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Overview of comments received on ICH E6 (R3) Guideline for good clinical practice – Annex 2 (EMA/CHMP/ICH/495903/2024)

Please note that comments will be sent to the ICH E6 (R3) EWG for consideration in the context of Step 3 of the ICH process.

1. General comments – overview

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
AFI	0	0		The Annex 2 often refers to applicable local regulatory requirements: in general, it could be appropriate to standardize the approach removing the reference to local requirements or to clarify what it is meant for regulatory requirements.	
AFI	0	0		It's very noticeable the openess of the Annex 2 on innovative study designs, however it seems still not clear the purpose of this guidance and the level of responsibilities and tasks assigned to the different stakeholders are still too high level.	
AFI	0	0		Annex 2 in its structure is confounding because follows the one of Annex 1 but it's not clear to understand the expectation of both parts.	The expectation is to have an Annex 2 really helpful for a daily practical management of work, not too high level but really hands - on.
Association of Clinical Research Organizations (ACRO)	0	0		The Association of Clinical Research Organizations (ACRO) represents the world's leading clinical research and clinical technology organizations. Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices, from pre-clinical, proof of concept and first-in-human studies through post-approval, pharmacovigilance and health data research. ACRO member companies manage or otherwise support a majority of all biopharmaceutical sponsored clinical investigations worldwide and advance clinical outsourcing to improve the quality, efficiency and safety of biomedical research. ACRO thanks the ICH for the *Draft Guideline for Good Clinical Practice E6(R3) Annex 2.* The objective of this draft guideline is to address the application of GCP in an increasingly complex clinical trial enterprise characterized by a growing range of technological advances, design elements, and data sources. The draft guideline focuses on three specific advances in clinical research: Decentralized elements – defined as *"those trial-related activities conducted outside the investigator's location (e.g., trial visit is conducted in the trial participant's home, local healthcare centre or mobile medical units or when data acquisition is performed remotely using digital health technologies (DHTs))"* (ICH Annex 2 draft guideline, lines 19-22)	

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Association of Clinical Research Organizations (ACRO)	0	0		Pragmatic elements – defined as "those that integrate aspects of clinical practice into the design and conduct of the trial (e.g., simplified protocols with streamlined data collection)" (ICH Annex 2 draft guideline, lines 23-24) Real-world data (RWD) – this is contrasted with "primary data" (data generated specifically in a trial) and defined as "data obtained from sources external to the trial that are collected for other purposes (secondary data use)). RWD incorporated in clinical trials include the use of data relating to patient health status collected from a variety of sources outside of clinical trials (e.g., electronic health records (EHRs), registries, claims data). These data from RWD sources may be used in various ways, including, but not limited to, ascertaining endpoints or outcomes or serving as an external control" (ICH Annex 2 draft guideline, lines 26-31) ACRO's comment is divided into three sections. The first section discusses how the draft guideline could go further in facilitating trials with decentralized elements (including facilitating the use of local healthcare providers (HCPs); clarifying investigator oversight of HCPs; clarifying safety reporting; and acknowledging vulnerable populations). The second section offers recommendations regarding the discussion of data variability in the draft guideline. The final section offers suggestions for strengthening participant engagement.	
Association of Clinical Research Organizations (ACRO)	0	0		I: The draft guideline could go further to enable trials with decentralized elements ACRO welcomes the extensive discussion of real-world data (RWD) in the draft guideline, which receives dedicated discussion in Section 3.5.1 on pages 8 to 9. However, we believe the draft guideline could go much further in facilitating and enabling trials with decentralized elements. Facilitating the use of local health care providers (HCPs) In its consideration of investigational product management, the draft guideline discusses the appropriate use of local pharmacists: The investigational product may be dispensed or supplied to the participant or to an appropriate designee (e.g., caregiver, home nurse, local pharmacist) for administration at the participant's location (e.g., participant's home, local healthcare centre) by appropriate parties (e.g., the investigator site staff, the participant, a home nurse or a local pharmacist).(ICH Annex 2 draft guideline, lines 73 to 77). Local HCPs are a valuable resource for decentralized trials. However, in the Annex 2 draft guideline, the use of local HCPs in decentralized trials is referenced in just one sentence: "Healthcare professionals may be involved in performing trial-related activities that are part of clinical practice." (ICH Annex 2 draft guideline, lines 110-111) The FDA's Final Guidance on Conducting Clinical Trials with Decentralized Elements provides a helpful summary of both the benefits of using local HCPs in decentralized trials and also the appropriately limited scope of a local HCP's contributions to a decentralized trial. (REFERENCE: FDA draft guidance on Conducting Clinical Trials with Decentralized Elements https://www.fda.gov/media/167696/download)	

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Association of Clinical Research Organizations (ACRO)	0	0		The value of using HCPs in a decentralized trial is the potential to increase the representativeness of trial participants: The clinical trial population should reflect the intended patient population for the medicalproduct being studied, including with respect to race, ethnicity, age, sex, and geographiclocation, as applicable. Outreach through local health care institutions (e.g., pharmacies, clinics) may facilitate recruitment of participants with diverse demographiccharacteristics more reflective of the intended patient population in areas where there are limited or no traditional clinical trial sites. Bringing trial-related activities to participants'homes may reduce the need for travel and improve engagement, recruitment, and retention amongst potential participants who have challenges accessing traditional clinical trial sites. The use of local HCPs close to potential participants' homes may further improve engagement, recruitment, and retention of a more representative participant population and reduce cultural or linguistic barriers to participation in clinical trials. (FDA final guidance, page 7) The scope of the HCP's contributions differs from that of trial personnel: Depending on the trial protocol, in-person visits and trial-related activities may also be conducted by HCPs who are located close to trial participants' homes. Investigators may use these local HCPs (such as doctors or nurses) to perform certain trial-related activities; for example, on a fee-for-service basis. The trial-related activities local HCPs perform should not differ from those that they are qualified to perform in clinical practice and should not require a detailed knowledge of the protocol, investigator's brochure, or IP (e.g., performing physical examinations or obtaining vital signs). These local HCPs would not be considered trial personnel, nor would they be considered subinvestigators in a drug trial.(FDA final guidance, pp 4 to 5) It would be valuable to see greater discussion of the benefit and scope of HCPs in the final guidance on Annex 2. The FDA draft guidance on Integrating Randomized Controlled Trials for Drug and Biological Products into Routine Clinical Practice further clarifies the role that local HCPs can play in modernized clinical trials (lines 201-243). According to this draft guidance, the use of local HCPs is appropriate when: (REFERENCE: FDA draft guidance on Integrating Randomized Controlled Trials for Drug and Biological Products into Routine Clinical Practice https://www.fda.gov/media/181871/download)	

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Association of Clinical Research Organizations (ACRO)	0	0		the HCP's tasks do not differ from those that they are qualified to perform in routine clinical practice. the HCP's tasks require only limited instructions to ensure that they are performed as required. the HCP's tasks do not: contribute directly and significantly to trial data. require trial-specific knowledge. require trial-specific training. require research expertise. require a detailed knowledge of the protocol. require a detailed knowledge of the investigational product. require a detailed knowledge of the investigator's brochure (FDA draft guidance on Integrating RCTs in Routine Practice, lines 177-185 and 203-208). We ask ICH to consider including discussion of the valuable role of local HCPs in innovative trials such as trials with decentralized elements. Further clarifying investigator oversight in a decentralized trial The Annex 2 draft guideline does address the role of investigator oversight of individuals such as local HCPs For trial-related activities conducted in clinical practice by healthcare professionals which do not require knowledge about the protocol, investigators' brochure, or other trial-related documents, appropriate arrangements and appropriate investigator oversight should be in place. Such arrangements should address plans for making relevant information and records available to the investigator. (ICH Annex 2 draft guideline, lines 116-120) The level of investigator oversight of the trial-related activities should depend on the nature of the activities and be proportionate to the risks to trial participant safety and data reliability, and the importance of the data being collected. Such oversight should ensure that the resulting records meet the relevant requirements of the protocol and thereby ensure reliable trial results, trial participant safety and appropriate decision-making. (ICH Annex 2 draft guideline, lines 121-125)	
Association of Clinical Research Organizations (ACRO)	0	0		However, we believe this discussion of investigator oversight would benefit from further clarification. The FDA Final Guidance on Decentralized Trials provides an enriched discussion of the investigator oversight role which we ask ICH to incorporate into the Annex 2 final guidance: Investigators are responsible for the conduct of the DCT and for protecting the rights, safety, and welfare of subjects under their care. Investigators must also maintain accurate records of each subject's case history, including observations and other data pertinent to the investigation. Consistent with these responsibilities, investigators should review data from other trial personnel and local HCPs, as applicable, and follow up on any data that are missing, concerning, or appear to be in error. Investigators must also ensure assessments are being completed consistent with the protocol and confirm that participants have received the IP.22 When permitted by the protocol, investigators can delegate trial-related activities to appropriate local HCPs. Investigators can work with enrolled participants to identify such providers when appropriate. Investigators must ensure that trial-related activities delegated to local HCPs are conducted according to the investigational plan and applicable regulations and remain responsible for the adequate supervision of those to whom they have delegated these activities. (FDA Final Guidance on Decentralized Trials, pages 8-9) Investigators do not need to maintain a log of local HCPs performing trial-related activities. However, as part of preparing and maintaining adequate case histories, investigators should ensure that reports from local HCPs include the name of the local HCP and the date when activities were performed. (FDA Final Guidance on Decentralized Trials, page 10)	

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Association of Clinical Research Organizations (ACRO)	0	0		Acknowledgement of vulnerable populations The section on the investigator and "Informed Consent Considerations" (Section 2.2.2) of the Annex 2 draft guideline states: The characteristics of the trial population (e.g., participants may lack familiarity with electronic systems) and the appropriateness of the method and tools used to obtain consent should be taken into consideration when developing the informed consent materials and process. Trial participants may be given the option to use a paper-based approach and/or in-person consent process, to the extent feasible, should they prefer this. (ICH Annex 2 draft guideline, lines 60-64) Since decentralized trials have great potential to benefit vulnerable populations in particular, due to their flexibility, ACRO would recommend incorporating a final sentence into this paragraph acknowledging the needs of vulnerable populations with an additional sentence such as: "The needs of vulnerable populations should be considered." Safety reporting in decentralized trials Section 2.5 on "Safety Assessment and Reporting" would benefit from greater clarity. In decentralized trials, the connection between investigator and trial participants must be clearly defined to ensure safety reporting. This should include details of safety assessment and how the patient will communicate with the investigator. Given its importance, ACRO recommends including a specific sentence in section 2.5 about the investigator's responsibility to explain safety related procedures and communication channels to the patient. We believe that, once again, the FDA Final Guidance provides valuable language that could be incorporated into the final version of the Annex 2 draft guideline: As in any clinical trial, the safety monitoring plan should describe how participants are expected to respond to and report adverse events, including where to seek medical assistance locally when necessary and where to receive follow-up care. (FDA Final Guidance on Decentralized Trials, page 15) Trial participants should have clear instructions about how to contact trial personnel to report adverse events and to have pertinent questions answered. Trial participants should also be able to arrange for an unscheduled visit with trial personnel using telehealth or an in-person visit, as appropriate (see section III.B). (FDA Final Guidance on Decentralized Trials, page 16)	
Association of Clinical Research Organizations (ACRO)	0	0		ACRO welcomes the draft guidance's recommendations regarding six potential issues to consider when using secondary data such as RWD – namely: Data format variability – due to differing terminologies and standards across a variety of sources. Data collection timing variability – due to a lack of standardization in the timing and frequency of clinical assessments. Data quality variability – due to the variety of routine care data sources. De-identification variability – due to differing methodologies for data protection. Validation status variability – due to the variety of routine care data sources Missing data. Many of these considerations also apply to pragmatic trials. However, we note that decentralized trials are distinct from both trials incorporating RWD and those with pragmatic elements, as decentralized trials frequently generate primary data. The only mention of data variability outside of RWD is in Section 3.2.2 of the discussion of sponsor responsibilities. The draft guideline states: Since data may originate from different sources or various practice settings (e.g., sources with different timing of data collection), there may be data variability within and/or between data sources/settings. The impact of such data variability should be considered in the trial design and discussed in the protocol or protocol-related documents (e.g., statistical analysis plan). (lines 170-174)	

