ACT EU workshop on ICH E6 (R3) Principles and Annex 1

Workshop report

19-20 February 2025

An agency of the European Union

Contents

Disclaimer

The report summarises the views expressed by the presenters, experts, and should not be understood or quoted as being made on behalf or reflecting the position of the European Medicines Agency, one of its committees or working parties or the ICH E6 Expert Working Group (EWG).

Introduction

Speakers: Emer Cooke (EMA), Peter Twomey (EMA), Momir Radulović (JAZMP) and Peter Arlett (EMA)

Peter Twomey (EMA) welcomed all participants and panellists.

Emer Cooke (EMA) provided introductory remarks highlighting the significance of the ICH E6 guideline in standardising clinical trial practices across the different countries, stressing the importance of Good Clinical Practice (GCP) in protecting patients and ensuring high-quality data for decision-making.

Momir Radulović (JAZMP) emphasised the European Medicines Agency (EMA) network's commitment to fostering innovation in clinical trials, in collaboration with national competent authorities and the European Commission. He also stressed the significance of the workshop as the first step in implementing the revised GCP guideline, which will come into effect in the European Union in July 2025.

Peter Arlett (EMA) introduced the Accelerating Clinical Trials in the EU (ACT EU) initiative, focusing on the new work plan for 2025-2026. This plan includes maximising the impact of clinical trials through the modernisation of GCP, consolidated advice on clinical trials, and advancements in clinical trial methodologies.

Peter Twomey (EMA) provided technical considerations and the outline of the Day 1 agenda.

Session 1 - Day 1

ICH E6 (R3) - Overview of Renovation and Key Concepts

Speakers: Lenita Lindström (EC), Peter Twomey (EMA) and Gabriele Schwarz (BfArM)

Key messages

- ICH E6 (R3) builds on the quality by design principle, encourages critical thinking, utilises proportionate, risk-based approaches minimising unnecessary complexity and reducing burden on trial participants and Investigators
- **Date coming into effect in the EU:** 23 July 2025

ICH guideline development and legal standing of ICH E6 in the EU

Lenita Lindström (EC) outlined the ICH guideline development process, focusing on the revision of ICH E6 as part of a broad initiative on "GCP renovation". The revision aims to drive the modernisation of clinical trials and reduce unnecessary burden, which aligns with the objective of making the EU a more attractive place for clinical trial conduct. The EU legislation provides that sponsors and Investigators shall take appropriate account of the ICH guideline on GCP and that all trials submitted as part of a marketing authorisation in the EU must have been conducted in accordance with GCP.

Overview of ICH E6 (R3) renovation

Peter Twomey (EMA) provided an overview of the ICH E6 (R3) renovation, explaining its history, reasons for change, and the need for a more flexible, future-proof guideline. Key changes include a new structure with the Principles at its core, Annex 1 replacing guidance previously outlined in ICH E6 (R2), and a dedicated section on data governance within Annex 1. Annex 2 was at the time of the workshop under public consultation.

The guideline incorporates support for new technologies and alternative trial approaches. The Principles outlined in the guideline may be satisfied using differing approaches and should be applied to fit the intended purpose of the clinical trial. Annex 1 and the Appendices, are intended to provide information on how the Principles can be appropriately applied to clinical trials. The guideline, effective 23 July 2025 in the EU, should be read alongside other ICH guidelines, such as ICH E8 (R1) (general considerations for clinical trials), ICH E2A/F (Clinical Safety Data Management/ Development Safety Update Report), ICH E3 (Structure and Content of Clinical Study Reports) and ICH E9 (Statistical Principles for Clinical Trials).

Key concepts of ICH E6 (R3)

Gabriele Schwarz (BfArM) outlined key concepts of ICH E6 (R3), including quality by design, operational feasibility, and the avoidance of unnecessary complexity and burden on trial participants and Investigators. These concepts are interlinked, with quality by design supporting

operational feasibility and well-structured protocols minimising complexity. The revision was driven by the evolving clinical trial ecosystem, including new trial designs, decentralised and pragmatic elements and new technologies. She also emphasised the importance of ensuring that processes and tools are fit for their purpose, carefully aligned with the specific scientific objectives of a trial, while safeguarding the rights, safety, and wellbeing of participants. The presentation also addressed risk-based quality management, introduced in Revision 2 of the GCP guideline and further refined in Revision 3, to support the efficient conduct of clinical trials, with particular emphasis on the value of proportionate approaches that reflect the relative importance of identified risks.

