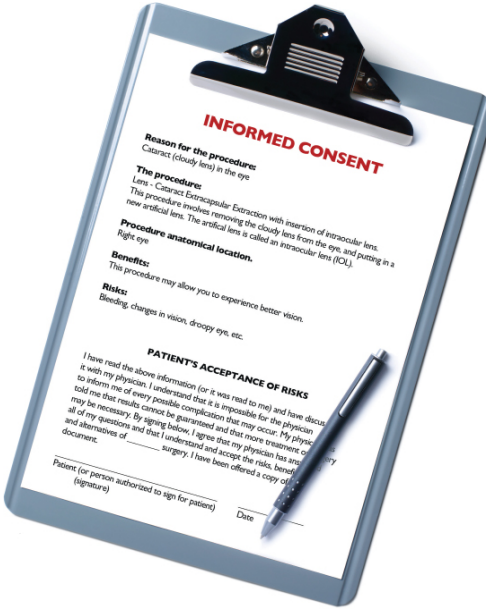
TOP 5 GCP VIOLATIONS

- Protocol adherence
- Clinical records
- Informed consent
- Drug accountability
- Adverse events

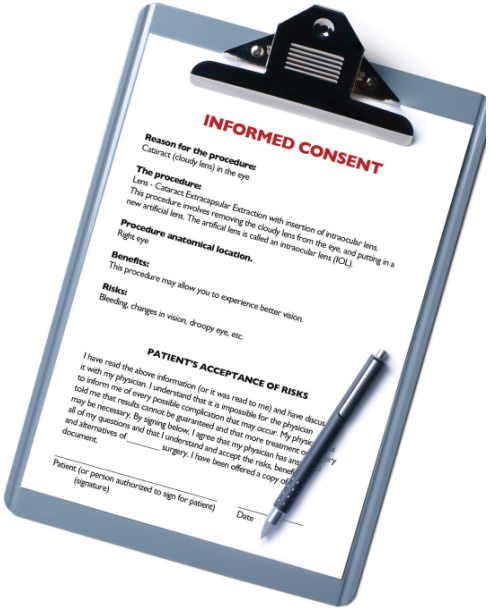
CASE STUDY - INFORMED CONSENT

- The Case of the HPV vaccination project for Informed Consent violations in clinical trials in India
- The States of Andhra Pradesh and Gujarat launched a research project for the vaccination against the human papilloma virus (HPV) in 2009 which causes cervical cancer.
- Adolescent girls between the ages of 10 and 14 in the States of Andhra Pradesh and Gujarat were to be vaccinated. The vaccines were provided by GlaxoSmithKline and Merck.



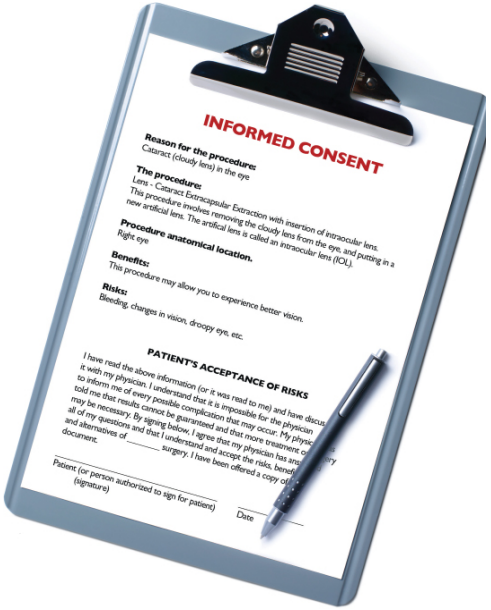
CASE STUDY - INFORMED CONSENT

- The project was designed and executed by PATH (Program for Appropriate Technology in Health) and funding was received from the Bill & Melinda Gates Foundation.
- In April 2010, however, the Government of India suspended the program due to several violations of ethical standards by PATH which were widely reported by human rights organizations but by that time, 24,000 girls were already vaccinated.