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Association of Clinical Research Organizations (ACRO)	0	0		We ask ICH to clarify this paragraph in the final guidance to explicitly state that data variability is not a concern unique to decentralized trials. Data variability is also a feature of conventional trials, as highlighted by ACRO in its 2023 comment letter to FDA. (REFERENCE: ACRO comment submission to FDA on Decentralized Clinical Trials for Drugs, Biological Products, and Devices; Draft Guidance for Industry, Investigators, and Other Stakeholders [FDA-2022-D-2870] https://www.acrohealth.org/wp-content/uploads/2023/11/ACRO-Final-Comment-on-DCTs.pdf) An excellent example of this is seen in an analysis of variability among clinicians when performing clinician reported outcomes (ClinROs). (REFERENCE: "Clinician-Reported Outcome Assessments of Treatment Benefit: Report of the ISPOR Clinical Outcome Assessment Emerging Good Practices Task Force," Value Health. 2017 Jan; 20(1): 2–14. Published online 2017 Jan 10. doi: 10.1016/j.jval.2016.11.005 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5379997/) Clinical trials today often involve global, multi-site studies. Data variability exists, and can be thoughtfully addressed, in both decentralized and conventional trials. Moreover, a recent article notes that variability analysis as a key element in data collection. (REFERENCE: "Variability in clinical data is often more useful than the mean: illustration of concept and simple methods of assessment," Int J Clin Pharmacol Ther. 2005 Nov;43(11):536-42. doi: 10.5414/cpp43536. https://pubmed.ncbi.nlm.nih.gov/16300169/)	
Association of Clinical Research Organizations (ACRO)	0	0		In a conventional, multi-site trial – where no decentralized elements are used – the sheer number of investigator sites around the globe (and multiple parties involved in assessments) introduces the possibility of data variability. In a decentralized trial, where data may be collected remotely, data variability can occur because various parties are conducting multiple, trial-related activities – including patients themselves. Data quality and integrity may, in some cases, be improved via the continuous data flows that decentralized elements such as wearables or sensors can offer. (REFERENCE: Examples include: the potential for objective, longitudinal data capture without a subjective interpretation on the part of a site clinician or other HCP (e.g., the six-minute walk test) to mitigate data variability, the potential for gathering continuous data rather than the "point-in-time" data gathered at the investigator site, the potential to gather data in the trial participant's natural, real-world setting (vs investigator site), the potential for the availability of continuous data (e.g. temperature) via the wearable sensor to facilitate the capture of safety issues, with the potential for more timely corrective action by trial personnel.) However, such methods may not be appropriate for all trials or participants. To mitigate potential data variability in a decentralized trial, ACRO has previously discussed options such as the implementation of Risk-Based Quality Management (RBQM), data flow mapping, and differentiated analysis/reporting of data from distinct data streams. (REFERENCE: "Navigating Change During Rapid Transformation: A Question-and-Answer Resource for Decentralized Clinical Trials" Association of Clinical Research Organizations (ACRO) https://www.acrohealth.org/wp-content/uploads/2023/11/ACRO_DCTResource_PAGES-1.pdf) It is notable that these approaches are no different from those presently being applied by sponsors and CROs in conventional clinical trials to manage the risks associated with data variability. Therefore, ACRO asks that ICH consider modifying the Annex 2 final guidance to clearly state that: data variability is a key consideration in both conventional and decentralized trials. currently, we have no empirical data or evidence that the variability and precision of the data obtained in a decentralized trial differs from the data in a traditional site-based clinical trial. a risk-based quality management approach should be used in all trials.	

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Association of Clinical Research Organizations (ACRO)	0	0		III. Strengthening patient engagement Annex 2 Section 3.1.1 (Engagement and Communication) encourages patient engagement in the development of protocols: Engaging patients, patient advocacy groups and their communities, as appropriate, can help ensure the successful integration and implementation of various operational approaches and data sources in trials. For example, involving patients early in the design of the trial may help ensure the suitability of DHTs (e.g., mobile apps, wearables) used in trials with decentralised elements. This engagement may bring attention to areas where additional training or support may be needed (e.g., digital literacy, physical ability or lack of access to technology that may require the use of alternative approaches, specialized training or the provision of technology). (lines 137-144) This is an important step forward but does not go far enough. ACRO recommends adding the following language to the final version of Annex 2 at the end of this existing paragraph (immediately after line 144): Across the clinical trial enterprise, we must pair innovative science with a fit-for-purpose participant communications program that effectively informs and engages participants in language that is understandable to them, with communications throughout the life cycle of the trial. Easily understood, fit-for-purpose participant communication programs can encourage participation in trials and support improved engagement, enabling patients to be partners in trials from beginning to end. Communication that effectively explains trials, investigational products, and trial findings can help increase participation and levels of scientific literacy. We thank ICH for the opportunity to provide these comments on Draft Guideline for Good Clinical Practice E6(R3) Annex 2. Please contact ACRO if we can answer any questions or provide additional details. Respectfully submitted, Karen Noonan Senior Vice President, Global Regulatory Policy	
DARQA	0	0		Suggest to re-emphasize that Annex 2 relates to interventional clinical trials. Some examples given / elements may also (or in particular) apply to observational studies (e.g. use of RWD), where specific requirements only apply to interventional trials. This is confusing the reader.	
DARQA	0	0		The word "may" is used 44 times in Annex 2, where "may" or "may be" should be avoided in a document which will be embedded in legislation in some of the countries. In general, it is expected that the guidance leaves as little room for interpretation as possible. The draft Annex 2 is raising sometimes more questions than answers. Example: Last sentence of art. 2.2.2.	
ESMO (European Society for Medical Oncology)	0			A general comment: As discussed in a prevoius meeting, the workload on the PI's from different online systems is tremendous and non-essential, and removes the focus from the actual and well intended PI oversight. So just a thought if possible, to ensure that the communication between sponsor and PI is kept to the essential and try to remove all the "noise", but not shure how though.	
EUCROF	0	0		The use of RWD combined with prospectively collected data in a clinical trial might challenge the traditional confirmatory statistical methods. It is not mentioned in the guideline that statistical methods should be considered for suitability when using non-traditional study designs and alternative data sources for (interventional) clinical trials. Along the same line (statistical methods), some hints would be beneficial how to handle different "RWD situations" like different visit intervals and missing data. Sensitivity analyses should be at least mentioned with a couple of examples to make the guidance more practical.	

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EUCROF	0	0		The guideline generally addresses alternative study designs and additional data sources, which are outlined as decentralised trials, pragmatice trials and use of RWD. Not every section applies to all scenarios, especially regarding RWD. It is not always clear to which of these three aspects the different sections/paragraphs of the document refer to: Example: Section 2.4: Oversight of investigators (how can an investigator apply oversight when using RWD?) or Section 3.6: Investigational Product Management (this section obviously applies to situations with primary data collection only, but it is not said so).	Make more easily understandable when the considerations refer to decentralised elements, to pragmatic elements or to RWD.
EUCROF	0	0		Throughout the entire document, the term "clinical practice" is used to refer to "normal clinical practice", "routine clinical practice", "standard clinical practice" or "standard of care". EUCROF recognises that the term "clinical practice" is in line with Annex 1, where "clinical practice computerised systems" and " activities performed as part of clinical practice" is being used. However, EUCROF is of the opinion that any of the above mentioned terms (e.g.,"normal or routine clinical practice") provides better clarity to refer to what is usually done in the field under real world conditions than the term "clinical practice". Especially for Annex 2, where RWD is targeted in the context of interventional clinical trials where "good clinical practice" applies as a quality standard, a more precise delineation between "good clinical practice" and "routine clinical practice" would be appreciated.	Exchange "clinical practice" with "normal clinical practice" or "routine clinical practice" (or anything similar).
EUCROF	0	0		EUCROF appreciates the opportunity to provide comments for this important Guideline E6(R3) Annex 2 which - for the first time - attemps to cover non-traditional study designs and alternative data sources. Although remaining very general, it addresses elements that the research community should be thinking of when discussing trial designs and data sources. This is highly beneficial. The guideline provides a number of examples for clinical trials with decentralised elements (e.g., shipment of investigational product to participants' homes, visits of nurses at participants' homes), however examples for the use of alternative data sources, especially in the field of secondary use of data, are missing. More concrete scenarios and clarification would be very helpful. For example, the creation of comparator arms using RWD or transition of a RCT to a pragmatic trial. Sample scenarios would be very much appreciated.	
European Huntington Association	0	0	I. INTRODUCTION	The use of subheadings in a document typically enhances readability.	roposed change: Create three subheadings similar to the ones created in the Introduction section of the Guideline for good clinical practice (GCP) E6(R3). Decentralized Documents; Pragmatic Elements; Real-Word Data (RWD)
François Houÿez, Eurordis	0			General comment: the recruitment of trial participants or their identification can also be made from real-world data sources. Services exist and operate already, and this should be under the supervision of the investigator(s). Lists and contact details of potential participants can be shared with service providers who will contact potential participants and explain the proposed trial, in which case the activity is directly supervised by the investigator(s). But other services can access large databases of patients, for the purpose of accessing data and identifying those who would match inclusion/exclusion criteria, and inform them about the trial.	

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Good Clinical Trials Collaborative (GCTC), https://www.goodtrials.org/	0	0	General	The Good Clinical Trials Collaborative (GCTC) has coordinated a multistakeholder expert response drawing on a diverse range of expertise globally. For the European Medicines Agency, we submit these comments with the endorsment of the following: - Biomedical Alliance in Europe (BioMed Alliance), https://www.biomedeurope.org/ - The Coalition for Reducing Bureaucracy in Clinical Trials (RBinCTs), https://bureaucracyincts.eu/ - Chris Decker, on healf of the Clinical Data Interchange Standards Consortium (CDISC), https://www.cdisc.org/ - Birge Berns and Sheuli Porkess, on behalf of the Faculty of Pharmaceutical Medicine (FPM), https://www.fpm.org.uk/ - Jan Geissler, Managing Director European Patient Advocacy Institute, Chair Acute Leukemia Advocates Network, CEO, Patvocates - Prof Sir Martin Landray, Senior Lead, Good Clinical Trials Collaborative, Professor of Medicine & Epidemiology, University of Oxford, Chief Executive Officer, Protas Our goal is to support the development of a fit-for-purpose Annex 2 that provides effective guidance and encouragement for clinical trials that incorporate pragmatic elements, decentralised elements and/or clinical trials that make use of Real-World Data (RWD). Our response is informed by the principles for good clinical trials as described in the World Health Organization (WHO) Guidance for Best Practices for Clinical Trials. We have also drawn from the extensive experience of designing, conducting and participating in innovative clinical trials from across members of the Good Clinical Trials Collaborative. In our response, we provide a prioritised set of actionable recommendations and/or suggested alternative text to respond to key issues we have identified. We have aimed to ensure that these are in keeping with the scope and nature of Annex 2 and the portfolio of ICH GCP Guidelines, to facilitate their implementation.	
Good Clinical Trials Collaborative (GCTC), https://www.goodtrials.org/	0	0	General	We note the publication of the finalised, updated ICH GCP Principles and Annex 1 on 14 January 2025. In most jurisdictions, this allows only six weeks (until 28 February 2025) to consider the draft Annex 2 in the context of the related final documents before the deadline for providing public comments. In Japan and China, it is 11 and 13 days respectively. We believe this timeframe is insufficient to support a robust and inclusive consultation process and risks missing opportunities to make important improvements or correct significant issues and errors. A longer consultation period would not only enhance the quality of stakeholder input but also build confidence in the ICH's commitment to transparency and collaboration. Ultimately, this approach would contribute to a more effective and widely accepted framework that aligns with the principles of Good Clinical Practice and supports global harmonisation efforts	Extend the timeframe for accepting public comments.
INNODIA (INPACT: INNODIA People with Type 1 Diabetes Community)	0	0		Accessibility of regulatory documents in multiple EU languages: this comment raises important concerns about inclusivity and transparency in the regulatory review process.	Consider options to reach out to non-english speakers to expand reach and ensure inclusivity of EMA procedures related to clinical trials
Lymphoma Coalition	0	0		The ICH E6(R3) Annex 2 guideline is a step forward in adapting clinical trial practices to modern methods, but it lacks a strong patient-centered approach in several areas. Including clearer guidance on patient involvement, informed consent accessibility, data transparency, and patient-reported outcomes would significantly enhance its applicability and effectiveness.	
Lymphoma Coalition	0	0		The guideline should strengthen the language regarding patient rights, involvement, and decision-making. While it mentions patient engagement (section 3.1.1), it does not consistently reinforce the role of patients as active stakeholders in trial design, consent, and oversight.	
Lymphoma Coalition	0	0		The guideline should acknowledge disparities in trial access due to socio-economic factors, digital literacy, and language barriers. Explicit guidance should be provided on mitigating these challenges.	

