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association for **clinical data management**

Highlights from ICH E6 R3

Annex 2

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On June 3, 2026, ICH published the eagerly awaited GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R3) Annex 2. This guideline applies to clinical trials and is not required for non-interventional studies.

The guideline stresses that Good Clinical Practice (GCP) as outlined in ICH E6 (R3) Principles and Annex 1 still apply, but that Annex 2 is intended to provide additional considerations for trials that include decentralised elements, pragmatic elements and/or real-world data (RWD). These elements are referred to as methodologies for the remainder of the guideline Another notable topic is the acknowledgement that sponsors might incorporate participation of local healthcare providers (HCP) to support the primary investigator and improve participant access to trials.

Overall, the document signals that trial designers must employ a Quality by Design (QbD) approach, as outlined in ICH E6 R3 Principles and Annex 1, that ensures the methodologies are fit for purpose and will generate data that can support decision making. QbD should also assess the impact on the participant, including their ability to utilize the technology and what participant burdens might need to be mitigated.

In addition to requiring a QbD approach, trial teams should utilize a risk proportionate approach which considers the critical to quality (CTQ) factors of the trial; participant safety and welfare and data integrity. When determining risk teams should consider the intended use of the data generated by the methodology. Those methods used to collect endpoint data represent a higher level of risk than those used to collect non-CTQ data. Teams should also proactively engage participants in trial design and assessing feasibility of methodologies.

The guideline provides expectations for the Investigator and Sponsor when using these methodologies. Several of these expectations also impact data managers directly or indirectly including:

2.2 Informed Consent Considerations

2.4 Investigator Oversight of Healthcare Providers

2.5 Safety Assessment and Reporting

3.1 Engagement and Communication

3.2 Protocol and Trial Design

3.4 Access to and Use of RWD

3.5 Data Considerations

3.7 Privacy and Confidentiality Considerations

3.8 Sponsor Oversight

3.9 Safety Assessment and Reporting

Data managers should view Annex 2 as a signal to shift from a retroactive clinical data management role to a proactive role as clinical data scientist, providing input on design strategies. The Data Manager role is now even more key in protocol planning discussions to ensure they can provide input on assessing methodologies to identify risks and ensure approaches are feasible and fit for purpose.

The DMEG also recommends that data managers review existing SOPs, TMF plans and document templates to ensure they align with Annex 2 expectations. In addition, the DMEG recommends reviewing related FDA guidance on Digital Health Technologies for Remote Data Acquisition in Clinical Investigations and Conducting Clinical Trials With Decentralized Elements for additional requirements for US trials. For Canadian trials we recommend review of Health Canada's GUI-0100: Good clinical practices and Draft guidance on decentralized clinical trials.

Annex 2 briefly discusses expectations for managing access to RWD (section 3.4 Access to and Use of RWD) and ensuring it is reliable and relevant (section 3.5.1 RWD Considerations). These are discussed at a high-level in Table 1 below, but the DMEG recommends teams using RWD review the EMA reflection paper on non-interventional studies which discusses the evaluation of real-world data to assess fitness for use and the FDA Guidance on Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products. These documents provide greater detail on these topics.

Additional details on these points and ACDM DMEG recommendations for implementation by data management are provided in Table 1 below.

Section # and Title	Section guidance	DMEG recommendation for data managers
2.2 Informed Consent Considerations	The guideline recognizes that Informed Consent may be obtained remotely. However, the trial designers must ensure the method used is fit for use. This includes considering the trial population characteristics that might impact their ability to gain access to or use the systems. Trial designers must also ensure that where appropriate all local regulations are followed.	While data managers do not usually own the Informed Consent process, we may assist in selecting the tools used to obtain consent and any integrations with other systems. Data managers should provide insight into potential risks and barriers including participant ease of use.
2.4.1 Investigator Oversight of Healthcare Professionals Conducting Trial Activities Within Usual Clinical Practice	The guideline recognizes that local healthcare professionals (HCP) may perform some trial related activities. When this occurs, the Investigator is still responsible for overseeing the activities of the local HCP. To facilitate this there must be documented agreements on how data are shared, records retained, data privacy is maintained and the mechanisms for ensuring data integrity.	Data managers should ensure that the DMP and other project plans clearly define roles and access to data and systems used by HCPs. Access considerations should include data privacy and methods for ensuring data quality and integrity.
2.5 Safety Assessment and Reporting (see also Annex 2 3.9 and Annex 1 3.13.2)	The guideline notes that safety information generated through decentralized methodologies must be provided to the Investigator so that they can make decisions related to participant care and safety.	When designing data collection tools including the EDC and DHT, the data manager must consider how safety information can be provided to the Investigator in a complete and timely manner. This includes the initial design of tools, access, rights, and roles as well as reporting processes. Data managers should consider the timing of EDC to central lab and other external data reconciliations to ensure Investigators have timely access to the most accurate and complete safety information.

3.1 Engagement and Communication		
3.1.1	Notes that involving participants, patient advocacy groups and communities in trial design can help ensure decentralized methodologies are fit for use. Participant input can also help identify areas where additional training or support may be needed for participants to effectively use the methodology. This also aligns with ICH E6 R3 and ICH E8 R1 2.3 which note the importance of obtaining participant input into trial design.	When evaluating, designing and providing training on use of decentralized methods or DHTs, data managers should seek input from participants, Investigators and HCP. Particular attention should be paid to how usable the methods are and what supports would reduce participant barriers and improve data quality.
3.1.2	Also encourages getting Investigator and HCP input on methodologies to assess usability and identify training and support needs.	Same as above.

