ICH E6(R2) to ICH E6(R3) Comparison

ACRP

AREA/TOPC	ICH E6(R2)	ICH E6(R3)
Focus	Risk-based quality management, data integrity, and electronic records	Incorporation of technological advances, patient-centric approaches, and modern trial methods
Glossary	**At the Beginning of the Guidance** Terms Removed: • Approval (in Relation to IRBs) • Contract • Coordinating Committee • Documentation • Opinion (in Relation to IEC) • Original Medical Record • Subject/Trial Subject • Subject Identification Code	**At the End of the Guidance** New Terms Include: • Agreement • Assent • Data Acquisition Tool • Data Integrity • Metadata • Reference Safety Information • Service Provider • Signature • Suspected Unexpected Serious Adverse Reactions (SUSAR) • Trial Participant • Trial Participant Identification Code
Terminology Changes	1. Subjects 2. CRO	1. Trial Participants 2. Service Provider
Terminology and Definition Change	**Source Documents and Data**	**Source Records** - Defined as original documents or data (that include relevant metadata) or certified copies of the original documents or data, irrespective of the media used. This may include trial participants' medical/health records/notes/charts; data provided/entered by trial participants (e.g., electronic patient-reported outcomes (epos); healthcare providers' records from pharmacies, laboratories, and other facilities involved in the clinical trial; and data from automated instruments, such as wearables and sensors.
Definition Change	**Good Clinical Practice** - In E6(R2), GCP is a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate and that the rights, integrity, and confidentiality of trial subjects are protected.	**Good Clinical Practice** - In E6(R3), the description of clinical trial processes and aspects to be assured is changed. GCP is a standard for the planning, initiating, performing, recording, oversight, evaluation, analysis, and reporting of clinical trials that provides assurance that the data and reported results are reliable and that the rights, safety, and well-being of trial participants are protected.

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Terminology and Definition Change	**Essential Documents** - Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.	**Essential Records** - Essential records are the documents and data (and relevant metadata), in any format, associated with a clinical trial that facilitate the ongoing management of the trial and collectively allow the evaluation of the methods used, the factors affecting a trial, and the actions taken during the trial conduct to determine the reliability of the trial results produced and the verification that the trial was conducted in accordance with GCP and applicable regulatory requirements.
Terminology and Definition Change	**Independent Data Monitoring Committee (IDMC)/Data and Safety Monitoring Board, Monitoring Committee, and Data Monitoring Committee** - An independent data monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.	**Independent Data Monitoring Committee (IDMC)** - An independent data monitoring committee (e.g., data safety monitoring board) that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify or stop a trial.
Definition Change	**Investigator** - A person responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals, the investigator is the responsible leader of the team and may be called the principal investigator.	**Investigator** - A person responsible for the conduct of the clinical trial, including the trial participants for whom that person has responsibility during the conduct of the trial. If a trial is conducted by a team of individuals, the investigator is the responsible leader of the team and may be called the principal investigator. Where an investigator/institution is referenced in this guideline, it describes expectations that may be applicable to the investigator and/or the institution in some regions. Where required by the applicable regulatory requirements, the "investigator" should be read as "investigator and/or the institution".
Terminology and Definition Change	**Investigator/Institution** - An expression meaning "the investigator and/or institution, where required by the applicable regulatory requirements."	**Investigator Site** - The location(s) where trial-related activities are conducted and/or coordinated under the investigator's/institution's oversight.
Enhanced Definition	**Investigational Product** - A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged), in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.	Investigational Product - A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled, (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use. ***Investigational products should be considered synonymous with drugs, medicines, medicinal products, vaccines, and biological products.***