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Lymphoma Coalition	0	0		Informed Consent & Readability: The document lacks guidance on ensuring consent forms are understandable for diverse populations, including those with low health literacy or limited access to digital tools.	
Lymphoma Coalition	0	0		There is no mention of incorporating patient-reported outcomes (PROs) as part of trial assessments, especially in real-world data (RWD) studies.	
Syneos Health	0	0	1, 2.2, 3.5.2, 3.9.1	In Annex 2, three types of trials are addressed - DCT, pragmatic and RWD. The considerations laid out are specifically for these types of studies.	We will appreciate additional clarification whether the protocol should be developed explicitly to call out these categories in order to use these approaches in the trial conduct. Are there any boundaries to differentiate between such studies utilizing Annex 2 and traditional studies, versus wanting to add elements of Annex 2 in a trial that is designed as a traditional trial?
Syneos Health	0	0		In Annex 2 there are no specific references to Diversity aspects.	It is acknowedged that the decentralized solutions should facilitate access to clinical trials therefore indirectly supporting diversity however, additional clarifications within the Guidance on how DCT can support diversity would be greatly appreciated.
Syneos Health	0	0		In Annex 2 there are several references to the "local regulatory requirements".	A high degree of variability may impact the study design, conduct and analysis; we would appreciate additional guidance on how to manage these aspects. This may be addressed in the statistical analysis plan but operationally, it may become very challenging to develop a protocol to address all the regulatory nuances and adhere to the multi-regional clinical trials (MRCT) principle. For example – will it be possible to have a main protocol with country addendums/variations?
Trials@home	0	0		In the context of trials with decentralized elements, Annex 2 regularly refers to "remote(ly)". Although conducting a trial using decentralized elements could be considered remote from the perspective of the site staff, it is not remote from the perspective of the trial participant.	For convenience and given the target audience of the ICH document, using terms like "remote" can be justifiable. However, it should be stated in (the beginning of) the document that when "remote" is being used, that this is remote from the perspective of the investigator.
UNICANCER	0			Unicancer wellcomes the approach to provide recommandations on specific categories of trials in the context of the growing number of these trials, and thanks EMA/ICH for the opportinity to comment.	
UNICANCER	0	0	New sections (Investigator,Sponsor)	Records maintenance: Investigator, sponsor: In decentralized cliical trials multiple systems, sites and parties adds complexity.	Unicancer recommendation is to add 2 sections (1 for investigator and 1 for sponsor) with provisions on Record keeping, retention and access in this context (flow-diagrams, source data location system, level of proof ...)

2. Specific comments on text

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation

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Association for Clinical Data Management (ACDM)	1	1	ToC	General Comment: Please consider to include a glossary for terms included on Annex 2 and not included in Annex 1 such as Real Word Evidence, Electronic Health Record, … DHTs, …	
EFPIA consoldiated comment	1	1	I. INTRODUCTION	Include a Glossary as many of the abbreviations and some systems (RWD, EHR, ...) are not included on Annex 1 Glossary	A glossary would be useful to define terms such as decentralized trial, real world data - in some cases the terms are described in the text, however a reference such as a glossary would be very helpful
Lymphoma Coalition	1	36	I	While the introduction acknowledges decentralized and pragmatic trial elements, it does not address the potential barriers patients may face in these models (e.g., digital access, data privacy concerns).	Add: Ensuring accessibility, patient support, and clear communication is crucial when implementing decentralized and pragmatic elements in clinical trials.
EFGCP	3	4	I. INTRODUCTION	Good Clinical Practice (GCP), as described in ICH E6(R3) Principles and Annex 1, is applicable Line 3 across clinical trial types, designs and settings, and remains relevant when various operational Line 4 approaches and data sources are used in a clinical trial	Complex & Real World Data trials may require more flexibility than proposed in Annex 1. Suggest reference only to the GCP Principles and applicable local legal requirements, to support this flexibility/pragmatism. Rely only on Annex 1 if information is not in the principles.
EFPIA consoldiated comment	3	5	I. INTRODUCTION	The applicability of Annex 2 is not indicated as being specific to 'interventional' clinical trials, as the Principles and Annex 1 are.	.....is applicable across **interventional** clinical trial types.....
Good Clinical Trials Collaborative (GCTC), https://www.goodtrials.org/	3	17	I. INTRODUCTION	The finalised Introduction to ICH E6 (R3) includes a number of positive statements about the focus on principles, the role of annexes in the GCP guideline, and the need for flexibility and proportionality, including the following: "The Annexes provide the basis for the appropriate interpretation and application of the principles and should therefore be appropriately considered; however, various approaches to the provisions in the Annexes may be considered provided they are justified and achieve the intended purpose of the application of the principles… …The principles outlined in this guideline may be satisfied using differing approaches and should be applied to fit the intended purpose of the clinical trial… …Annex 1, including its Appendices, is intended to provide information on how the principles can be appropriately applied to clinical trials." [Introduction, ICH E6 (R3)]. Taken together, these statements substantially advance the potential for ICH GCP to address two major challenges that have undermined previous versions of the guideline, namely: - The dangers of rigid, disproportionate or over-interpretation of the guideline's text. - The risk of rapid redundancy or obsolescence of the guideline in relation to unforeseen innovative approaches or technologies at the time of writing. Although Annex 2 refers to the principles of GCP in many places, it is not consistent in doing so and refers to Annex 1 in multiple places. If this cross-referencing is retained, the flexibilities described in Annex 2 that are designed to improve the quality of trials will be constrained by Annex 1 requirements that are not suitable for the types of clinical trial approaches Annex 2 is intended to address. Unless this issue is dealt with, Annex 2 will likely be interpreted as requiring the user to first do everything required by Annex 1 and then also do everything required by Annex 2 – in direct conflict with its stated ambition to support flexibility, proportionality and innovation. Such an interpretation or obligation would be unhelpful and stifle the use of modern methods to evaluate medicines in clinical trials.	Include within the Introduction to Annex 2 a statement that re-iterates the focus on the Principles of GCP: "Annex 2 provides the basis for the appropriate interpretation and application of the principles and should therefore be appropriately considered; however, various approaches to the provisions in Annex 2 may be considered provided they are justified and achieve the intended purpose of the application of the principles." Addtionally, we recommend systematically replacing or removing references to Annex 1 with the text of Annex 2 to support the objective of Annex 2 to provide the basis of appropriate interpretation and application of the principles of Good Clinical Practice (GCP). The following specific changes are suggested: Line 17: We suggest deleting the current reference to Annex 1. Line 34: We suggest replacing the current reference to Annex 1 with a reference to Principles 6, 7, and 9. Section 2.1 Communication with the IRB/IEC (Line 48): We suggest replacing the current reference to Annex 1, Section 1.1, with a reference to Principle 3.1. Section 2.2 Informed Consent Considerations (Line 53): We suggest replacing the current reference to Annex 1, Section 2.8, with a reference to Principle 2.2.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Good Clinical Trials Collaborative (GCTC), https://www.goodtrials.org/	3	17	I. INTRODUCTION		Section 2.3 Investigational Product Management (Line 81): We suggest deleting the current reference to Annex 1, Section 2.10. Section 2.5 Safety Assessment and Reporting (Line 127): We suggest replacing the current reference to Annex 1, section 2.7, with a reference to Principle 1.2. Section 2.5 Safety Assessment and Reporting (Line 130): We suggest deleting the current reference to Annex 1, section 3.13.2. Section 3.2 Protocol and Trial Design (Lines 161 and 169): We suggest replacing the current reference to Annex 1, Appendix B, with a reference to Principle 8.3. Section 3.2 Protocol and Trial Design (Line 177): We suggest replacing the current reference to Annex 1, Section 2.3.2, with a reference to Principle 5.1. Section 3.3 Communication with the IRB/IEC (Line 192): We suggest replacing the current reference to Annex 1, Section 1.1, with references to Principles 3.1 and 8.3. Section 3.5 Data Considerations: We suggest replacing the current reference to Annex 1, Section 4.3.3, with references to Principles 1.6 and 9.3 to 9.6. Section 3.6 Investigational Product Management (Line 257): We suggest deleting the current reference to Annex 1, Section 3.15.3. Section 3.8 Sponsor Oversight: We suggest replacing the current reference to Annex 1, Sections 3.9 to 3.11 and Appendix C with a reference to Principle 10.
Medicines for Europe	3	36	I. INTRODUCTION	Clearer instructions on how to apply flexibility without compromising trial integrity are missing	Adding instructions on flexibility and adaptability of the guideline
Teva Pharmaceuticals	3	36	I.	Clearer instructions on how to apply flexibility without compromising trial integrity are missing	Adding instructions on flexibility and adaptability of the guideline
Miroslava Calegari	5	8	I. INTRODUCTION	The current text assumes that all participants can independently manage trial participation, which is not true for children and individuals who require caregiver support. Explicitly mentioning these populations ensures that trial designs account for their unique safety challenges. Additionally, when decentralized or remote elements are introduced, there is a need to ensure that caregivers receive adequate training and that emergency response protocols are in place. This aligns with global guidelines such as the EU Clinical Trial Regulation (CTR), the Declaration of Helsinki, and FDA guidance on decentralized trials, which highlight the importance of additional safeguards for vulnerable participants. Regulatory bodies emphasize the need for special safeguards for vulnerable participants, particularly in decentralized trial settings where caregiver involvement may be essential.	As clinical trial designs evolve and technological advances occur, the appropriate and proportionate application of GCP will support these approaches while safeguarding participants' rights, safety, and well-being, particularly for vulnerable groups such as children and individuals who require caregiver support. When trials incorporate decentralized or remote elements, special consideration should be given to ensuring appropriate caregiver training and establishing clear emergency response protocols for remote monitoring.
European Huntington Association	8	8	I. INTRODUCTION	In a clinical trial, validity and reliability are both essential to ensuring that the results are meaningful and trustworthy. Reliability in a clinical trial usually refers to the consistency of measurements or results, whereas validity refers to the accuracy of measurements or results.	Proposed change - "helping to ensure the validity and reliability of trial results" instead of "helping to ensure the reliability of trial results".
Medicines for Europe	9	11	I. INTRODUCTION	Decentralized trials: Annex 2 does not provide guidance on how to handle specific challenges	More detailed guidance should be provided on handling specific challenges such as data integrity, participant monitoring, and regulatory compliance in these settings