Panel and audience discussion

Moderator: Momir Radulović (JAZMP)

Speakers: Gabriele Schwarz (BfArM), Lisbeth Bregnhøj (DKMA), Peter Twomey (EMA), Rebecca Stanbrook (EFPIA) and Susanne Nørskov (EFPIA)

- **Transition/Implementation period:** Many concepts from E6 (R2) are already in place, and preparation for E6 (R3) can start before 23 July 2025. Regulators, including Inspectors will begin applying the E6 (R3) guideline after 23 July 2025. It is crucial to apply change control activities and consider necessary adjustments. The transition/implementation should be fit-for-purpose and well-considered.
- **Training:** The ICH EWG is currently developing training materials, with the first modules expected towards the end of 2025. Several events are organised by other EU regulatory agencies, and attendees are encouraged to stay connected with their networks for other training opportunities. A customised training approach, informed by existing clinical trial practices, is recommended. Performing a gap analysis to identify priority training needs—and addressing these needs promptly—is particularly important for sponsors implementing decentralised or pragmatic trial designs, or incorporating novel tools and technologies
- **Harmonisation:** Considerable efforts have been made to achieve and maintain harmonisation while acknowledging and accounting for local regulatory requirements. Extensive training and engagement will ensure a harmonised application of the new guideline.
- **Implementation of risk-proportionate approach:** A proportionate approach is necessary, incorporating quality by design and defining critical data. It is important to assess whether each element in the trial design is necessary. Engaging stakeholders and designing practical, feasible trial protocols are essential to prevent overburdening both Investigators and participants. Assessing new information for re-consent is crucial, though it may only apply to new participants.
- **Sponsors' risk-based approach:** Sponsors should provide clear and concise documentation of key decisions and their rationale, especially when deviating from established procedures. This ensures decisions are well-justified and understandable. Significant decisions, such as addressing omissions or non-compliance, should always be documented to explain actions taken. The goal is to create useful documentation that serves its purpose without becoming overly burdensome.

Session 2 – Day 1

ICH E6 (R3) main changes – Investigator oversight

Speaker: Susanne Nørskov (EFPIA)

Key messages

- Responsibilities: Investigators retain ultimate responsibility for delegated activities. Oversight should be proportionate to the importance of the activity, data collected, and risks to participant safety and data reliability.
- Training requirements for delegated activities should be proportionate to the task complexity.

Investigator: Main changes

Susanne Nørskov (EFPIA) introduced the session on key changes from ICH E6 (R2) to ICH E6 (R3), focusing on the Investigator section. The new structure of ICH E6 (R3), includes Investigator roles and responsibilities in section 2 of Annex 1.

- **Qualifications and training:** It was clarified that regarding expected evidence for the Investigator and delegated team members' qualifications, proportionate flexibility outlined in ICH E6 (R3) should be considered. For example, training requirements for delegated activities should be proportionate to the task complexity, taking into consideration routine medical care.
- **Safety reporting:** Adverse events and/or abnormal test results should be reported to the sponsor according to the reporting requirements and within specified protocol timeframes. Unfavourable medical events before investigational product administration should be considered and reported as well, when required by the protocol.
- **Responsibilities:** The Investigator retains ultimate responsibility for persons or service providers to which they delegate activities. The concept of proportionate Investigator oversight is determined by the delegated activity, the importance of the data collected and risks to trial participant safety and data reliability.
- **Early trial end:** When participants withdraw or are discontinued, the Investigator should appropriately follow the protocol and adhere to instructions to prevent data loss and ensure trial validity in line with applicable requirements.
- **Investigational product management:** Investigators are responsible for oversight of investigational products, with adjusted procedures for products with limited safety data. Investigators should be able to perform unblinding in case of emergencies to protect participant safety.
- The term "**supervision**" has been replaced with "**oversight**". Oversight levels should be proportionate to the importance of the data and the risks to participant safety and data reliability.

