



ICH E6(R2) Breakdown by Section

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.

This guideline should be read in conjunction with other ICH guidelines relevant to the conduct of clinical trials (e.g., E2A (clinical safety data management), E3 (clinical study reporting), E7 (geriatric populations), E8 (general considerations for clinical trials), E9 (statistical principles), and E11 (pediatric populations)).

This ICH GCP Guideline 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. In the event of any conflict between the E6(R1) text and the E6(R2) addendum text, the E6(R2) addendum text should take priority.

ICH E6 Section Reference	Section Title	Addendum Text
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.
2.10	The Principles of ICH GCP	All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification. R2 Addendum: This principle applies to all records referenced in this guideline, irrespective of the type of media used.

ICH E6 Section Reference	Section Title	Addendum Text
2.13	The Principles of ICH GCP	<p>Systems with procedures that assure the quality of every aspect of the trial should be implemented.</p> <p>R2 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.</p>
4.2.5	Investigator: 4.2 Adequate Resources	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	Investigator: 4.2 Adequate Resources	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.
4.9.0	Records and Reports	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).

ICH E6 Section Reference	Section Title	Addendum Text
5.0	Quality Management	<p>The sponsor should implement a system to manage quality throughout all stages of the trial process.</p> <p>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.</p> <p>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.</p>
5.0.1	Critical Process and Data Identification	<p>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.</p>

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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, personnel) and clinical trial level (e.g., trial design, data collection, informed consent process).
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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5.0.4	Risk Control	<p>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.</p> <p>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.</p>
5.0.5	Risk Communication	<p>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.</p>
5.0.6	Risk Review	<p>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.</p>

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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).
5.2.2	CRO	Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing. R2 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).

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5.5.3	Trial Mgmt, Data Handling, and Record Keeping	<p>When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:</p> <p>(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). R2 Addendum: 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.</p> <p>(b) Maintains SOPs for using these systems. R2 Addendum: 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.</p> <p>R2 Addendum: (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.</p>

ICH E6 Section Reference	Section Title	Addendum Text
5.18.3	Extent and Nature of Monitoring	<p>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.</p> <p>R2 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).</p>

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5.18.3	Extent and Nature of Monitoring (Continued)	<p>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). 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:</p> <ul style="list-style-type: none"> (a) identify missing data, inconsistent data, data outliers, and 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.

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5.18.6	Monitoring Report	<p>Monitoring Report</p> <p>(a) The monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication.</p> <p>(b) Reports should include the date, site, name of the monitor, and name of the investigator or other individual(s) contacted.</p> <p>(c) Reports should include a summary of what the monitor reviewed and the monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to secure compliance.</p> <p>(d) The review and follow-up of the monitoring report with the sponsor should be documented by the sponsor's designated representative</p> <p>R2 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.</p>

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5.18.7	Monitoring Plan	<p>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.</p>
5.20.1	Non-compliance	<p>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.</p> <p>R2 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.</p>

ICH E6 Section Reference	Section Title	Addendum Text
8.1	Essential Documents for the conduct of a clinical trial - Introduction	<p>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.</p> <p>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.</p> <p>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.</p> <p>When a copy is used to replace an original document (e.g., source documents, CRF), the copy should fulfill the requirements for certified copies.</p> <p>The investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during, and after the trial.</p>

Engage with one of our specialists to find out how we can help your firm become ICH E6 (R2) compliant.

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