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Teva Pharmaceuticals	9	11	I.	Decentralized trials: Annex 2 does not provide guidance on how to handle specific challenges	More detailed guidance should be provided on handling specific challenges such as data integrity, participant monitoring, and regulatory compliance in these settings
Lymphoma Coalition	10	29	I	No mention of post-trial access to interventions proven effective during the trial.	Add: For trials involving interventions with demonstrated efficacy, sponsors should develop plans for post-trial access, particularly in low-resource settings or for participants with ongoing medical needs, as part of ethical trial design.
Lymphoma Coalition	10	29	I	Lack of emphasis on culturally appropriate trial materials and processes.	Add: Trials incorporating decentralised or pragmatic elements must ensure materials and processes are culturally sensitive (e.g., language localization, respect for cultural practices) to promote equitable participation and understanding.
UNICANCER	10	11	Intro.	The sentance specifies that Anx 2 provides additional GCP considerations for trials that incorporate pragmatic elements. The guidance provides common provisions for decentralized trials and trials incorporating pragmatic elements (on Informed consent, Remote Data collection) but there is no specific provision for trials specifically designed with pragmatic elements (Protocol simplification, suitable study drugs, streamlined data collection...). [§ 2.3.2. applicable].	It should be useful to identify and to develop more clearly specific provisions for the prospective trials incorporating in their design pragmatic elements. The trial protocol is designed on a risk based approach with proportionate provisions, such provisions for these "Real world studies" should take into account particularly the US FDA draft guidance <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/integrating-randomized-controlled-trials-drug-and-biological-products-routine-clinical-practice>
Good Clinical Trials Collaborative (GCTC), https://www.goodtrials.org/	12	14		Modern clinical trials often involve contributions from many different individuals and organizations with issues such as data collection, data management, supply and destruction of the investigational medicinal product (IMP), laboratory and imaging services, as well as for enrolment and assessment of trial participants being performed by a range of different parties. The role of sponsor and of investigator may each be performed by multiple organizations. In other trials, including those with regulatory intent, the sponsor and investigator organization may be one and the same (for example in fully decentralized or investigator-initiated trials). There are existing, successful implementations of all these organizational structures and more. For example: • Some services that might otherwise be delivered by the Investigator may sensibly be delivered by the Sponsor (e.g. central pharmacy and laboratory functions with direct-to-participant services). • Some data may be acquired centrally by the Sponsor (e.g. laboratory data, claims and registry data). • The investigator may be based at the same organization as the sponsor (this is particularly true for trials conducted by or with academic, healthcare or non-profit organizations, the results of which might be submitted to regulators). • The sponsor of the trial may be different to the organization submitting for a licensing approval (this is often the case in platform trials, trials conducted by or with academic, healthcare or non-profit organizations). We are familiar with examples of all of these and many other variations. We are concerned that Annex 2 retains an unduly restrictive distinction between the roles of Sponsors and Investigators, which may hinder the implementation of sensible and transparent arrangements that can increase the quality and efficiency of a trial – particularly those that use decentralised or pragmatic elements or make use of RWD.	Enhance the Introduction to Annex 2 to clarify that Sponsor and Investigator roles and responsibilities may be assigned flexibly provided that this is documented and agreed by relevant parties in advance. Following the existing text "Annex 2 is not meant to be comprehensive of all the design elements since clinical trial ecosystems may continue to evolve, and the operational approaches and data sources utilised may expand" (lines 12-14) add: "For example, in some trials the roles of Sponsor may be covered/divided across multiple organizations or responsibilities for certain data collection or logistical tasks may be undertaken by the Sponsor or a third-party organization, and in some trials the role of Sponsor and Investigator may be performed by the same organization. These and other alternative ways to assign the Sponsor and Investigator responsibilities are permissible as needed to best meet the Principles of GCP, ensure the reliability of the trial results and maintain the safety, rights and well-being of participants. In such cases the full range of roles must be covered and responsibility for each should be clearly documented and agreed by the relevant parties. Where such documentation does not exist or is unclear, responsibility will be assumed to fall to the organization described in ICH E6 (R3)."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Association for Clinical Data Management (ACDM)	13	14	I. INTRODUCTION	Suggestion to change: “meant to be comprehensive” to provide principles to use on design elements. Please note that there is no guidance on that, and this Annex 2 will be the one to provide advice on that. It is our understanding that the scope of Annex 2 is to provide principles to apply in decentralized trials or trials working with decentralized elements.	
Miroslava Calegari	13	16	I. INTRODUCTION	The current text does not ensure equal access for underrepresented populations, including children with chronic illnesses, rural patients, and non-digital users. Without explicit mention, there is a risk these groups will be unintentionally excluded as trials increasingly use digital and remote methods. Addressing these barriers upfront ensures inclusivity and accessibility. Regulatory agencies should ensure that clinical trials account for digital accessibility, caregiver involvement, and geographical barriers to promote inclusivity.	As clinical trial ecosystems continue to evolve and the operational approaches and data sources utilized expand, considerations provided in this Annex may apply in accordance with local regulatory requirements. To ensure equitable access to clinical trials for all populations, particular attention should be given to underrepresented groups, including children, individuals with chronic illnesses, rural populations, and non-digital users. Trials should proactively address barriers related to technology access, geographic location, and support systems for these participants.
Trials@home	14	15	1	...may apply in accordance with local regulatory requirements. How to proceed in case there is no local legal base (regultory requirement) about conducting certain DC elements e.g. shipment to patient's home?	There was at least one case where due to lack of legal basis, local authorities would not allow certains procedures. In such case could it be suggested to consider a higher level available regulation such as national or regional (e.g. EU) regulation?
European Huntington Association	16	16	I. INTRODUCTION	The use of the verb "interpret" emphasizes the meaning or implications of the Annex, i.e., how the content should be understood or what conclusions should be or not be drawn from it.	Proposed change - "This Annex should not be interpreted as an endorsement" instead of "This Annex should not be read as an endorsement"
EFGCP	17	17	I. INTRODUCTION	Annex 1 is not relevant	…in the Principles ~~and Annex 1~~
EFPIA consoldiated comment	17	30	I. INTRODUCTION	Overall, the guidance document did a good job being general, across modalities, while also citing specific concerns with each modality (decentralization, RWE, clinical practice). The guidance puts all uses in the same level but that is not very realistic. One would not apply the same level of scrutiny for example at missing values for a primary endpoint than they would for a secondary endpoint. Also, most HA would not inspect data unless it was an important factor in the decision about benefit-risk. Therefore, when some of these triggers may be put in place would be helpful. Clarify that those modalites are used to generate evidence that is essential to the evaluation of benefit-risk, or that an evaluation of how important violation of the principles be done take into account the weight of evidence in the regulatory decision.	Line 17: A**s in the Principles and Annex 1 proportionality of approach should be considered in relation to particpant rights, safety and well-being and the reliablity of trial results.**
Breakthrough T1D	19	24	I. INTRODUCTION	Breakthrough T1D is supportive on the use of decentralised and pragmatic trials as it likely increases the number and diversity of clinical trial participants. This is important in type 1 diabetes where the pool of participants can be lower than other diseases. Decentralised and pragmatic trials can also accommodate the work-life balance of participants as there is less interference in the daily activities, and hence a barrier to participate, in clinical trials.	
GQMA	19	20	I. INTRODUCTION	he definition of decentralised elements as 'those trial-related activities conducted outside the investigator's location' is not precise enough. There are many trial-related activities occuring outside the investigator's location that are clearly not meant here, e.g. sample analysis in a central lab, IRB/IEC reviews, and all activities conducted at sponsor or CRO offices.	Change wording to: 'For the purpose of Annex 2, decentralised elements in a clinical trial are those trial-related activities directly involving the participants but conducted outside the investigator's location (… '

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Miroslava Calegari	19	22	I. INTRODUCTION	The current text does not address how urgent medical situations will be handled in remote trials. Patients with Type 1 Diabetes (T1D) and other chronic illnesses require real-time interventions in emergencies, making it essential to include clear protocols in trial design. Decentralized trials must ensure that safety measures match those in traditional clinical settings, particularly for conditions with acute risks like T1D.	For the purposes of Annex 2, decentralized elements in a clinical trial are those trial-related activities conducted outside the investigator's location. When using decentralized trial elements, sponsors should establish clear emergency response protocols, particularly for participants who may experience acute medical events, such as children, individuals with chronic illnesses, or those in remote locations. These protocols should include access to real-time medical support, defined escalation procedures, and caregiver training where necessary.
Trials@home	19	22	I. INTRODUCTION	In my opinion this definition may leave room for uncertainty about telemedicine visits, where the investigator is at site but the participant is at home, since all examples provided for visits are examples of visits where the HCP and participant meet in the same physical location.	Recommendation is to be consider adding telemedicine visits as an example
AFI	22	32	I. INTRODUCTION	RWD is considered a pragamatic element? It's not clear, please clarify.	
Association for Clinical Data Management (ACDM)	22	24	I. INTRODUCTION	Pragmatic elements needs better definition - are you referring to "centralized" clinical trials?	
UNICANCER	22	23	Intro.	Same comment	
EFPIA consoldiated comment	23	24	I. INTRODUCTION	...aspects of clinical practice' would make more sense to read' aspects of 'routine' clinical practice - to make the distinction between clinical practice specifically for a clinical trial.	include 'routine' in the sentence
EUCROF	24	24	I.	It is not clear what is meant by "streamlined data collection".	Please explain "streamlined data collection" or use another - more common - term.
EUCROF	24	27	I.	Even though the two types of data are described within the two rounded brackets, it is not clear which are the two types of data.	Proposal: "Data can be broadly classified into two types, both of which may be used in a clinical trial: primary data, which are specifically generated for the trial, and secondary data, which are obtained from external sources and originally collected for other purposes."
EORTC	27	31	I. INTRODUCTION	RWD are not necessarily coming outside clinical trial. RWD could be collected during a pragmatic clinical trial for instance. IF RWD are collected within a clinical trial, they are part of the data collection as any other data. Actually, clinical trials do collect data from RW for the majority of needed data, trials are just a method to question and structure the data to solve a question. Trials are methods and RW is a resource and cannot be compared or opposed. Therefore the dichotomy is confusing. Pragmatic trials may actually only collect RWD, therefore, they should be part of the definition of RWD.	Revisit the definition of RWD to include datasets generated by pragmatic clinical trials