Panel and audience discussion

Moderator: Rebecca Stanbrook (EFPIA)

Speakers: Denis Lacombe (EORTC), François Houÿez (EURORDIS), Gabriele Schwarz (BfArM), Monique Al (CTCG/CCMO), Pirkko Lepola (EnprEMA) and Susanne Nørskov (EFPIA)

- **Investigator oversight of external service providers:** When a service provider is contracted by the sponsor on behalf of the Investigator, for example a Home Nurse, the Investigator should have appropriate oversight of this person. The sponsor should provide sufficient information to allow the Investigator to evaluate the suitability of this person for undertaking this delegated task.
- **Data endorsement by the Investigator and Investigator decision-making**: The key issue for consideration is whether data points should be sent directly to the Electronic Data Capture (EDC) system without Investigator endorsement, or if Investigators should manually review all data. Allowing participants to submit data directly without healthcare professional oversight raises concerns about data quality and the impact on medical decision-making. On the other hand, requiring Investigators to validate all data could lead to an overwhelming influx of information, making timely assessments impractical. To address this, data should be aggregated and presented in a manageable, actionable format, enabling Investigators to focus on key clinical decisions when endorsing.

Session 2 (continuation)

ICH E6 (R3) main changes – Informed consent

Speakers: Gabriele Schwarz (BfArM), Denis Lacombe (EORTC) / François Houÿez (EURORDIS)

Key messages

- Avoidance of unnecessary complexity and greater clarity in the informed consent form is emphasised.
- Proportionate consent processes should remain relevant and appropriate throughout the trial, especially with new forms of clinical trials emerging.
- Varied approaches in the informed consent process may be used; considerations should be made for re-consent based on trial stage and relevance.
- Age-appropriate assent for minors should be provided and discussed and a process for consent should be considered if the minor reaches the age of legal consent during the trial.

Setting the scene

Gabriele Schwarz (BfArM) presented the key considerations in the ICH E6 (R3) guideline with regards to the informed consent process and information provided. She emphasised the

importance of a clear, concise, and participant-friendly informed consent process which should use simple language and avoid unnecessary complexity, ensuring accessibility for diverse populations. The guideline allows for the use of various formats such as text, images and interactive tools, with both paper-based and electronic options permitted. Where appropriate, remote consent may be considered.

Informed consent should be obtained prior to trial participation, ensuring it is freely given and fully understood. The Investigator is required to sign after the consent by the participant has been provided. Consent should always be voluntary, with no waivers of legal rights. Provisions are made for minors, incapacitated individuals, and emergency situations in accordance with applicable regulatory requirements. Re-consent should be considered when appropriate, and participants should be able to withdraw without undue influence, with clear communication between the Investigator and participant during the withdrawal process. These updates reflect input from public consultation, ensuring they align with ethical standards and evolving regulatory requirements.

Informed consent

Note: the views provided below are insights on challenges and opportunities of the informed consent process. These are not requirements as outlined in ICH E6 (R3).

Denis Lacombe, of the EORTC, underscored the importance of bringing clinical trials closer to real-life clinical practice. He pointed out the increasing complexity of clinical trials and the need for simpler designs to ensure quality and reduce the burden on trial sites and participants.

Denis Lacombe emphasised the integration of real-world data and pragmatic practices into clinical trials, highlighting the necessity of incorporating evolving trial practices into routine clinical care. He discussed the potential for improving informed consent through technological advances and interactive communication solutions, aiming to enhance trial accessibility and convenience.

He raised concerns about maintaining the accessibility and simplicity of informed consent in complex trial designs, suggesting that consent discussions should focus on the additional risks posed by the trial rather than those from routine clinical practice.

Denis Lacombe proposed a staggered approach to providing trial and consent information, reducing the volume given at any one time to avoid overwhelming participants.

François Houÿez, EURORDIS, presented key insights on the topic on informed consent from a patient's point of view. He started by emphasising the importance of a three-step informed consent process (explaining, obtaining and documenting), which can be facilitated through both paper and electronic formats. This approach aims to make the consent process more accessible and understandable for participants. As clinical trials become more complex, the traditional methods of providing written information for consent can be overwhelming. Technological advances such as e-consent and video conferencing have the potential to make the consent process more accessible and convenient. However, it is essential to balance convenience with the integrity of the consent process. Additionally, he proposed a dynamic consent model, where participants receive less information at the start and more as the trial progresses. This method helps prevent information overload and ensures participants remain informed throughout the trial.