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Annexes	N/A	Added to make it easier to add information as new innovations happen. Annex 1 is contained in the main ICH E6(R3) Guideline. Annex 1 contains four sections: 1. IRB 2. Investigators 3. Sponsor 4. Data Governance
Appendices	N/A	NEW - ICH E6(R3) contains three appendices: • Appendix A - Investigator Brochure • Appendix B: Clinical Trial Protocol and Protocol Amendment(s) • Appendix C: Essential Records for the Conduct of a Clinical Trial
Additions, Emphases, and Changes	• Risk-based approach to quality management in clinical trials • Focus on data integrity and management of trial data • Specific guidelines for electronic records and essential documents • Emphasis on sponsor oversight and the delegation of tasks to CROs • Detailed requirements for trial monitoring • Reinforcement of the responsibilities of investigators and sponsors	• Expanded and updated principles to accommodate advances in technology and methodology • Greater emphasis on patient-centric approaches and patient safety • Enhanced focus on risk-based and quality management principles • Incorporation of new methods in clinical trials, including adaptive designs and decentralized trials • Updates to reflect the increasing use of electronic systems and data handling • Enhanced guidance on the use of data from non-traditional sources • Increase focus on transparency and ethical conduct of trials
Principles of ICH GCP *See the "Updated ICH E6 Principles" document for more information on Principle updates.* (Continued on the next page)	Lists 13 principles focusing on ethics, safety, rights of trial subjects, scientific integrity, and quality of data	• Provides an introduction to explain that the Principles of GCP are designed to be flexible and applicable to a broad range of clinical trials. These Principles are intended to support efficient approaches to trial design and conduct. These principles also allow for great use of technology along with a wider and more diverse population of participants. The principles are interdependent and should be considered together to assure ethical conduct and reliable results. • Lists 11 Principles including enhanced focus on patient involvement, risk-based approaches, transparency, and adaptability to technological advancements. Each principle includes sub-bullets providing additional information on how the principle is to be accomplished. • Although there are fewer principles in this revision, none of the previous R2 principles were removed, but combined into these 11 principles.

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Principles of ICH GCP (continued)	Lists 13 principles focusing on ethics, safety, rights of trial subjects, scientific integrity, and quality of data	• In addition, there are two new principles added. ◦ **Risk Proportionality: Principle 7** - Clinical trial processes, measures, and approaches should be implemented in a way that is proportionate to the risks to participants and to the importance of the data collected. ◦ **Roles and Responsibilities: Principle 10, 10.1** - The sponsor may transfer, or the investigator may delegate some or all their tasks, duties, or functions (hereafter referred to as activities), but they retain overall responsibility for their respective activities.
Pillars of ICH E6(R3)	Patient safety and data integrity	• Protecting the rights, safety and well-being of trial participants • Ensuring scientific soundness of the trial design • Conducting the trial with quality and integrity • Upholding ethical principles through informed consent and independent review
IRB/IECs	Details responsibilities, composition, and operations to ensure ethical review of clinical trials	**Responsibilities** • Added: Reasonable reimbursement of expenses incurred by participants, such as for travel and lodging, is not coercive. **Records** • Removed the number of years needed to be retained, and instead lists it as "in accordance with applicable regulatory requirements"
Investigator *(Continued on the next page)*	Details responsibilities for conducting the trial, ensuring compliance and protecting subjects	**Qualifications and Training** • Does not specify how evidence of qualifications should be provided; E6(R2) provided examples **Responsibilities (NEW SECTION in INVESTIGATOR ANNEX)** • Provides specific detail about delegation of trial-related activities and investigator oversight • Outlines need for documented training and documentation of delegation of activities • Documented agreements with service providers **Communication with IRB/IEC** • Give specific examples of reasons to provide updates to IRB, e.g., changes in risk, changes affecting conduct of the study **Participant Medical Care and Safety Reporting** • Added: "Other appropriately qualified healthcare professionals may be involved in the medical care of trial participants, in line with their normal activities and in accordance with local regulatory requirements."

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Investigator
 	
(Continued on the next page)
	Details responsibilities for conducting the trial, ensuring compliance and protecting subjects	**Safety Reporting**
		• 2.7.2 (a) Removed "critical" in from of safety evaluations that should be reported to the sponsor. Also added "Unfavorable medical events occurring in participants before investigational product administration (e.g., during screening) should be considered and reported to the sponsor if required by the protocol.
		• (b) REWORDED - "All serious adverse events (SAEs) should be reported immediately (after the investigator reasonably becomes aware of the event) to the sponsor. The investigator should also include an assessment of causality. In accordance with applicable regulatory requirements, the protocol may identify SAEs not requiring immediate reporting; for example, deaths or other events that are endpoints. Subsequent information should be submitted as a follow-up report, as necessary.
		• (d) ADDED - "The investigator may delegate activities for safety reporting to qualified investigator site staff but retains the overall responsibility for safety of participants under their responsibility and compliance with the reporting requirements."
		