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Miroslava Calegari	27	31	I. INTRODUCTION	The variability in RWD sources (e.g., different Continuous Glucose Monitors for diabetes patients) can introduce inconsistencies that affect trial outcomes. Standardizing data collection and validation ensures accuracy and comparability across different trial sites. FDA and EMA guidance on RWD emphasizes the need for clear validation methodologies to avoid discrepancies in multi-site trials.	RWD incorporated in clinical trials includes the use of data relating to patient health status collected from various sources outside of clinical trials. Given differences in data collection methods across healthcare systems and medical technologies, sponsors should ensure consistency in data handling while accounting for the diverse characteristics of studied populations. Trials should define appropriate data processing and validation methods based on the specific condition and patient needs, ensuring reliable and comparable results across all study participants.
Trials@home	27	29	I. INTRODUCTION	Definition of RWD is more narrow than FDA and EMA definition (EMA: Real-World Data are routinely collected data relating to patient health status or the delivery of health care from a variety of sources other than traditional clinical trials	Recommendation is to add 'traditional' to 'clinical trials'
EFPIA consoldiated comment	29	30	I. INTRODUCTION	The guidance implies that the principles apply when "individual level-data" is concerned, especially for the use of RWD. It would be helpful to spell this out in the scope as it was not clear that summary-level, or use of historical data is not covered here. Clarify in the scope, that the intent is for individual level data, as opposed to summary-level, to be used from the different modalities. It would be useful to confirm if it includes both summary/aggregate level data or individual. We thought possibly individual level, so made that proposal.	After line 29: D**ata of individual level nature is in scope, whereas summary level data across individuals is considered out of scope for the purposes of this guideline.**
European Huntington Association	29	29	I. INTRODUCTION	Home-based and community-based assessments are becoming increasingly important for studying topics related to healthcare.	Proposed change: "(e.g., electronic health records (EHRs), home-based and community-based screenings and assessments, registries, claims data)" instead of "(e.g., electronic health records (EHRs), registries, claims data)".
Medicines for Europe	33	36	I. INTRODUCTION	Quality by design: more practical tools and templates could be provided. The annex should provide more detailed guidance on how sponsor can effectively implement a QbD approach in clinical trials incorporating decentralized elements or real-word data. Could the document include practical examples?	Practical examples, tools and templates will help implement QbD principles effectively in various trial designs
Miroslava Calegari	33	36	I. INTRODUCTION	The current text does not account for potential disparities in data access and quality across different trial populations. Standardizing data collection and ensuring equitable access will improve trial integrity and inclusivity. Ensuring consistency in data sources across different patient populations is critical to making reliable conclusions in clinical trials.	Regardless of the operational approaches and data sources used, a quality by design (QbD) approach should be used in clinical trials as stated in Annex 1. The design elements, DHTs, and data sources adopted should be fit for purpose, ensuring consistency in data quality and equitable access to participation. Trial designs should proactively address barriers that could limit inclusion and ensure that data collection methods remain reliable across diverse healthcare settings.
Teva Pharmaceuticals	33	36	I.	Quality by design: more practical tools and templates could be provided	Practical tools and templates will help implement QbD principles effectively in various trial designs
EFGCP	34	34	I. INTRODUCTION	Annex 1 is not relevant but Principle 1 is	… approach should be used in clinical trials as stated in ~~Annex 1~~. ICH GCP Principle 1.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
European Huntington Association	36	36	I. INTRODUCTION	Valid and reliable findings provide a solid foundation for making informed and good decisions.	Proposed change: "are sufficient to support good decision making and valid and reliable findings" instead of "are sufficient to support good decision making."
Medicines for Europe	36	36	I. INTRODUCTION	The text "sufficient to support **good** decision making" sounds subjective.	The following change is suggested: "sufficient to support informed decision making".
Lymphoma Coalition	37	43	1	IRB/IEC: The guideline misses the opportunity to clarify that ethics committees should include patient representatives to enhance the patient-centeredness of decision-making.	Add: IRBs/IECs should include patient or participant advocates to ensure ethical reviews incorporate direct perspectives from populations affected by the trial, particularly for trials involving vulnerable groups or novel operational approaches.
Miroslava Calegari	37	43	I. INTRODUCTION	The current text lacks explicit guidance on ethical oversight for vulnerable groups, such as children, chronic illness patients, and rural populations. Without these considerations, digital and decentralized trials may exclude or compromise the safety of these groups. IRBs/IECs should explicitly consider digital literacy barriers, coercion risks in remote consent, and special protections for pediatric trials.	The ethical principles and standards for the evaluation of clinical trials by IRBs/IECs as described in the Principles and Annex 1 provide a sound basis for the conduct of clinical trials, including those incorporating decentralised elements, pragmatic elements and/or RWD. In addition to privacy and confidentiality, IRBs/IECs should ensure ethical safeguards for vulnerable populations, such as children, individuals with chronic illnesses, and those with limited access to digital tools. Ethical review should also address specific considerations for remote and digital data collection, including ensuring informed consent clarity, minimizing barriers to participation, and assessing risks related to data accessibility and security.
EFGCP	40	40	I. INTRODUCTION	Annex 1 is not relevant	…in the Principles ~~and Annex 1~~
EUCROF	42	43	1.	"…, to privacy and confidentiality of the participants and security of their data." It should be emphasized that these principles are applying no matter which method of data collection is being used.	Supplement as follows: "…, to privacy and confidentiality of the participants and security of their data, irrespective of primary data collection or secondary use of data is applied."
Miroslava Calegari	45	48	2.1	The current text does not provide sufficient guidance on how IRBs/IECs should evaluate novel trial methodologies that incorporate digital health technologies and decentralized elements. Including safety and accessibility considerations will ensure these approaches do not inadvertently exclude or endanger participants. Ensuring that IRBs/IECs assess decentralized trials for safety and accessibility is critical for maintaining ethical trial standards.	The investigator, in accordance with local regulatory requirements, should provide the IRB/IEC with the information needed to evaluate the appropriateness of various operational approaches and data sources being used (see Annex 1, section 1.1). This should include considerations for participant safety, accessibility, and the ethical implications of decentralized elements and digital health technologies, particularly for vulnerable populations.
Teva Pharmaceuticals	45	48	2.1.	More explicit guidance on communication flows.	The ICH should consider including recommendations for communication flows between investigators and central vs. local IRBs.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Trials@home	45	48	2.1	Does this require this additional emphasis? Any protocol submitted should contain enough information for the IRB/IEC to appropriately evaluate the trial. I agree that better explaining the operational approach in trial protocols would be very useful, but this should then apply to all trials. I'm afraid that with a statement like this it may be interpreted as needing to justify the approach, specifically when it is decentralised or pragmatic	Recommendation is to add 'as in any trial' or leave this out altogether
Trials@home	46	48	2.1	"...in accordance with local regulatory requirements." How to proceed in case there is no local legal base (regultory requirement) about conducting certain DC elements e.g. shipment to patient's home?	There was at least one case where due to lack of legal basis, local authorities would not allow certains procedures. In such case could it be suggested to consider a higher level available regulation such as national or regional (e.g. EU) regulation?
UNICANCER	46	48	2.1.	Communication with the IEC: various operational approaches and data sources being used (investigator): this sentence covers decentralized elements, pragmatic elements and RWD. Development of specific forthcoming guidances will be necessary for each. Level of details should be based on a risk-based approach in terms of patient safety and data reliability, taking into acount the impact of data in study results (safety and primary efficacy criteria).	
EUCROF	49	69	2.2	The Informed Consent Considerations are not addressing the fact that participants' data may be stored in countries with lower data protection rules than in the own country. Annex 1, section 2.8.11 (m) would only address data of primary data collection whereas in Annex 2 it could also affect data from secondary use of data, e.g., health record data, that, in the frame of the trial, could end up in other countries with lower data protection rights. This must be made clear to the participants. It should be ensured that the data are not less protected than in the country of origin where the trial participant has given informed consent. This comment also links with section 3.4 of the guideline.	
EUCROF	49	55	2.2	Participant comprehension of alternative consent methods might be of importance with diverse populations.	Recommend adding guidance on monitoring participant comprehension during the informed consent process, especially in remote or technology-driven trials.
European Cystic Fibrosis Society Clinical Trials Network (ECFS-CTN)	49	69	2.2	We welcome the explicit sentence in line 56 stating that "informed consent may be obtained remotely, where appropriate." To allow sites to operationalise this, we would welcome further guidance in this section regarding electronic signature, including details about whether signatures should be simulataneous and guidance on how to chose a robust provider of electronic signature technology. Suchclear guidance is needed to encourage institutions to allow use of remote consent and electronic signatures.	
François Houÿez, Eurordis	49		2.2	Information and consent are two different steps. The consent is informed only if understandable information is provided via different methods and processes adapted to each trial participant.	Considerations for the Information and Consent
Lymphoma Coalition	49	69	2.2	The section "2.2 Informed Consent Considerations" discusses the use of digital tools (eConsent, remote consent) but does not provide safeguards for ensuring comprehension among patients with low digital literacy. I addition, it lacks explicit requirement for informed consent materials to be accessible to participants with disabilities (e.g., Braille, sign language, screen-reader compatibility).	Add: Informed consent processes should incorporate health literacy assessments, offer multiple formats (video, verbal, plain language documents), and provide the option for human interaction (e.g., a patient navigator or advocate). In addition, informed consent materials should be provided in formats accessible to participants with disabilities (e.g., Braille, audio, sign language interpretation, or screen-reader-compatible digital formats) to ensure equitable understanding and participation.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Lymphoma Coalition	49	69	2.2	The section lacks a provision for re-consent if trial scope, risks, or data uses change during the study.	Add: For long-term trials or those involving secondary data reuse, participants shall be offered periodic updates and opportunities to re-consent if significant changes to the trial's purpose, risks, or data handling occur.
Miroslava Calegari	49	53	2	While the current text acknowledges different consent formats, it does not explicitly ensure accessibility for populations with low literacy or cognitive impairments. Providing adapted consent materials would improve participant comprehension and ensure the ethical inclusion of diverse populations. Ensuring informed consent comprehension is a regulatory priority, aligning with ethical guidelines on patient autonomy.	The informed consent process is an integral part of the conduct of interventional clinical trials. Varied approaches (e.g., text, images, videos, and other interactive methods) may be used in the informed consent process, including for providing information to the participant and for supporting the participant's understanding of the trial (see Annex 1, section 2.8). To ensure inclusivity, sponsors should provide consent materials in accessible formats for individuals with cognitive impairments or low literacy levels, such as simplified text, caregiver-assisted consent, or interactive audio-visual explanations.
Association for Clinical Data Management (ACDM)	50	50	2.2	"The informed consent process is an integral part of the conduct of interventional clinical trials. " Are you referring to interventional clinical trials? Is this Annex 2 only applicable to interventional clinical trials? If so, a clarification need to be done on that	
CCMO	50	50	2.2	The term 'interventional clinical trials ' is introduced while in the rest of annex 2 the term 'clinical trials' without the wording interventional is used. The term 'interventional clinical trials' is mentioned in the scope of the ICH E6(R3) guidance (inlcuding annex 1) but no definition of interventional clinical trial is given. The guidance only gives a definition of a clinical trial. The difference between an interventional clinical trial and a clinical trial (if any) should be clarified.	The difference between an interventional clinical trial and a clinical trial should be clarified.
EORTC	50		2.2	Patient consent is an integral part of any type of clinical study. "Interventional" should be removed	
EUCROF	50	53	2.2	The document reads "The informed consent process is an integral part of the conduct of interventional clinical trials". This is not consistent with principle 2 of ICH E6 (R3) which reads "Informed consent is an integral feature of the ethical conduct of a trial" (see ICH E6 (R3), section II, principle 2).	Suggestion that the Annex 2 wording is made consistent with the "mother" document, ICH E6 (R3) Principles and Annex 1 Guideline
European Huntington Association	50	50	2.2	The clearer and more explicit the text of a guideline, the easier it is for the reader to understand and implement it.	Proposed change: "Obtaining and documenting informed consent (in paper or electronic format, in-person or remotely) is an integral part of…" instead of "The informed consent process is an integral part of…"
ESMO (European Society for Medical Oncology)	51	53	2.2	If other approaches are accepted (video, images, etc) maybe it should be then allowed also for trial participants that speak other languages, for example with subtitles, etc.	
Fondazione per la ricerca farmacologica Gianni Benzi onlus (FGB) for the European Rare Diseases Research Alliance (ERDERA)	52	53	2.2	Informed consent can be provided not only by participants but also by parents and legally designated representatives in case of minors and vulnerable subjects unable to provide consent by themselves	including for providing information to the participant or parents or legally designated representative and for supporting the their understanding of the trial