3.2 Protocol and Trial Design		
3.2.1	Design elements, data sources, and key operational approaches should be described in the protocol along with justification for their use. This should include rationale, fitness for purpose, and feasibility. This information can also be supplemented in additional detail in the protocol related documents.	As part of the QbD data managers should assist the team in determining the fitness for purpose and feasibility of data collection tools and methodologies as part of the justification for their use in the trial. Data managers should ensure this is documented in the protocol or other protocol related documents.
3.2.3	Since data may come from different sources or settings, there is potential for data variability. The potential impact should be considered and discussed in the protocol or protocol related documents.	While data managers will not be solely responsible for assessing the potential for data variability, they should consider and communicate to the team how different methods might introduce variability. Data managers should also evaluate and implement strategies for identifying and addressing variability in the collected data. How data would be standarised to ensure compliance with regulatory purposes. These strategies should be documented in the data validation and/or data management plan. Consider clarifying expectations for predefined handling of data variability when data originate from different sources, settings, or collection schedules. While Section 3.2.3 appropriately recognizes that variability in data source, timing, and practice setting should be considered in trial design and discussed in protocol-related documents, additional clarification may be helpful regarding how such variability should be addressed in data handling and analysis planning. This may include consideration of source hierarchy, visit or timepoint mapping, conflicting values, missing or delayed data, acceptable collection windows, and downstream impact on analysis datasets or interpretation of trial results.
3.4.1 Access to and Use of RWD	When sponsors use RWD in a clinical trial, they must ensure both participant protection (data privacy and data protection) and the reliability of trial results. The Fitness for purpose evaluation should be documented in the protocol or related documentation including limitations and justification for the assessment approach.	Data managers are not likely to have sole responsibility for evaluating RWD. But where possible, they should participate in the assessment and provide input into potential limitations of the data. Data managers should also consider how to limit collection of participant personal data to reduce privacy risks. Data managers utilizing RWD should review the EMA reflection paper on non-interventional studies which discusses the evaluation of real-world data to assess fitness for use and the FDA Guidance on Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products.

3.5 Data Considerations		
3.5.1 (a)	Sponsors must ensure RWD is fit for purpose by being both relevant and reliable. Sponsors must evaluate variability, potential bias, generalisability and traceability of RWD.	Data managers should participate in the evaluation of RWD and provide input into the accuracy and completeness of the data as well as what quality control measures should be put in place. Data managers should ensure that the project team documents the rationale supporting the fit-for-purpose determination, including how the strengths, limitations and risks of the RWD were considered in relation to intended use. The level of risk should be proportionate to the importance of the RWD to the trial objectives, with more robust documentation where RWD are used to support key efficacy or safety endpoints or regulatory decision-making.
3.5.1 (b)	Sponsors should apply a risk-proportionate approach when evaluating the quality, integrity and governance of the RWD considering trial objectives and potential impact of data limitations.	
3.5.1 (c)	Multiple data sources might need to be linked to support the reliability, including completeness of RWD. When data are linked, accurate matching to the individual should be assured, and the sponsor should ensure adequate measures to sufficiently protect both data privacy and the reliability of trial results. If data are to be linked, this should be prespecified in the protocol or protocol-related documents.	When planning to link RWD sources data managers should include assessment and documentation of linkage quality, potential linkage errors, residual uncertainty, and any resulting impact on critical endpoints or analyses. For more specifics the DMEG recommends review of the EMA Reflection paper on use of real-world data in non-interventional studies to generate real-world evidence.

3.5.2 (see also Annex 1, 4.3.3. and Annex 2, 3.5.1 and 3.7)	Remote data collection requires special attention to data security, including cybersecurity and data privacy. Some of the RWD considerations noted in Annex 2 3.5.1 may also apply to remote clinical trial data collection.	When evaluating, designing, and defining access to remote data collection technologies data managers should ensure appropriate security measures are in place, including ensuring access to view or modify participant data is restricted to authorized and necessary users. Data managers should also follow principles of data minimization when designing data collection systems.
3.7 Privacy and Confidentiality Considerations	Sponsors should employ processes and technology to ensure security, privacy and confidentiality of participant information. This includes appropriate informed consent and access restriction to authorized individuals. Sponsors should evaluate and address the risk of data breach.	
3.8 Sponsor Oversight	Sponsors should take a risk-proportionate approach to oversight these methodologies. This includes oversight of service providers, including ensuring service providers maintain essential records.	Data managers are likely to have oversight responsibilities for these methodologies and service providers. When defining and implementing the oversight plan data managers should focus on CTQ factors and otherwise implement a risk-proportionate approach
3.9.1 Safety Assessment and reporting	When using decentralised and/or pragmatic methodologies the sponsor must ensure the investigator receives this information in a manner that supports participant care and safety.	Same comments as noted in 2.5 Safety Assessment and Reporting (see also Annex 2 3.9 and Annex 1 3.13.2). Data managers should also ensure completeness and traceability of safety information across multiple sources and systems, including clear responsibility for integration, reconciliation, and timely communication of incomplete or delayed safety data.

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