Mr. Houÿez stressed the importance of securing data already collected if a participant withdraws consent, maintaining the integrity of the trial while respecting the participant's decision. Clear communication about the legal value of consent is crucial. Participants need to understand what

they are agreeing to and the implications of their consent. Finally, the need for proportionate consent processes that remain relevant and appropriate throughout the trial was highlighted.

Panel and audience discussion

Moderator: Peter Twomey (EMA)

Speakers: Denis Lacombe (EORTC), François Houÿez (EURORDIS), Gabriele Schwarz (BfArM), Hilde de Keyser (CFE), Monique Al (CTGG/CCMO), Petr Szturz (EORTC) and Sally Hofmeister (WDO CAB)

- **Innovative approaches to informed consent**: The panel discussed the benefits and challenges of incorporating new technologies like e-consent, videos, and virtual reality in clinical trials. These innovations can improve information standardisation and reduce patient burden, but they also raise concerns about accessibility, infrastructure, and technical compatibility. Flexibility in consent options and clear, simple language are essential, as is ensuring participants can raise any questions during the whole process.
- **Technology and inclusion in clinical trials**: The importance of age-appropriate informed consent was emphasised, with a focus on simple language, visuals, and interactive tools. For paediatric participants, approaches such as role-playing and using images were suggested, while legal and ethical considerations, including national regulations, should be carefully addressed. Concerns were raised about the intended exclusion of older individuals due to technological barriers. A collaborative approach between sponsors, Investigators, ethics committees and patients is essential to developing fit-for-purpose informed consent processes.

Session 3 – Day 1

ICH E6 (R3)– Overview of draft ICH E6 (R3) Annex II

Speaker: Andrew Thomson (EMA)

Key messages

- Annex 2 should be read in conjunction with the ICH E6 (R3) Principles and Annex 1 document
- It addresses the GCP considerations that arise from the increased use of a wider range of design elements and data sources and has its foundations in the key concepts of quality-by-design, fitness for purpose and risk proportionality
- Annex 2 is anticipated to be adopted in the second half of 2025

Draft ICH E6 (R3) Annex II update

Andrew Thomson (EMA) introduced the ICH E6 (R3) Annex 2, under public consultation at the time of the workshop, which provides guidance on integrating decentralised and pragmatic

elements and real-world data (RWD) into clinical trials. Annex 2 should be read in conjunction with ICH E6 (R3) Principles and Annex 1. The focus of Annex 2 is on practical considerations for using various design elements and data sources, with an emphasis on Investigator and sponsor oversight in trial management, including the management of investigational products. It also outlines specific considerations for RWD, highlighting the sponsor's responsibility to apply special care depending on how the data is collected and its acquisition process. Key aspects of safety assessment and reporting are emphasised, as well as the importance of effective communication with institutional review boards and independent ethics committees and addressing informed consent considerations. Annex 2 further underscores the need for engagement and communication between sponsors, patients, patient advocacy groups, healthcare professionals, Investigators, and regulatory bodies. The consultation phase aims to refine the framework, with finalisation expected in 2025. The goal is to ensure the guideline remains fit-for-purpose and aligned with emerging trial designs that safeguard participant rights and enhance data reliability.

Session 4 – Day 1

ICH E6 (R3) – The role of Community Advisory Boards (CABs) and patients

Speakers: François Houÿez (EURORDIS), Hilde de Keyser (CFE), Sally Hofmeister (WDO CAB)

Key messages

- Community Advisory Boards (CABs) play an important role in making clinical trials more patient-centred, enhancing feasibility, and minimising patient burden.
- Sponsors benefit from patient feedback, leading to better trials. Increased visibility through publications and conferences strengthens CAB adoption.

Meaningful engagement of patients in clinical trials: Community Advisory Boards

The panel began with François Houÿez explaining the role of Community Advisory Boards (CABs) in clinical research. Hilde de Keyser (Cystic Fibrosis Europe (CFE) CAB) and Sally Hofmeister (World Duchenne Organisation (WDO) CAB) then introduced their respective CABs, outlining their structures and impact.