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Association for Clinical Data Management (ACDM)	54	55	2.2	Depending on the design elements - there would be some risk on data privacy, for example…	
INNODIA (INPACT: INNODIA People with Type 1 Diabetes Community)	54		2.2	**Ethical Aspects and Informed Consent:** Many T1D trials involve children and adolescents, requiring more stringent ethical considerations and informed consent from parents. This comment applies to disorders other than T1D.	It is essential to ensure that families understand the risks and benefits of participation.
Breakthrough T1D	56	59	2.2.1	Many T1D trials involve children and adolescents, requiring parental or legal guardian consent and assent from minors, which can be complex in decentralized trials. This may also be the case with other disorders.	For trials involving children and adolescents that require parental or legal guardian consent and assent from minors, investigators should follow appropriate applicable regulatory requirements.
EUCROF	56	59	2.2.1	Point 2.2.1 requires the investigator to assure themselves of the identity of the participant in cases in which informed consent is obtained remotely; however there are no details of how this can be achieved. Some examples would be appreciated.	Add examples of how an investigator can ascertain the identity of a participant in the case of remote informed consent, e.g. ID verification via a video call or electronic identity verification (eIDV) systems that use government-issued IDs, facial recognition, and biometric authentication.
EUCROF	56	59	2.2.1	Because of the vulnerability of such data communication we propose to include the following sentence:	Add sentence: "In such cases, the methods for secure identification of the participants and associated methods to safeguard data privacy should be documented."
Fondazione per la ricerca farmacologica Gianni Benzi onlus (FGB) for the European Rare Diseases Research Alliance (ERDERA)	56	59	2.2.1	The national/local legislation allows or not the lawful way to obtain consent	Informed consent may be obtained remotely, where appropriate. When informed consent is obtained remotely, the investigator should assure themselves of the identity of the participant (or legally acceptable representative where applicable) in accordance with applicable regulatory requirements and local laws.
François Houÿez, Eurordis	56	59	2.2.1	Information and consent are two different steps. The consent is informed only if understandable information is provided via different methods and processes adapted to each trial participant.	Information can be provided remotely, and consent may also be obtained remotely, where appropriate. When informed consent is obtained remotely, the investigator should assure themselves of the identity of the participant (or legally acceptable representative where applicable) in accordance with applicable regulatory requirements.
Ipsen	56	56	2.2.1	"Informed consent may be obtained remotely, where appropriate." Add clarification for potential local regulation retrictions.	"Informed consent may be obtained remotely, where appropriate **and accordance with applicable regulatory requirements**."
Syneos Health	56	59	2.2.1	In Annex 2 there are several references to the "local regulatory requirements".	As not all countries will have all requirements for all aspects (eg, section 2.2.1, investigator should confirm ID of participant if consent is obtained remotely) we do estimate that this may be challenging. It would be helpful if the Guideline could provide some minimum expectations for when a local regulatory authority is silent on expectations and also, to encourage greater harmonization of expectations across countries.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Trials@home	56	56	2.2.1	This section states that "informed consent can be obtained remotely, where appropriate". However, it is not stated when obtaining consent remotely can be considered or how this could be determined. Section 2.2.2 reflects on the characteristics of the trial population and provides considerations on how remote consenting could be accomodated. In acute settings, informed consent will - per definition - be obtained on-site. However, are there additional considerations that should be taken into account when determining whether obtaining informed consent remotely is appropriate?	
Trials@home	56	59	2.2	...in accordance with applicable regulatory requirements. How to proceed in case there is no local legal base (regultory requirement) about conducting certain DC elements e.g. shipment to patient's home?	There was at least one case where due to lack of legal basis, local authorities would not allow certains procedures. In such case could it be suggested to consider a higher level available regulation such as national or regional (e.g. EU) regulation?
Trials@home	56	59	2.2.1	Why is the remark about the assurance of identity here and not in Annex 1, since for all type of trials the investigator should be sure of the identity of the participant, correct?	Proposed change is to move this to Annex 1
EFGCP	59	59	2.2	Suggest an addition for pragmatic trials and/or RWD which by agreement of ethics, have participant affirmation for participation documented in the medical record. Rationale: if usual care is all that is required, affirmation for data use is all that is necessary as no additional assessments will be conducted.	
EFGCP	59	59	2.2.1	Additional text after statements regarding assurance of identity is required	“The mechanism used for this assurance should be documented or directed by the Protocol/written procedures/usual practice”
EUCROF	60	64	2.2.2	It would be good to mention that the method and tools of the IC process must not introduce a bias in participant selection	Add sentence: "The method and tools of the informed consent process must not introduce a selection bias in screening of participants."
European Huntington Association	60	61	2.2.2	In many contexts, digital exclusion is not only about familiarity, but also about access to modern technology systems and devices.	Proposed change: "(e.g., participants may lack familiarity or may not have access to electronic systems and devices)" instead of "(e.g., participants may lack familiarity with electronic systems)
Association for Clinical Data Management (ACDM)	63	64	2.2.2	*Trial participants may be given the option to use a paper-based approach and/or in-person consent process, to the extent feasible, should they prefer this* paper based approach is not always applicable (blind people, babies) - so the option on paper is not always feasible to anyone. We should also consider caregiver, legal authority…	Recommendation to expand options and to refer to Annex 1 section 2.8 as ICF should cover all aspects stated on that section.
EFGCP	63	63	2.2.2	Additional text proposed after ‘materials and process’.	Add “and described in the Protocol”
EFPIA consoldiated comment	63	64	2.2.2	The requirement of Provision is ambigious 'option to use a paper-based approach and/or in-person consent process,' Its not clear if econsent is included because even for paper based the participant need to be in person. Suggest ot provide / clarity for mode of consent - econsent / paper based	**When electronic and/or remote consent is used** trial participants may be given the option

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
European Huntington Association	63	64	2.2.2	The facilitation of individuals' informed decision-making regarding their participation in a clinical trial should be one of the key priorities in the informed consent process.	Proposed change: "Trial participants should be given the option to use a paper-based approach and/or in-person consent process, to the extent feasible, if they prefer this" instead of "Trial participants may be given the option to use a paper-based approach and/or in-person consent process, to the extent feasible, should they prefer this."
Ipsen	63	64	2.2.2	When mentioning paper-based approach, it would help to specify if it still refers to a remote consent method (e.g. by post)	"...option to use a paper-based approach (e.g. via post)…"
Association for Clinical Data Management (ACDM)	65	65	2.2.3	Nothing is covered about withdrawn consent and how to manage the data once the patient withdrawn and participants rights on their data, Participant as data owner of their data can decide the longer user of the data … How is this going to affect to these systems?	Please refer to Annex 1 section 2.8.11 (m)
EFPIA consoldiated comment	65	69	2.2.3	It is implied in Annex 2, section 2.2.3, that informed consent should describe what type of data will be collected". This requirement seems to be too technical and can lead for interpretation that all data sources must be indicated in the ICF and the mode of collection. Annex 1 expectation is broad "the ICF and the informed consent materials should explain the following (n) the process by which the paticipant´s data will be handled, including in the event of the withdrawal or discontinuation.."	Can it be considered to change "should describe how **~~what type of~~ the** data will be collected **and ~~, how the data~~** maybe used and who will have access to the trial participant´s personal information…"
EUCROF	65	69	2.2.3	The period of time for which data will be stored is not mentioned.	Suggest changing to: "The informed consent materials should describe what type of data will be collected, how the data may be used, how long data will be stored and who will have access to the trial participant’s personal information, such as health records and home address (e.g., when trial-related activities are conducted at the participant’s home or local healthcare centre or when data are collected remotely via DHTs)."
European Huntington Association	65	69	2.2.3	Clinical trial participants often express concern about where their personal data is stored.	Proposed change: "The informed consent materials should describe what type of data will be collected, how the data may be used, where the data will be stored, and who will have access to the trial participant’s personal information, such as health records and home address." instead of "The informed consent materials should describe what type of data will be collected, how the data may be used and who will have access to the trial participant’s personal information, such as health records and home address (e.g., when trial-related activities are conducted at the participant’s home or local healthcare centre or when data are collected remotely via DHTs)."
François Houÿez, Eurordis	65	69	2.2.3	For the consent, information should also include the notion of training necessary for the trial participant to operate some devices or IT systems remotely	The informed consent materials should describe what type of data will be collected, how the data may be used and who will have access to the trial participant’s personal information, such as health records and home address (e.g., when trial-related activities are conducted at the participant’s home or local healthcare centre or when data are collected remotely via DHTs). The materials should also explain the need for appropriate training for trial participants, when applicable, to operate devices or IT systems (apps, website etc.).

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Trials@home	65	69	2.2.3	Same comment as above, this should be described in any IC, correct?	Proposed change is to move this to Annex 1
European Huntington Association	67	69	2.2.3	I believe these examples make the sentence more confusing and less straightforward for the reader.	Proposed change: delete "(e.g., when trial-related activities are conducted at the participant's home or local healthcare centre or when data are collected remotely via DHTs).
Fondazione per la ricerca farmacologica Gianni Benzi onlus (FGB) for the European Rare Diseases Research Alliance (ERDERA)	69	69	2.2.3	In accordance with the EU rules including European Health Data Space (EHDS) regulation, individuals shall have the right to access their personal data: They also have the right to insert information; such information should be clearly distinguished from the data entered by healthcare professionals.	2.2.4. Informed consent should make clear that participants have the right to access their health records and enter information, if these are acquired electronically. Information added by participants must be clearly distinguishable from information entered by healthcare professionals
Lymphoma Coalition	70	108	2.3	Lack of guidance on emergency protocols for participants administering investigational products remotely.	Sponsors and investigators must provide participants with 24/7 access to emergency medical support (e.g., hotlines, telehealth) and clear instructions for managing adverse events during self-administration of investigational products.
Teva Pharmaceuticals	70	108	2.3.	The guideline appears to suggest administrative management tasks be completed by investigators, which may be difficult for them to complete. A later section (3.6) places certain administrative management responsibilities on the sponsor.	It is recommended that ICH reconsider the feasibility of placing any of these responsibilities on investigators.
Syneos Health	73	76	2.3	In Annex 2 it is specified that "the investigational product may be dispensed or supplied to the participant or to an appropriate designee (e.g., caregiver, home nurse, local pharmacist) for administration at the participant's location (e.g., participant's home, local healthcare centre) by appropriate parties (e.g., the investigator site staff, the participant, a home nurse or a local pharmacist).	We will appreciate additional clarification whether a caregiver can administer IP at the participant's location (if appropriate training is given and documented).
Association for Clinical Data Management (ACDM)	77	78	2.3	*These approaches should be arranged and conducted in accordance with applicable regulatory requirements* But also local requirements, IMP requirements on destroying medication, etc. Protocol should cover IMP management and in according to regulatory requirements.	
Trials@home	77	78	2.3	...in accordance with applicable regulatory requirements.How to proceed in case there is no local legal base (regultory requirement) about conducting certain DC elements e.g. shipment to patient's home?	There was at least one case where due to lack of legal basis, local authorities would not allow certains procedures. In such case could it be suggested to consider a higher level available regulation such as national or regional (e.g. EU) regulation?
AFI	78	81	2.3	The requirement in regards to the level of Investigator oversight is described at a very high level leading to interpretation with the risk to put in place non compliant approaches. As a guideline, it should support a more comprehensive approach.	To add some examples to clarify expectations on Investigator oversight according to what done for Annex 1. As a suggestion, in case of vendor involvement for home nurse services, initial qualification and/or contract agreement definition with a well described selection process and training program should be implemented by the Sponsor.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFGCP	81	81	2.3	Suggest addition of text for pragmatic trials:	"For trials that have risks no higher than and equivalent to usual care, additional records may not be necessary. The risk-based approach should be documented in the trial records and/or protocol."
INNODIA (INPACT: INNODIA People with Type 1 Diabetes Community)	81		2.3	**At-home administration**: At-home administration/use of investigational products may increase risk of administration errors. Some T1D investigational therapies require precise dosing (e.g., closed-loop insulin delivery trials, adjunctive therapies like SGLT inhibitors)—home-based administration may lead to unintentional misdosing.	Sponsors should ensure proper participant training and consider minimal oversight (e.g., self-reporting logs, virtual check-ins) where appropriate.
INNODIA (INPACT: INNODIA People with Type 1 Diabetes Community)	81		2.3	**Standardization of Glycemic Control:** Variability in therapeutic regimens (insulin use, continuous blood glucose monitoring technology, insulin pumps) makes it difficult to standardize inclusion and exclusion criteria.	Define clear clinical endpoints that demonstrate significant improvement compared to standard therapy.
INNODIA (INPACT: INNODIA People with Type 1 Diabetes Community)	81		2.3	**Continuous Glucose Monitoring (CGM)**: Variability in CGM algorithms can bias trial outcomes. Different CGM devices (e.g., Dexcom vs. FreeStyle Libre) use different glucose calculation algorithms, leading to potentially non-equivalent time-in-range (TIR) metrics across trial sites.	Ensure protocols define harmonized measurement intervals, data processing methods, and calibration requirements for CGMs.
Association for Clinical Data Management (ACDM)	82	84	2.3.1	Who is responsible for delivering the IMP to the patient? We should be more explicit here, if it is the investigator or the sponsor. Who is ultimately responsible on that. Maybe Sponsor is responsible for delivering the IMP to site and investigator to participants home - A delegation from sponsor to the investigator should clarify. The Study Protocol should describe the different accountabilities on IMP management.	
Trials@home	82	83	2.3	"...in accordance with applicable regulatory requirements." How to proceed in case there is no local legal base (regultory requirement) about conducting certain DC elements e.g. shipment to patient's home?	There was at least one case where due to lack of legal basis, local authorities would not allow certains procedures. In such case could it be suggested to consider a higher level available regulation such as national or regional (e.g. EU) regulation?
GQMA	85	93	2.3.1	It is important for the shipment of IP that an appropriate courier is used and that drivers are trained on relevant processes (e.g. handing over IP to trial participant, not leaving (returned) IP alone etc.).	Please add "If IP is being shipped, an appropriate courier specialized in transporting medical products should be used and it should be verified that respective staff is trained on the handling of medical products".
François Houÿez, Eurordis	87	88	2.3.1 (b	When the investigational product is to be sent to a PO box, or locker boxes that some transporters propose for the delivery of parcels, adequate measures should be in place to ensure eg storage temperatures are checked for suitabililty	That the investigational product is being received by the intended recipient (e.g., the participant or their appropriate designee, such as a caregiver), or when delivered to a PO box, that conditions for storage comply with the protocol.
EFPIA consoldiated comment	89	90	2.3.1 c	The guideline states, "The process for the receipt, storage, handling, administration, return, destruction or alternative disposition and accountability of the investigational product." The description of Handling is not consistent with Line 71.	Suggest word replacement: The process for the receipt, storage, handling, **dispensing,** administration, return, destruction or alternative disposition and accountability of the investigational product.
ESMO (European Society for Medical Oncology)	89	90	2.3	During the sending of the investigation product, some quality issues may arise such as temperature and handling.	It should be added that investigator should guarantee that IP would be sent with quality tests such as temperature monitoring system if required.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ESMO (European Society for Medical Oncology)	89	90	2.3.1.	How disposition and accountability of the investigational product outside the trial center will be ensured. Also in the ICF, the patients/outside centers, etc need to know what will be required of them should be detailed in the protocol.	May be additional text should be added "Procedures to ensure accountability should be clearly stated in the protocol and ICF".
Association for Clinical Data Management (ACDM)	92	93	2.3.1 e)	On top of that, Investigator is also responsible to train the patient on the use of the IMP, as well as, storage, reception, destruction of the IMP and to check that participant is following instructions properly - as per Annex 1 section 2.10.6	Recomendation to expand investigator responsabilities on training
European Huntington Association	94	94	2.3.2	The term investigator site is always used throughout the main document and annex 1, so I believe it is more coherent to stick to it.	Proposed change: "used in the investigator site" instead of "used in the institution/healthcare centre"
Trials@home	94	96	2.3.2	"...in accordance with applicable regulatory requirements." How to proceed in case there is no local legal base (regultory requirement) about conducting certain DC elements e.g. shipment to patient's home?	There was at least one case where due to lack of legal basis, local authorities would not allow certains procedures. In such case could it be suggested to consider a higher level available regulation such as national or regional (e.g. EU) regulation?
Breakthrough T1D	101	101	2.3.3	"See section 2.3 on the level of oversight": Clarification is sought if this sentence refers to section 2.3 of Annex 1 (Responsibilities) or to the section on oversight in (this) Annex 2, in which case it should read "See section 2.4 on Investigator Oversight."	Clarification is sought from the EMA.
EFPIA consoldiated comment	101	101	2.3.3	Section 2.4 of the document refers to "Investigator oversight". However line 101 states " See section 2.3 on the level of oversight"	Please confirm that section **2.4** should be referenced instead of section 2.3 in line 101 ?
EUCROF	101	101	2.3.3	Reference to section 2.3 on the level of oversight is confusing and misleading. The reader might think this is a typo and the reference should read "See section 2.4 on the level of oversight" as the heading of 2.4 is "Investigator Oversight. EUCROF understands that the reference to section 2.3 is reference to lines 78 - 81 in section 2.3.	Change to "See section 2.3 above on the level of oversight."
GQMA	101	101	2.3.3	A reference to section 2.3 regarding the investigator oversight is made. However, it may be that section 2.4 in Annex 2 is meant to be referenced here instead.	Change wording to: "See section 2.4 on the level of oversight."
Ipsen	101	101	2.3.3	"See section 2.3 on the level of oversight." Clarify if this is referring to Annex 1 or section 2.4 of Annex 2 (Investigator Oversight)	"See **Annex 1,** section 2.3 on the level of oversight." or correct section typo
Trials@home	101	101	2.3.3	"See section 2.3 on the level of oversight"	Should this be a reference to section 2.4 Investigator Oversight instead of section 2.3 (i.e., Investigational Product Management)?
Association for Clinical Data Management (ACDM)	103	106	2.3.3	"alternative disposition" is not a clear term. Disposition should be according to the protocol as well - Do we expect accountability by the participant? Do we expect some kind of control on IMP disposition at participant (temperature exclusion, etc…)	Recomendation on how IMP management at home should be provided and different accountabilties on patient, investigator and sponsor as well on oversight.
Syneos Health	104	106	2.3.3	In Annex 2 there are several references to the "local regulatory requirements".	It would be helpful if the Guideline could provide additional guidance on who would be an appropriate designee to receive IMP delivered to the participant.