CASE STUDY - INFORMED CONSENT

- A parliamentary enquiry committee in 2011, found that the process of informed consent was inadequate (especially questioning the fact that **school headmasters signed consent forms on behalf of the children, calling it wrongful authorization**).
- Informed consent is the process in which trial volunteers are informed about the nature, significance, implications and risks of the trial and their participation in the **trial is voluntary** and hence **cannot be forced to participate in the trial.**



ICH E6(R2) INTEGRATED FORMAT OF THE ADDENDUM

- ICH GCP Guidance Integrated Addendum provides a **unified standard** for the European Union, Japan, the United States, Canada, and Switzerland to facilitate the **mutual acceptance of data from clinical trials** by the regulatory authorities in these jurisdictions
- The addendum supplements ICH E6(R1) with additional text.
- This guideline should be read in conjunction with other ICH guidelines relevant to clinical trial conduct (for example, ICH E2A, E3, E7, E8, E9, and E11).
- In the event of any conflict between E6(R1) text and the addendum text, the **addendum text should take priority**.

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EXAMPLE OF THE INTEGRATED FORMAT OF THE ADDENDUM

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

ADDENDUM

(e) Reports of on-site and/or centralized monitoring 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. Results of monitoring activities should be documented in sufficient detail to allow verification of compliance with the monitoring plan. Reporting of centralized monitoring activities should be regular and may be independent from site visits.

DEFINITIONS

- Certified Copy (section 1.63)

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.

- Monitoring Plan (section 1.64)

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

DEFINITIONS

- Validation of Computerized Systems (section 1.65)

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.

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ICH E6(R2) GCP PRINCIPLES

GCP Principles

E6(R1) 2.10 - All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

ADDENDUM

Applicability of GCP standards to **all records, irrespective of the type of media used** (section 2.10)

ICH E6(R2) GCP PRINCIPLES (CONTINUED)

GCP Principles

E6(R1) 2.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

ADDENDUM

Systems that assure quality should focus on the aspects of the trial that are essential to **human subject protection and reliability of trial results** (2.13)

INVESTIGATOR RESPONSIBILITIES

ICH E6(R2) INVESTIGATOR RESPONSIBILITIES

Investigator Responsibilities

Supervise individuals or parties to whom trial-related duties and functions are delegated (4.2.5).

ADDENDUM

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.

ICH E6(R2) INVESTIGATOR RESPONSIBILITIES (CONTINUED)

Investigator Responsibilities

Ensure individuals and parties are qualified and implement procedures to ensure integrity of study tasks and data (4.2.6).

ADDENDUM

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.

ICH E6(R2) INVESTIGATOR RESPONSIBILITIES (CONTINUED)

Investigator Responsibilities

Maintain adequate and accurate source documents and trial records (4.9.0).

- Source data should be attributable, legible, contemporaneous, original, accurate, and complete.

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).

CASE STUDY - PROTOCOL

- The principal investigator, Dr. Smith, is attending the IRB meeting during the review of a new study protocol ABC-YZ-12-002. Members of the board ask Dr. Smith some questions about the drug and the protocol. Dr. Smith is not able to answer the questions and is not familiar with the contents of the IRB submission documents.

SPONSOR RESPONSIBILITIES

ICH E6(R2) SPONSOR RESPONSIBILITIES

5.0 Sponsor Responsibilities

➢ Implement Quality Management Systems

- For trial activities essential to ensuring **human subject protection** and the **reliability of trial results**
- Include the design of efficient clinical trial protocols, tools, and procedures for data collection and processing, as well as the collection of information that is essential to decision making
- Develop methods that are **proportionate to the risks** inherent in the trial and the importance of the information collected
- Ensure all aspects of the trial are operationally feasible and **avoid unnecessary complexity, procedures, and data collection.** Protocols, case report forms, and other operational documents should be clear, concise, and consistent**.**

ICH E6(R2) SPONSOR RESPONSIBILITIES (CONTINUED)

Quality Management (section 5.0)

ADDENDUM

Use a risk-based approach to the quality management system.

- Identify critical processes and data

5.0.1 Critical Process and Data Identification
During protocol development, the sponsor should identify those processes and data that are critical to ensure human subject protection and the reliability of trial results.