- **Role of Community Advisory Boards (CABs) in clinical trials:** CABs may play an important role in ensuring that clinical trials are patient-centred, improving feasibility and reducing patient burden. Their early involvement allows them to contribute to trial design, and communication is key in facilitating this process effectively.
- **CAB impact:** measuring the impact of CABs remains complex due to the nature of clinical trials, but tools like decision trackers, surveys, and post-trial assessments help determine whether sponsors implement their recommendations. CABs may influence trial designs including the number of interventions, ensuring that unnecessary procedures are eliminated to enhance the patient experience. One key indicator of success is when future trials incorporate CAB feedback, leading to more efficient and patient-friendly research.

- **Examples of success:** CABs have successfully contributed to reducing invasive procedures, introducing decentralised trial elements like home nursing, refining clinical endpoints, and advocating for more inclusive trial designs. Their collaboration with multiple sponsors is an ongoing learning process that facilitates knowledge-sharing across the industry, helping to standardise best practices and improve trial development.
- **Independence, transparency and governance**: Maintaining independence is critical for CAB credibility. Strict policies ensure that sponsors have no influence over CAB member selection, with patient organisations nominating representatives.
- **Interactions with regulators**: While CABs do not communicate directly with regulators, they provide structured feedback through formal letters on specific topics.
- **Training and capacity building**: Training is encouraged but not always a prerequisite for joining a CAB. A combination of formal education, mentorship from experienced members, and hands-on learning ensures that CAB representatives are well-equipped to engage effectively with stakeholders. This balance helps maintain both expertise and fresh perspectives within the group.

Session 5 – Day 1

Interactive Q&A on all sessions on revised ICH E6 (R3)

Summary of Q&A

- **Proportionate oversight and risk-based approach:** A central theme was the need for proportionate oversight in clinical trials, especially in the context of audits and inspections. Emphasis was placed on ensuring that trial sponsors clearly communicate and justify their risk-based approach.
- **Subcontracting, delegation, and Investigator responsibilities**: The importance of clear agreements and oversight measures when subcontracting activities in clinical trials was a major point of discussion. Sponsors and Investigators need to ensure that all parties, including subcontracted service providers, are appropriately overseen. Challenges were reported when activities were delegated to external providers, such as Home Nurses, and the responsibility for oversight became blurred. The need for clear delegation documentation and communication was stressed, as well as defining the expectations around Investigator oversight for external parties. Appropriate training, contracts, and pre-qualification of service providers were seen as essential to maintain effective oversight.
- **Data governance and integration in clinical trials:** The importance of data governance and efficient data management in clinical trials was raised, with a focus on integrating source data management systems. The potential benefits of such integration, including increased efficiency and reduced errors, were acknowledged, but so were the risks related to data integrity and confidentiality. The need for validation of processes to ensure accurate data transfer and quality was emphasised. Furthermore, the terminology-change in the guideline from 'documents' to 'records' in relation to data management was discussed, with an emphasis on the hybrid nature of most trial master files (TMFs), which often span multiple systems. However, it was emphasised that there was no intention to materially change what was in the TMF due to the terminology change. Sponsors are

expected to ensure that all relevant data, whether from electronic health records or laboratory systems, were properly indexed and integrated into the trial oversight process.

- **Ethics Committee assessment of clinical trial applications:** The discussion highlighted the challenges in harmonising ethical oversight across Europe, particularly regarding the Clinical Trial Regulation (CTR). Regulators are preparing for the implementation of ICH E6 (R3) through training, impact assessments, and guideline reviews to ensure a proportionate and risk-based approach. The conversation touched on discrepancies between what information and/or documents were required by ethics committees and what was feasible under the current systems. There was recognition that, despite efforts for harmonisation, discrepancies persisted across member states, potentially creating conflicts when ethics committees verified compliance with the regulation.

Opening remarks day 2

Peter Twomey (EMA), Kim Pietsch (EMA)

The speakers welcomed all participants, outlined the sessions of the day, and clarified that questions were requested and collected prior to the workshop and therefore a not only live questions were and will be addressed.