		Informed Consent
		• The section on non-therapeutic trials (E6(R2) 4.18.14) has been removed.
		• New in E6(R3):or
		  ◦ 2.8.10 The informed consent discussion and the informed consent materials to be provided to participants should explain the following as applicable:
		  ◦ ADDED: (m) The follow-up procedure for participants who stopped taking the investigational product, withdrew from the trial, or were discontinued from the trial;
		  ◦ ADDED: (n) The process by which the participant's data will be handled, including in the event of the withdrawal or discontinuation of participation in accordance with applicable regulatory requirements;
		  ◦ ADDED: (v) That trial results and information on the participant's actual treatment, if appropriate, will be made available to them should they desire it when this information is available from the sponsor.

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AREA/TOPC	ICH E6(R2)	ICH E6(R3)
Investigator *(Continued on the next page)*	Details responsibilities for conducting the trial, ensuring compliance and protecting subjects	**End of Participation in a Clinical Trial (NEW SECTION)** **Investigational Product Management** • NEW - Section 2.10.1 - Responsibility for investigational product (including accountability, handling, dispensing, administration and return, rests with the investigator/institution. The sponsor may facilitate aspects of investigational product management (e.g., by providing forms and technical solutions, such as computerized systems, and arranging distribution of investigational product to trial participants). • NEW - Section 2.10.3 - Where the investigator has delegated activities related to investigational product management or aspects of these activities have been facilitated by the sponsor, the level of investigator oversight will depend on a number of factors, including the characteristics of the investigational product, route and complexity of administration, level of existing knowledge about the investigational product's safety and marketing status. • NEW - Section 2.10.8 - The investigational product may be shipped to the participant's location or supplied to/dispensed at a location closer to the participant (e.g., at a local pharmacy or a local healthcare center). The investigational product may be administered at the participant's location by investigator site staff, the participant themselves, a caregiver or a healthcare professional. • NEW - Section 2.10.9 - Investigational product management should be arranged and conducted in accordance with applicable regulatory requirements, and safeguards should be in place to ensure product integrity, product use per protocol, and participant safety. **Randomization Procedures and Unblinding** • ADDED: "In case of emergency, to protect participant safety, the investigator should be prepared and capable from the start of the trial to perform unblinding without undue delay and hindrance." **Records** • ADDED: In generating, recording and reporting trial data, the investigator should ensure the integrity of data under the responsibility, irrespective of the media used. • ADDED: The investigator should be provided with timely access to data by the sponsor and be responsible for the timely review of data, including relevant data from external sources that can have an impact on, for example, participant eligibility, treatment or safety (e.g., central laboratory data, enterally read imaging data, other institution's records, and if appropriate, electronic patient-reported outcome (ePRO) data). The protocol may provide exceptions for access, for instance, to protect blinding.