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ICH E6(R2) SPONSOR RESPONSIBILITIES (CONTINUED)

Quality Management (section 5.0)

ADDENDUM

- Identify risks to critical trial processes and data

5.0.2 Risk Identification
The sponsor should identify risks to critical trial processes and data. Risks should be considered at both the system level (e.g., standard operating procedures, computerized systems, and personnel) and clinical trial level (e.g., trial design, data collection, and informed consent process).

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ICH E6(R2) SPONSOR RESPONSIBILITIES (CONTINUED)

Quality Management (section 5.0)

ADDENDUM

- Evaluate risks

5.0.3 Risk Evaluation
The sponsor should evaluate the identified risks, against existing risk controls by considering:
(a) The likelihood of errors occurring.
(b) The extent to which such errors would be detectable.
(c) The impact of such errors on human subject protection and reliability of trial results.

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ICH E6(R2) SPONSOR RESPONSIBILITIES (CONTINUED)

Quality Management (section 5.0)

ADDENDUM

- Control risks

5.0.4 Risk Control
The sponsor should decide **which risks to reduce and/or which risks to accept**. The approach used to reduce risk to an acceptable level should be proportionate to the significance of the risk. Risk reduction activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedures, and training in processes and procedures.

ICH E6(R2) SPONSOR RESPONSIBILITIES (CONTINUED)

Quality Management (section 5.0)

ADDENDUM

- Control risks (continued)

  5.0.4 Risk Control
  Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial results. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

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ICH E6(R2) SPONSOR RESPONSIBILITIES (CONTINUED)

Quality Management (section 5.0)

ADDENDUM

- Communicate risks

5.0.5 Risk Communication
The sponsor should document quality management activities. The sponsor should communicate quality management activities to those who are involved in or affected by such activities, to facilitate risk review and continual improvement during clinical trial execution.

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ICH E6(R2) SPONSOR RESPONSIBILITIES (CONTINUED)

Quality Management (section 5.0)

ADDENDUM

- Review risks

5.0.6 Risk Review
The sponsor should periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience.

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ICH E6(R2) SPONSOR RESPONSIBILITIES (CONTINUED)

Quality Management (section 5.0)

ADDENDUM

- Report risks

5.0.7 Risk Reporting
The sponsor should describe the quality management approach implemented in the trial and summarize important deviations from the predefined quality tolerance limits and remedial actions taken in the clinical study report (ICH E3, section 9.6 Data Quality Assurance).

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ICH E6(R2) SPONSOR RESPONSIBILITIES (CONTINUED)

- Oversee trial-related duties and functions, including those that are subcontracted by Contract Research Organizations (CROs) (section 5.2.2).
- E6(R1) 5.2.2 Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing.

ADDENDUM

The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s).

ICH E6(R2) SPONSOR RESPONSIBILITIES (CONTINUED)

- E6(R1) 5.5.3 When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

  (a) Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation).

ADDENDUM

When using computerized systems, base the validation approach on a risk assessment, maintain standard operating procedures, and ensure data integrity (5.5.3(a) and 5.5.3(h)).

ICH E6(R2) SPONSOR RESPONSIBILITIES (CONTINUED)

ADDENDUM 5.5.3(a)

The sponsor should base their approach to validation of such systems 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.

(b) Maintains SOPs for using these systems.

ADDENDUM 5.5.3(b)

The SOPs should cover **system setup, installation, and use**. The SOPs should describe system validation and functionality testing, data collection and handling, system maintenance, system security measures, change control, data backup, recovery, contingency planning, and decommissioning. The responsibilities of the sponsor, investigator, and other parties with respect to the use of these computerized systems should be clear, and the users should be provided with training in their use.

ICH E6(R2) SPONSOR RESPONSIBILITIES (CONTINUED)

ADDENDUM 5.5.3(h)

Ensure the integrity of the data, including any data that describe the context, content, and structure. This is particularly important when making changes to the computerized systems, such as software upgrades or migration of data.

ICH E6(R2) SPONSOR RESPONSIBILITIES (CONTINUED)

- **Monitoring (section 5.18.3)**
  - Develop a systematic, prioritized, risk-based approach.

ADDENDUM

5.18.3 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).