Session 1 - Day 2

ICH E6 (R3) main changes - Sponsor oversight and data governance

Speakers: Rebecca Stanbrook (EFPIA), Lisbeth Bregnhøj (DKMA) and Gabriele Schwarz (BfArM)

Key messages

- Focus on critical to quality factors throughout the course of a clinical trial
- Emphasis on not placing unnecessary burden on participants and Investigators
- Apply data integrity and metadata throughout the data life cycle
- Apply proportionate approaches towards computerised system responsibilities

Sponsor: Main changes

Rebecca Stanbrook (EFPIA) highlighted key updates in ICH E6 (R3) regarding trial design and sponsor oversight. Sponsors are now explicitly responsible for ensuring sufficient resources to properly oversee trials. The focus in trial design is on clarity, defining the research question, and collecting only essential data, adhering to the principle of "quality by design." Sponsors are encouraged to determine critical to quality factors and the associated risks, focussing their attention on important data affecting participant safety, rights and well-being and trial results. Engaging patients and "interested parties" such as patient groups and health care professionals early in the design phase is crucial. There is also a push for alignment between all trial-related documents to avoid discrepancies. Sponsor oversight is now formally included, focusing on the assurance of participants' rights, safety and well-being and the reliability of trial results, meaning focussing on those important data points. This focus is rooted in the application of a risk-based and proportionate approach in trial design and conduct.

Specific points raised included:

- Sponsors should ensure clear roles and responsibilities and that appropriate agreements are in place to document them where necessary.
- The protocol encourages a flexible approach with acceptable ranges to facilitate focus on the data that matters most.
- Proportionality is emphasised, including with investigational products already authorised for the market.
- Sponsors are responsible for ensuring data integrity, particularly around randomisation and blinding.

- Monitoring strategy should consider factors such as the trial purpose, design, blinding, safety profile, and endpoints that have the most potential to impact participant rights, safety and well-being in line with the risk proportionate approach for that investigational product in that participant population.
- Timely, clear documentation is stressed, including clinical trial reports and timely filing of essential records in the trial master file as its maintenance can support oversight activities.
- Simplification of processes and reduction of unnecessary burdens on participants and Investigators is a priority.
- Protocol deviations should be assessed carefully, distinguishing between those that impact trial integrity and those that don't.

In conclusion, the focus is on a proportionate approach throughout the trial, ensuring participant safety and the reliability of results, with clear roles and responsibilities, appropriate processes for managing data and the input from relevant parties in the design of the trial.

Data Governance

Lisbeth Bregnhøj (DKMA) highlighted the importance of reading this new section along with the re-written Investigator and sponsor responsibilities. The guideline prioritises fit-for-purpose computerised systems, efficient record management, and introduces new key glossary terms for data integrity, acquisition tools and metadata as well as clarifying that an audit trail is one kind of metadata. The new data governance section guides the responsible parties (i.e. Investigators and sponsors) in managing data integrity, covering e.g. data protection, computerised systems and essential elements like randomisation and blinding. Data governance should span the full data and system lifecycle, ensuring appropriate data and metadata review and data correction procedures.

The sponsor should ensure that their computerised systems meet expectations in a risk-proportionate manner. They should assess whether the systems used by the Investigator are fit for the trial. If the Investigator implements systems specifically for the trial, they should address and apply expectations in the data governance section proportionally.

In section 2.12 it is reported that the Investigators are responsible for data integrity for their data. They should ensure that data acquisition tools and other systems deployed by the sponsor are used as specified in the protocol.

In section 3.16.1 it is reported that sponsors should ensure data integrity, e.g. by applying quality control to critical data and metadata, pre-specifying collected data and ensuring the safeguarding of the blinding. Sponsors should not modify Investigator or trial participant data unless justified and documented and after receiving Investigator approval, ensuring timely corrections to prevent bias. Sponsors should manage data preparation steps like cleaning, coding, and locking the database, adapting processes for interim and final analyses. They must oversee computerised systems, ensuring validation, audit trails, security, and proper user access aligned with Investigator delegations. Sponsors should develop a statistical analysis plan unless the protocol fully covers it. Statistical programming and analysis require traceability, documented deviations, and protection against unauthorised changes.