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Trials@home	104	106	2.3.3	"...in accordance with applicable regulatory requirements." How to proceed in case there is no local legal base (regultory requirement) about conducting certain DC elements e.g. shipment to patient's home?	There was at least one case where due to lack of legal basis, local authorities would not allow certains procedures. In such case could it be suggested to consider a higher level available regulation such as national or regional (e.g. EU) regulation?
EFPIA consoldiated comment	107	108	2.3.3 (b)	The guideline states, "Commencement, continuation, dose and dose adjustments of the allocated investigational product in accordance with the protocol." This statement is too brief and may not be easy to understand. It is recommended to provide a more detailed description.	Suggest replacing text: "~~Commencement, continuation, dose and dose adjustments of the allocated investigational product in accordance with the protocol"~~ to " **Allocating the investigational drug, prescribing the dosage, adjusting the dosage, and monitoring ongoing use in accordance with the protocol."**
EFGCP	108	108	2.3.3	Addition of extra bullet to cover the various orgs involved	(c) Service providers, Pharmacists and/or the Sponsor may support the investigator in this aspect, for example through the provision of delivery, utilization and return reports
François Houÿez, Eurordis	109	120	2.4	Among healthcare professionals who are part of medical practice, more and more interim staff is employed. Or unplanned replacements by colleagues form other hospital departments. Staff might not be fully aware than some routine practice data are also collected for the purpose of a clinical trial, or might not have been fully trained / explained about the protocol, or th einvestigator(s) might not be fully aware of which other healthcare professionals are part of the clinical practice.	
GQMA	109	125	2.5	It is important for the investigator and/or sponsor to keep oversight on service providers by the Investigator (e.g. Home Care Nurses) and also if contracted by the sponsor. A respective paragraph should be added in regards to this responsibility.	Please add "The investigator should perform oversight on relevant healthcare personnel provided by a service provider irrelevant if contracted by the sponsor or by the investigator / trial site".
Lymphoma Coalition	109	125	2.4	There is a gap in this section, as it lacks to mention the mechanisms for participants to report concerns or grievances during the trial.	Investigators shall establish clear, accessible channels for trial participants to report concerns or grievances (e.g., dedicated hotlines, third-party ombudspersons). Participants must be informed of these mechanisms during the consent process.
EFPIA consoldiated comment	110	111	2.4	Edited to provide clarity that it is their routine clinical practice Suggest inserting 'routine' before clinical practice to make the clear distinction that this is not just part of the clinical trial	Healthcare professionals **that are not directly involved in a clinical trial m**ay be involved in performing trial-related activities ~~that are~~ **as a part** of **their routine** clinical practice.
Medicines for Europe	110	120	2.4	Investigator oversight: The document addresses the involvement of healthcare professionals in trial-related activities within clinical practice. The annex should clarify the specific expectations regarding training and oversight of these professionals when they are not directly under the principal investigator authority.	Clarify expecations regarding training and oversight of these professionals

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ESMO (European Society for Medical Oncology)	112	125	2.4	Oversight in clinical trials is a critical component in the conduct of the trial; it is critical to ensure that trial-related activities conducted by HCPs outside of the trial do not jeopardize the trial, thus it should be clear to non trial HCPs treating a clinical trial patients that a patient is part of a trial and that their actions could affect trial data and patient wellbeing (adding or omitting medication), interventions etc.	Add: Adequate oversight in clinical trials is essential to maintaining data integrity and ensuring patient safety. It is crucial that healthcare professionals (HCPs) not directly involved in the trial are aware when they are treating a patient enrolled in a clinical trial. Their clinical decisions—including the addition, modification, or omission of medications or interventions—may impact trial data validity and patient well-being. Therefore, clear mechanisms should be established to ensure effective communication between trial investigators and non-trial HCPs to mitigate risks and maintain protocol adherence.
FVR – Finnish Vaccine Research	112	118	2.4	There is confusing information in Annex1, Annex 2 and the presentation in the ACT EU workshop on ICH E6 R3 19th Feb, 2025 (Principles and Annex 1). During the ACT EU workshop on ICH E6 R3 we learned, that "Healthcare professionals may be involved in performing trial-related activities that are part of clinical practice. For such activities, *delegation or appropriate arrangements should be in place* ". Annex 1, section 2.3.3:says: "In situations where the activities are performed as part of clinical practice, *delegation documentation may not be required* ". Now Annex 2, section 2.4. (rows 112-115) says "If knowledge about the protocol, investigator's brochure or other trial-related document is necessary to perform a trial-related activity, this activity should be performed by delegated persons or parties who are under appropriate oversight of investigator and have been appropriately trained, if needed". However, chapter 2.4 (rows 116-118) says: **"For trial-related activities conducted in clinical practice by healthcare professionals which do not require knowledge about the protocol, investigators' brochure, or other trial-related documents, appropriate arrangements and appropriate investigator oversight should be in place".** The requirement for *investigator oversight and delegation* would make impossible e.g. a large phase 4 pragmatic pneumococcal vaccine trial, in which the primary endpoint is invasive pneumococcal disease (IPD, a pneumococcal finding in a blood culture sample) obtained according to routine clinical practices in any health care setting throughout the country, with obligation to transfer the information of the finding into the National Infectious Diseases Register, where the investigator can get access to. See https://pubmed.ncbi.nlm.nih.gov/23158882/	"For trial-related activities conducted in clinical practice by healthcare professionals which do not require knowledge about the protocol, investigators' brochure, or other trial-related documents, appropriate arrangements ~~and appropriate investigator oversight~~ should be in place, **but the need of investigator oversight, delegation and training should be proportionate to the risks to trial participant safety and data reliability**".