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Investigator (continued)	Details responsibilities for conducting the trial, ensuring compliance and protecting subjects	**Records (continued)**
		• ADDED: The investigator should ensure that data acquisition tools and other systems deployed by the sponsor are used as specified in the protocol or trial-related instructions.
		• ADDED: The investigator/institution should implement appropriate measures to protect the privacy and confidentiality of personal information of trial participants in accordance with applicable regulatory requirements on personal data protection.
		• ADDED: Data reported to the sponsor should be identified by an unambiguous participant code that can be traced back to the identity of the participant by the investigator/institution.
		• ADDED: For systems deployed by the investigator/institution that maintain and retain trial data/information, the institution should ensure that such data are protected from unauthorized access, disclosure, dissemination or alteration and from inappropriate destruction or accidental loss.
		• ADDED: When using computerized systems in a clinical trial, the investigator/institution should do the following:
		  ◦ (a) For systems deployed by the investigator/institution, ensure that appropriate individuals have secure and attributable access;
		  ◦ (b) For systems deployed by the sponsor, notify the sponsor when access permissions need to be changed or revoked from an individual;
		  ◦ (c) For systems deployed by the investigator/institution specifically for the purposes of clinical trials, ensure that the requirements for the purposes of clinical trials, ensure that the requirements for computerized systems in section 4 are addressed proportionate to the risks to participants and to the importance of the data
		  ◦ (d) Where equipment for data acquisition is provided to trial participants by the investigator, ensure that traceability is maintained and that participants are provided with appropriate training
		  ◦ (e) Ensure that incidents in the use and operation of computerized systems, which in the investigator's/institution's judgement may have a significant and/or persistent impact on the trial data or system security, are to report to the sponsor and, where applicable, to the IRB/IEC
		• REMOVED: Specific number of years required for retention of essential documents. Now stated as "required retention period in accordance with applicable regulatory requirements or until the sponsor informs the investigator/institution that these records are no longer needed, whichever is the longest."
		• ADDED: The investigator/institution should keep the sponsor informed of the name of the person responsible for maintaining the essential records during the retention period; for example, when the investigation site closes, or an investigator leaves the site.

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Sponsor	Describes sponsor responsibilities including trial management, data handling, and ensuring compliance	**Trial Design (Section 3.1)**
		• **Section was redesigned.** Wording added regarding sufficient safety and efficacy data is available to support human exposure by route, at the dosages, for the duration and in the trial population to be studied. Also added wording speaking to incorporating quality into the design and identifying factors critical to quality. Indicates sponsors should consider input from a wide variety of interested parties when developing informed consent and other patient-facing materials as well as ensure that all aspects of the trial are operationally feasible and avoid unnecessary complexity, procedures, and data collection. Emphasizes fit for purpose without unnecessary burden on participants and investigators.
		• **Sections Added:** Resources (Section 3.2), Management (Section 3.10.1), Quality Assurance (Section 3.11.1), Portions of the Monitoring Report (Section 3.11.4.6 (c)), Noncompliance (Section 3.12.2, 3.12.3), Safety Assessment and Reporting (Section 3.13), Insurance/Indemnification/Compensation of Participants and Investigators (Section 3.14), Supplying and Handling Investigational Product(s) (Section 3.15.3), Portions of Data and Records (Section 3.16), Reports (Section 3.17)
		• **Sections that have been reworded but have similar meaning:** Allocation of Activities (Section 3.3), Qualification and Training (Section 3.4), parts of Agreements (Section 3.6), Communication with IRB/IEC and Regulatory Authority(ies) (Section 3.8), Quality Management (Section 3.10), Risk Control (Section 3.10.1.3), Audit (Section 3.11.2), Portions of Monitoring (Section 3.11.4), Portions of Monitoring Plan (Section 3.11.4.3), Portions of Monitoring Report (Section 3.11.4.6 (b))
		
		Significant Changes:
		
		• **Section 3.6 - Agreements -** E6(R2) spoke just to investigator/institution, E6(R3) includes service providers and any other parties (e.g., independent data monitoring committee (IDMC), adjudication committee)
		• **Section 3.6 - Agreements** - No longer states "given approval/favorable opinion by the IRB/IEC"
		• **Sections 3.6.5-3.6.11** - Adds more extensive information on interactions with service providers
		• **Section 3.9 - Sponsor Oversight**
		  ◦ Does NOT list documents requiring approval.
		  ◦ Does NOT list approval required for changes or amendments, ICFs, or modifications.
		  ◦ Does NOT list reapproval, withdrawals, or suspensions.
		• **Section 3.10.1 - Risk Management ADDED** - States that "A proportionate approach to the identification and management of risk is described below."
		• **Section 3.11.1 - Quality Assurance ADDED** - States "Quality assurance should be applied throughout the clinical trial and includes implementing risk-based strategies to identify potential or actual causes of serious noncompliance with the protocol, GCP and/or applicable regulatory requirements to enable their corrective and preventive actions."