Panel and audience discussion

Moderator: Spiros Vamvakas (EMA)

Speakers: Gabriele Schwarz (BfArM), Lisbeth Bregnhøj (DKMA), Rebecca Stanbrook (EFPIA), Denis Lacombe (EORTC) and Jan Geissler (Patvocates)

- **E-tools and patient's perspective**: From a patient perspective, using technologies in trials can provide valuable insights into symptoms and disease burden. However, it's crucial to consider the return on engagement for patients. ICH E6 (R3) now includes a strong recommendation to engage stakeholders, participants, and healthcare professionals in designing tools to ensure they are fit for purpose. Engaging patients and healthcare professionals in e-tool development is key to ensuring they are appropriate. Ensuring inclusivity and simplicity in technology is an important consideration.
- **Electronic systems validation:** The responsibility for validating sponsor systems lies with the sponsor, not the Investigator. The Investigator's role is to use the systems as intended, report who needs access, and report any incidents, but not to validate the system itself. In cases where the sponsor is also the Investigator, they would have the responsibility to choose a system that is fit for purpose, including validated, as appropriate.
- **Oversight of the Investigator on data integrity**: The expectation is not to have continuous signoffs for each eCRF page. Instead, the focus is on key milestones where the Investigator acknowledges the data and endorses its completeness and accuracy. Investigator oversight can also be maintained through other means, such as reviewing reported data to check for misunderstandings by staff. It should be ensured that the Investigator has enough time to review data, identify issues, and take corrective or preventive actions, particularly when data is missing or entered incorrectly.
- **GCP requirements and service providers**: If existing systems and processes meet the required standards and criteria, use of these may be deemed acceptable without the need to develop separate systems specifically for clinical trials. The sponsor needs to assess whether the service provider's system, including procedures and processes, is adequate in the clinical trial context.
- **Statistical considerations:** If the details and considerations are sufficiently described in the protocol, there may be no need for a separate statistical analysis plan. However, the protocol should in this case fulfil the expectations of a statistical analysis plan e.g. clearly outline the statistical intent, specifying the analysis type and how the data will be used. This ensures the analysis aligns with the data and methodology for valid conclusions. Regarding the numerous coding and programming tasks usually involved in a clinical trial, a risk-proportionate approach to coding and appropriate QC measures should be taken.
- **Sample size:** This should be justified in the protocol and the calculations documented.
- **Timeline for clarifying data reported by trial participants or Investigators**: The guideline emphasises that corrections should be supported by source data recorded around the time of the event to avoid recall bias and manipulation of data.

Session 2 - Day 2

ICH E6 (R3) main changes – Essential records and safety management

Speakers: Susanne Nørskov (EFPIA), Gabriele Schwarz (BfArM), Elke Stahl (chair of the safety-CTCG subgroup), Rebecca Stanbrook (EFPIA), Petr Szturz (EORTC)

Key messages

- Updated guidance on what makes a record essential; and on the content and maintenance of such records
- Revised new safety information and glossary terms

Essential records

Susanne Nørskov (EFPIA) reported that records in clinical trials, according to the new guideline, are documents and data that ensure the evaluation of trial methods and verify compliance with regulatory standards. These records are necessary for reliable results, maintaining data integrity, and supporting informed decision-making throughout the trial. As per Principle 9 of ICH E6 (R3), both sponsors and Investigators are responsible for ensuring that essential records are accessible and well-maintained, with appropriate safeguards against unauthorised access and accidental destruction. Appendix C of ICH E6 (R3) clarifies the types of essential records that should be maintained, including records related to safety, trial conduct and participant data. It further stresses that Investigators should be prepared to ensure these records are accessible and readable throughout the retention period. The Essential Records Table in the guideline offers a useful tool to distinguish essential records according to their purpose and regulatory requirements. The process of identifying, maintaining, and securing essential records is vital for clinical trials, supporting both the transparency of the trial and the reliability of its outcomes.