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ICH E6(R2) SPONSOR RESPONSIBILITIES (CONTINUED)

- **Monitoring (section 5.18.3)**

  - May use varied approaches to monitoring (for example, combination of on-site and centralized monitoring) to improve effectiveness and efficiency.

ADDENDUM

5.18.3 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).

ICH E6(R2) SPONSOR RESPONSIBILITIES (CONTINUED)

- **Monitoring (section 5.18.3)**
  - Centralized monitoring to improve effectiveness and efficiency.

ADDENDUM

5.18.3 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**.

ICH E6(R2) SPONSOR RESPONSIBILITIES (CONTINUED)

- **Monitoring (section 5.18.3)**
  - Review data from centralized monitoring.

ADDENDUM

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.

ICH E6(R2) SPONSOR RESPONSIBILITIES (CONTINUED)

- **Monitoring Report (section 5.18.6(e))**
  - Document results of monitoring activities.

ADDENDUM

5.18.6 (e) Reports of on-site and/or centralized monitoring 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. Results of monitoring activities should be documented in sufficient detail to allow verification of compliance with the monitoring plan. Reporting of centralized monitoring activities should be regular and may be independent from site visits.

ICH E6(R2) SPONSOR RESPONSIBILITIES (CONTINUED)

- **Monitoring (section 5.18.7)**

  - Develop a monitoring plan tailored to the human subject protection and data integrity risks of the trial.

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.

ICH E6(R2) SPONSOR RESPONSIBILITIES (CONTINUED)

Noncompliance (section 5.20.1)

- Follow-up of non-compliance that has or may significantly affect human subject protection or reliability of trial results, by performing a root cause analysis and implementing corrective and preventive actions).

ADDENDUM

Ensure the integrity of the data, including any data that describe the context, content, and structure. This is particularly important when making changes to the computerized systems, such as software upgrades or migration of data.

ICH E6(R2) SPONSOR RESPONSIBILITIES (CONTINUED)

- **Vendor Oversight of Transferred Trial-Related Duties and Functions**
  - Contract Research Organizations (CROs) and other vendors
  - Sub-Contractors contracted by the CRO (e.g. CRAs, Regulatory, Biostats) or vendor (e. g. Drug Depot)

- **Trial Management, Data Handling, Recordkeeping**
  - Validation of electronic systems should be based on a risk assessment and "fit for purpose" or intended use and the potential of the system to affect human subject protection and reliability of trial results.
  - Maintain SOPs for system setup, installation, and use. The SOPs should describe system validation and functionality testing, data collection and handling, system maintenance, system security measures, change control, data backup, recovery, contingency planning, and decommissioning. The responsibilities of the sponsor, investigator, and other parties with respect to the use of these computerized systems should be clear, and the users should be provided with training in their use.

ICH E6(R2) ESSENTIAL DOCUMENTS

8.0 Trial Documents

- 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.

ICH E6(R2) ESSENTIAL DOCUMENTS (CONTINUED)

8.0 Trial Documents

- 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.

SUMMARY

- The integrated addendum has several updated areas, but specifically expanded the Sponsor responsibilities for clinical studies including:
  - Implementing Quality Management during clinical studies
  - Use of a risk-based approach to Quality Management
  - Sponsor monitoring of clinical studies
- New definitions.
- More investigator responsibilities.
- Requirements for computer system validation.
- Additional requirements for essential documents.

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ICH GUIDANCE DOCUMENTS

E6(R1/R2) – GCP With Integrated Addendum

E2a - Clinical Safety Data Management

E3 - Clinical Study Reporting

E7 - Geriatric Populations

E8 - General Considerations For Clinical Trials

E9 - Statistical Principles

E11 - Pediatric Populations

REFERENCES

- FDA 21 CFR Part 11, 50, 54, 56, 312, 314
- FDA BIMO Manual; Sponsors, Contract Research Organizations, and Monitors Chapter 48_Program 7348.810 (April 19, 2017)
- EU Clinical Trial Directive 2001/20/EC
- REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014
- The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
- Annual report of the Good Clinical Practice Inspectors Working Group 2016 EMA/INS/GCP/2018

QUESTIONS

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