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Sponsor	Describes sponsor responsibilities including trial management, data handling, and ensuring compliance	**Significant Changes (continued):** • **Section 3.11.4.5.3 - Monitoring of Investigational Product Management - ADDED** ◦ (a)(ii) - That supplies are sufficient through the trial and are used within their shelf life ◦ (a)(iv) and (v) Added the terms using, destroying, or alternative disposition ◦ (a)(vii) Where product available on the market is dispensed and used in accordance with applicable regulatory requirements, some of the previously outlined considerations may not be applicable.] • **Section 3.11.4.6 - Monitoring Report - ADDED** ◦ (c) - When needed, the report should describe findings requiring escalation for action and resolution. The sponsor should decide on the appropriate action to be taken, and these decisions and the resolution of the actions involved, where needed, should be recorded. • **Section 3.12 - Noncompliance** ◦ 3.12.2 Addition "…confirm their adequacy unless otherwise justified. Where the sponsor identifies issues that are likely to significantly impact the rights, safety, or well-being of the trial participant(s) or the reliability of the trial results (i.e., serious noncompliance), the sponsor should notify the regulatory authority and/or IRB/IEC, in accordance with applicable regulatory requirements, and/or investigator as appropriate." ◦ 3.12.3 Addition - If significant noncompliance is identified on the part of an investigator/institution or service provider that persists despite efforts at remediation, the sponsor should consider terminating the investigator's/institution's or service provider's participation in the trial. In these circumstances, the sponsor should promptly notify the regulatory authority(ies) and IRB/IEC of the serious noncompliance, as appropriate, and take actions to minimize the impact on the trial participants and the reliability of the results. • **Section 3.13 - Safety Assessment and Reporting - NEW** ◦ Includes subsections on: ▪ 3.13.1 - Sponsor Review of Safety Information ▪ 3.13.2 - Safety Reporting ▪ 3.13.3 - Managing an Immediate Hazard • **Section 3.14 - Insurance/Indemnification/Compensation to Participants and Investigators - NEW** • **Section 3.15 - Investigational Product** ◦ NEW - Section 3.15.3 - Supplying and Handling Investigational Product • **Significant Additions to Section 3.16 - Data Handling** ◦ Includes subsections on: ▪ 3.16.1 - Data Handling ▪ 3.16.2 - Statistical Programming and Data Analysis ▪ 3.16.3 - Record Keeping and Retention ▪ 3.16.4 - Record Access

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AREA/TOPC	ICH E6(R2)	ICH E6(R3)
Sponsor (continued)	Describes sponsor responsibilities including trial management, data handling, and ensuring compliance	**Significant Changes (continued):** • **Section 3.17 - Reports** ◦ 3.17.1 ADDITION - "Where appropriate, the sponsor should provide the investigator with information about potential subsequent therapy(ies) and follow-up for the participants." ◦ 3.17.2 (a) ADDITION - …" or an interim analysis is undertaken for regulatory submission...including interim reports. ICH E3 or are otherwise in accordance with applicable regulatory requirements. (NOTE: ICH E3 specifies that abbreviated trial reports may be acceptable in certain cases.)be ◦ 3.17.2(b) ADDITION - "Where a coordinating investigator is involved in a trial, consideration should be given to them being a signatory on the clinical trial report (see ICH E3)."
CRO	Have a separate section dedicated to their responsibilities.	Referred to as 'service providers.' Their responsibilities are intertwined within the Sponsor responsibilities section.
NEW SECTION! Data Governance	Not directly addressed	• Focus on system and data that will impact the safety and rights of participants and reliability of trial results (Section 4) • Discusses the role of safeguarding blinding and reduce the risk of inadvertently unblinded (Section 4.1) • Includes information on data retention, access, and destruction (Sections 4.2.7 and 4.2.8) • Recommends comprehensive approach to computerized systems and tools (Sections 4.3) • Periodic review may be appropriate to ensure computerized systems remain in a validated state throughout the life cycle of the system (Section 4.3.4 (d)) • States a process should be in place to ensure user access and assigned roles and permissions are periodically reviewed (Section 4.3.9 (b))
Clinical Trial Protocol and Amendments	Provides detailed requirements for the content and structure of the protocol	• Focuses on sufficient safety and efficacy data and/or real-world data being available to support human exposure • Incorporating quality into the design of the trial of the clinical trial by identifying factors that are critical to the quality (CtQ) of the trial and by managing risks to those factors • Consideration of a wide variety of stakeholders in support of the development of both the trial plan, protocol, and the informed consent and other participant facing material • Ensuring all aspects of the trial are operationally feasible and unnecessary complexity, procedures, and data collection is avoided. All items (protocol, data acquisition tools, etc.) should be fit for purpose, clear, concise, and consistent. No unnecessary burden should be placed on the participants and investigators.