Safety management

Gabriele Schwarz (BfArM) highlighted that participants' safety should be reviewed in a timely manner when new information emerges which could have an impact on their safety, their willingness to continue their participation, or have an impact on the conduct of the trial, as emphasised in Principle 1 of ICH E6 (R3). The guideline now addresses unfavourable medical events occurring before investigational product administration, such as during the screening phase. Furthermore, it clarifies the term "immediate" in relation to the reporting of serious adverse events (SAEs) by Investigators to the sponsor and emphasises the requirement to include a causality assessment in these reports. Sponsors should review new safety information promptly and update relevant trial documents, such as protocols, Investigator's brochures and informed consent forms, as needed. Additionally, sponsors should ensure that Investigators have timely access to safety-related data, including data from external sources, to enable them to make informed decisions about the safety of participants. The updated guideline also includes a more detailed definition of key safety terms like Adverse Drug Reactions (ADR), SAEs and Suspected Unexpected Serious Adverse Reactions (SUSAR). It clarifies the level of certainty required to classify an ADR and the implications for reporting and safety assessments. Finally, sponsors may

consider establishing an Independent Data Monitoring Committee (IDMC) to evaluate trial progress and safety data at regular intervals.

Panel and audience discussion

Elke Stahl (chair of the safety-CTCG subgroup), Gabriele Schwarz (BfArM), Rebecca Stanbrook (EFPIA), Petr Szturz (EORTC), Susanne Nørskov (EFPIA)

- **Terminology changes in clinical trial records:** The terminology change from "reconstruction" to "appropriate evaluation" reflects the importance of maintaining records that facilitate the evaluation of trial conduct rather than attempting to reconstruct past events.
- **Impact of revision on essential records and Investigator files:** There is a focus on the evolving nature of essential records, particularly regarding the trend of increased volume of TMFs and Investigator site files. The discussion underscores the need for a proportionate approach to organising, accessing and managing these records, considering the use of existing models and the adoption of electronic tools. The concern about fragmentation and inefficiency in handling records across different sponsors and systems was highlighted.
- **Defining essential records:** The panel discussed the importance of understanding what qualifies as essential to a clinical trial, suggesting that not all records need to be kept. Factors such as trial risk, the nature of the investigational product, and the type of trial (e.g., low-risk trials) influence what should be considered essential. There was agreement that essential records should be those critical to trial conduct, with the flexibility to adapt based on the trial's specific needs.
- **Risk-based and proportionate approach:** The difference between "risk-based" and "risk-proportionate" approaches was clarified. A risk-based approach focuses on identifying critical factors in the trial design and mitigating those risks, while the risk-proportionate approach tailors mitigation efforts to the severity and probability of risks. This distinction is important for determining how much effort and resources should be invested in addressing specific risks.
- **Safety reporting and EU legislation:** The panel emphasised that relevant EU regulations, such as the CTR, take precedence over guidelines like ICH E6 (R3) in safety reporting. The need for proportionate approaches in safety reporting, based on the current knowledge of the safety profile of the investigational product in relation to its specific use in a clinical trial, was also highlighted. The panel clarified that while the Important Medical Event (IME) terms list can serve as a reference to support decision-making, it is not a binding or definitive checklist, as the assessment of IMEs depends on the specific safety profile and stage of development of a clinical trial.
- **Mitigation measures for non-validated electronic health records:** The panel addressed the challenges of using non-validated electronic health records (EHRs) in clinical trials and the practice of printing and signing medical records as a compliance measure. While such mitigation strategies have been used, inspectors emphasised that direct access to source data is essential for monitoring, auditing, and inspections, as discrepancies in source data are frequently identified. Although some EHR systems lack the necessary functionality to restrict access to trial participants' data, sponsors and system owners should work towards solutions that ensure compliance while maintaining data integrity. The overarching goal remains to transition towards EHR systems that are

fit for clinical trials, and while temporary measures may be accepted out of necessity, they will still be considered deviations, reinforcing the need for improved electronic systems across institutions and regions.

Closing remarks

Peter Twomey (EMA)

Peter Twomey closed the event by thanking everyone for their participation, highlighting the high attendance and collaborative effort in revising the ICH E6 guideline to ensure its relevance for future trials. He emphasised the importance of proportionality, risk-based approaches, and patient-centred guidance. He expressed gratitude to the speakers, panellists, and EMA staff for their contributions and encouraged participants to complete the survey, submit comments on Annex 2 and look for the event recording and upcoming training.

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