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AREA/TOPC	ICH E6(R2)	ICH E6(R3)
Risk-Based Approach	• Introduced risk-based monitoring with limited scope • Suggested type of monitoring should match the risks of the trial	• Discusses risk-based approaches in clinical trials inclusive of trial design and conduct • Use of a proportionate approach to the identification and management of risk • Encourages proactive identification and mitigation of risks to patient safety and data quality
Risk Management	• Risk management established as a process • Introduced the concept of Quality Tolerance Limits (QTLs)	• Focuses on risk critical to quality (CtQ) • Stresses need to consider quality and risk management prior to trial initiation • Clarifies that any type or level of risk may have an impact and focus should be on those that have a meaningful impact • Discusses acceptable ranges of risk within Quality Tolerance Limits (QTLs)
Critical Data and Critical Process Identification	Factors affecting critical data and critical processes first introduced	Critical to quality items used to generate discussion on risk management (Section 6.2, 7.3, 3.10, 3.10.1.1, 3.10.1.3, 3.11.4.3, B.12.1)
Innovative Trial Designs	Notes traditional trial designs with some flexibility; focused on conventional randomized, controlled trials	• Provides guidance for adaptive trials, master protocols, and other possible innovative designs • Encourages the integration of real-world data and evidence in clinical trials • Facilitate innovations in trial design, technology, and digitalization
Technology	• Emphasizes electronic records and essential documents • Provides guidelines for eTMF and eDC systems	• Opens the door to digital health technologies, electronic informed consent, decentralized trials, etc. (in more detail) • Addresses mobile health applications and other ways to enhance/encourage participant engagement and understanding
Diversity and Inclusion	Briefly touches on patient diversity	• Emphasizes the importance of inclusion of diverse participant populations to improve the accuracy and usability of trial results • Discusses strategies to enhance recruitment and retention of underrepresented groups to ensure trial results are broadly applicable • Highlights the need to consider multiple demographic factors when designing trials

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Quality Management	Stresses the need for standard operating procedures (SOPs) for trial conduct	• Outlines a systematic approach to quality while integrating risk management and continuous improvement processes • Proportionality and risk-based approaches with focus on quality • Emphasizes the need to focus on quality and risk management throughout the lifecycle of the trial, beginning at trial design, and focus efforts on what matters most • Requires detailed documentation and evaluation of quality management activities
Patient-centric Focus	Centered on trial processes and data integrity	• Great emphasis on patient safety, experience, and engagement throughout the life of their participation in the trial • Encourages consideration of the 'burden on participants' when designing a trial • Supports the use of patient-reported outcome devices and other measures to capture patient perspectives
Essential Records	**1.23 Essential Documents** - Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see section 8. "Essential Documents for the Conduct of a Clinical Trial")	• States careful consideration should be given to sharing records when there are blinding considerations and when records are subject to applicable data protection legislation • E6(R3) recognizes that essential records, including source records, may exist outside TMF or ISF repositories and requires sponsors and investigators to keep track of record locations and version histories

Disclaimer: This Comparison Document is not an all-inclusive list of the line-by-line changes within ICH E6(R3) and is designed to serve as a reference document. Organizations are advised to perform a detailed review of the changes to their quality management system.

For the most accurate and up-to-date information related to clinical research guidelines and regulations—and tools to navigate the ICH E6(R3) changes—please visit the ACRP Guidelines and Regulations Resource Center.