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Good Clinical Trials Collaborative (GCTC), https://www.goodtrials.org/	112	120	2.4	In section '2.4 Investigator Oversight', it is helpful to have guidelines on appropriate involvement of healthcare professionals. Lines 121 to 125 are useful in emphasising proportionality and a focus on participant safety and reliability of results. However, we are concerned that lines 112 to 115 will be overinterpreted. This paragraph suggests that "if knowledge about the protocol, investigator's brochure or other trial-related document is necessary to perform a trial-related activity", then delegation, oversight and training are required. While the text does add some nuance and qualification (e.g. "if needed"), we believe that it should be clearer that for many activities little if any knowledge of the protocol is required and thus oversight, delegation and training obligations for those should likewise be minimal or none. For example, phlebotomists may be required to do an additional blood draw or take an extra tube of blood, or a radiographer may be required to send a copy of the x-ray to a particular person for reporting/filing. Requiring delegation of duties logs for that is disproportionate, burdensome, and will require extensive monitoring, review and updating for no gain in participant safety or data reliability.	Lines 112 to 115 should be edited to read: "If substantial or detailed knowledge about the protocol… is necessary…" Lines 116 to 120 should be adapted as follows: "For trial-related activities conducted in clinical practice by healthcare professionals which do not require knowledge about the protocol, investigators' brochure, or other trial-related documents or where activities are within Usual Care Competence, appropriate arrangements and appropriate investigator oversight should be in place. Such arrangements should address plans for making relevant information and records available to the investigator." Add a definition of "Within Usual Care Competence" as follows: "Within Usual Care Competence: An activity that an organization or individual is competent to undertake (through current staff experience/training and facilities), but the activity would not happen in quite the same way and/or at the same point in the care pathway if the research study was not taking place." [Note: This is based on the UK Health Research Authority definition of Usual Care Competence.]
Trials@home	112	115	2.4	This sentence ends with "if needed". Are there situations when knowledge about the protocol, IB or other trial-related documents is required but appropriate training is not needed?	Leave out "if needed" from line 115.
Trials@home	112	115	2.4	Investigator Oversight: If knowledge about the protocol, investigator's brochure or other trial-related document is necessary to perform a trial-related activity, this activity should be performed by delegated persons… The use of the term "trial-related document" could be interpreted as anything that is in additional to Routine Clinical Practice, so may unintentionally exclude the use of instructions to the local HCP (e.g. instructions to HCP of where/how to send the results, or if assessments need to be done in a particular order).	Amend the wording so that it is feasible that a local HCP can follow "trial-related" instructions while not being delegated, and performing activities as they are clinically trained to do. For example add a sentence to the effect "Note that this does not exclude the HCP performing activities following some trial-related instructions, be they operational/administrative such as: how data will be shared (e.g. encrypted email, software platform), how data is attested (e.g. certified copy), how data privacy of participant data is maintained in transfer, how to access to systems/software, etc.; or clarifying expectations and roles and responsibilities such as: reporting any change of health condition and safety concern to the PI within timelines, the responsibility of trial-related decision-making and interpretation remains with the PI, specific process / sequence required of the trial."
Association for Clinical Data Management (ACDM)	116	118	2.4	Please include reference to Principles and Annex 1, as this is stated there. Appropiate training to investigator staff to perform their task. - we recommend to update sentence 116 "which do not require" as it may be confusing and contradicting with Annex 1 section 2.3.2 As on Annex 1 section 2.3.2 - Trial-related training to persons assisting in the trial should correspond to what is necessary to enable them to fulfil their delegated trial activities that go beyond their usual training and experience.	we recommend to update sentence 116 "which do not require" as it may be confusing and contradicting with Annex 1 section 2.3.2 Would it be better to include reference to the delegation log - as stated on Annex 1 section 2.3.3.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUCROF	116	125	2.4	If a healthcare professional does not have to know the protocol and consequently is not trained on the protocol, this person is usually not listed on the investigator's Signature and Delegation Log (or is not listed as sub-investigator on the FDA 1572 Form). It is not clear how an investigator should exercise oversight over those who only perform routine procedures (according to normal clinical practice) and produce routine data. It could also be that the data come from secondary use of data sources - what would be the appropriate oversight in that case? The requirement for appropriate oversight over those who do not need to know the protocol and consequently are not trained, is not totally conclusive and details are missing how such an oversight might look like.	If this section applies exclusively to decentralised trials, it should be said so. If not (i.e. it also applies to the use of RWD), more guidance (like examples) is needed as to how investigator oversight can be implemented.
Ipsen	116	118	2.4	Not sure what trial-related activities are covered here while performed by "non-delegated" persons. Is this referring to exams conducted as per the usual standard of care?	Please clarify section to improve understanding
PTC Therapeutics Limited	116	117	2.4	Provide an example or specific cases where for trial-related activities conducted in clinical practice by healthcare professionals which do not require knowledge about the protocol.	
Trials@home	116	120	2.4	"appropriate arrangements and appropriate investigator oversight should be in place". What should these include? Section could benefit from clarification.	
GQMA	118	120	2.4	It is unclear why the Investigator should receive relevant information and records. Instead that information should be made available to that staff not requiring training on protocol, IB etc.	Change wording to: "Such arrangements should address plans for making relevant information and records available to those healthcare professionals."
Ipsen	118	120	2.4	"...appropriate arrangements and appropriate investigator oversight should be in place. Such arrangements should address plans for making relevant information and records available to the investigator." Does this mean that the Investigator must have a documention of the arrangements?	Please clarify section to improve understanding
EFGCP	120	120	2.4	New text addition relating to standard care considerations	“Consideration should be given to specific guidance on adverse event reporting where standard care is relied upon.”
Association for Clinical Data Management (ACDM)	121	121	2.4	Risk proporcionate approach should be also considered on the level of oversight	
European Huntington Association	121	125	2.4	I believe the section's readability will improve with a rearrangement of the content.	Propsed change: Move the paragraph "The level of investigator oversight of the trial-related activities should depend on the nature of the 121 activities and be proportionate to the risks to trial participant safety and data reliability, and the 122 importance of the data being collected. Such oversight should ensure that the resulting records 123 meet the relevant requirements of the protocol and thereby ensure reliable trial results, trial-124 participant safety and appropriate decision-making." to line 112.
European Huntington Association	122	122	2.4	In a clinical trial, validity and reliability are both essential to ensuring that the results are meaningful and trustworthy. Reliability in a clinical trial usually refers to the consistency of measurements or results, whereas validity refers to the accuracy of measurements or results.	Proposed change: "risks to trial participant safety and data validity and reliability…" instead of "risks to trial participant safety and data reliability,…"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
FVR – Finnish Vaccine Research	126	130	2.5	Individual level evaluation of each SAE may not be necessary in a large phase 4 pragmatic trial. Registers can be used to monitor e.g. all hospitalisations, deaths, AESIs or other defined events and to assess the causality by detecting and confirming safety signals in a timely, unselected and objective epidemiological/statistical analysis, together with individual case analysis, if needed. See https://pubmed.ncbi.nlm.nih.gov/39691210/	For the safety monitoring of ~~**individual**~~ trial participants (see Annex 1, section 2.7), the investigator should review and assess information on the health status of participants across the sources of safety-related information (e.g., home nursing, remote trial visits, use of DHTs **or registers**).
FVR – Finnish Vaccine Research	126	130	2.5	Chapter text is confusing. Sentence 1 deals with investigator role in monitoring individual trial participants, while sentence 2 deals with sponsor role in informing investigator of the safety events reported elsewhere. Is the "Annex 1, section 3.13.2." correct?	Sentence 2: See section 3.9 and Annex 1, section 3.13.2 for details on how **the safety information reported elsewhere will be provided to the investigator by the sponsor.**
Miroslava Calegari	126	130	2.5	The current text does not account for variability in data collection methods across different settings, which can introduce inconsistencies. Standardized protocols for data collection and validation are necessary to ensure reliable monitoring, comparability, and completeness across participants and sites. Ensuring consistency in data collection is especially important in decentralized trials and those incorporating real-world data sources. Change proposed aligns with global recommendations on safety data collection in decentralized and real-world data-based trials. Standardization ensures data integrity and enhances regulatory acceptance.	For the safety monitoring of individual trial participants (see Annex 1, section 2.7), the investigator should review and assess information on the health status of participants across the sources of safety-related information (e.g., home nursing, remote trial visits, use of DHTs). The protocol should define standardized methods for capturing and reporting safety data across different trial settings to ensure consistency and comparability. Special consideration should be given to participants using real-world data sources (e.g., electronic health records, patient-reported outcomes) to address data completeness and reliability. See section 3.9 and Annex 1, section 3.13.2 for details on how this information will be provided to the investigator.
Trials@home	126	130	2.5	I would like to question whether it is always necessary for an investigator to review and assess information on the health status of participants across the sources of safety-related information. For example, if in a conventional trial safety assessment would be done at every monthly site visit would the investigator still need to review the patient diary for additional possible safety issues or not? If not, then we should apply the same priniciple here, e.g. if there are 4-weekly telemedicine visits to assess safety issues, is it then still necessary to, on top of that, review all other data that come in through other sources such as DHTs?	Recommendation is to reword this sentence in that it should be done adequately and may involve review of information accross the sources if safety-related information. Now it is written down as something mandatory.
EFGCP	127	127	2.5	New text addition relating to risk based approach and use of ICH E19	"For pragmatic trials and real world data, Sponsors should consider a risk-based approach to safety data collection as guided by ICH E19, and the objectives of the study. The burden to Investigators and the trial team should be considered in managing this information when reporting events and receiving reports from the trial Sponsor."
INNODIA (INPACT: INNODIA People with Type 1 Diabetes Community)	130		2.5	**Lack of Clear Accountability for Safety Oversight in Multi-Provider Trials**:In decentralized trials, safety monitoring may involve third-party providers (e.g., home nurses, telemedicine platforms), but the guidance does not define who is responsible for ensuring timely adverse event (AE) reporting	Require sponsors to define accountability measures for safety monitoring across service providers.
INNODIA (INPACT: INNODIA People with Type 1 Diabetes Community)	130		2.5	**Intervention needs:** Decentralized trials must account for real-time intervention needs. People with Diabetes require immediate action in case of severe hypoglycemia or ketoacidosis, but decentralized trials assume patients can self-manage emergency situations.	Require real-time alert mechanisms (e.g., CGM-based alarms) and caregiver involvement where needed.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
INNODIA (INPACT: INNODIA People with Type 1 Diabetes Community)	130		2.5 & 3.9	**Lack of Explicit Protections for Vulnerable Populations**: The guidance does not clearly require additional safeguards for participants needing caregiver support (e.g., children, elderly, cognitively impaired patients).	Explicitly mention these groups in trial safety planning and investigational product management.
Lymphoma Coalition	132	153	3.1	While this section of the guideline highlights the value of engaging patients and advocacy groups, it does not mandate their inclusion in trial design or protocol review. In addition, there is no acknowledgment of compensating patients or advocacy groups for their time and expertise in trial design.	Add: Sponsors should engage patients and advocacy groups at early stages of protocol design, ensuring that patient-relevant endpoints, recruitment strategies, and digital tool accessibility are adequately addressed. Sponsors should consider providing fair compensation (monetary or non-monetary) to patients, caregivers, or advocacy groups for their contributions to trial design, ensuring ethical and non-coercive practices.
EFPIA consoldiated comment	133	133	3.1	Revise 'stakeholders' to be consistent with terminology used in Annex 1.	Revise 'stakeholders' to **'interested parties'.**
Medicines for Europe	133	159	3.1	More detailed guidance on how to engage with different stakeholders could be provided to enhance the practical application of the guideline	Adding a guidance on how to engage with different stakeholders, including patients, regulators, and sponsors, throughout the trial process
Teva Pharmaceuticals	133	159	3.1.	More detailed guidance on how to engage with different stakeholders could be provided to enhance the practical application of the guideline	Adding a guidance on how to engage with different stakeholders, including patients, regulators, and sponsors, throughout the trial process
Association for Clinical Data Management (ACDM)	137	137	3.1.1	Where the trial is being conducted, which countries should be also considered. Depending on the region there would be some potential gaps on internet connection, availability to new technologies, etc..	Recomendation to include alignment with ICH GCP E8 (engaging patients) but also, need to include countries characteristics
Breakthrough T1D	137	144	3.1.1	Breakthrough T1D welcomes and supports the inclusion of patients and patient advocacy groups early in trial design (e.g., suitability of digital health technologies in decentralised trials) and where additional training/support could be required e.g., digital literacy, physical ability. However, this section can be strengthened by using the principle from the World Health Organization's Guidance for Best Practices for Clinical Trials guidance, particularly the final sentence: "This activity is particularly important in trials that incorporate decentralised elements, pragmatic elements and/or RWD, where particular skills requirements, technologies or practical considerations may only be identified through such engagement."	Incorporate and link the WHO guidance to give a a more global perspective to Annex 2.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
European Cystic Fibrosis Society Clinical Trials Network (ECFS-CTN)	137	139	3.1.1	We note that the ICH E6(R3) Principles document addresses the broad benefits of patient engagement in planning and conducting clinical trials. We strongly suggest expaning Section 3.1.1 by more explicitly stating the different ways in which community engagement benefits a trial with decentralised or RWE elements. These benefits could be listed in bullet point form in Section 3.1.1 (similarly to 3.1.2). For example, patients can give crucial input into **choosing** the correct operational approach or data source, as well as advising on how to optimise integration and optimisation. We advise repeating the general benefits of community enagagement in Section 3.1.1 of Annex 2, to drive home the message that community engagement and involvement is key to trial success. WE provide some example text in cell G17.	Engaging patients, patient advocacy groups and their communities, as appropriate, can help ensure successful clinical trials, by giving expert input into the successful choice, integration and implementation of various operational approaches and data sources in trials. Early engagement can help: (a) identify issues related to practicability and integrability of the operational approach into the participants' everyday lives (b) assessing the burden of a study and the willingness to participate leading to higher participation rates, and how decentralised and real-world trial elements can influence this. (c) to determine the benefit of study results for the community, to address real patients needs and to increase real-world applicability (d) to find out about information needs regarding the study to enable informed decision making
François Houÿez, Eurordis	137	144	3.1.1	Engaging patients, patient advocacy groups and their communities can also help select which data are most relevant for the clinical trial, not just the sources of data. Ideally, patients and their advocacy groups should review which data are needed to respond to the research question(s), and exclude other unnecessary data from the trial data.	
François Houÿez, Eurordis	137	144	3.1.1	When engaging with trial participants remotely, investigator(s) should ensure appropriate communication flows are in place. Emails or text messages can be sent at a time where the trial participant is not receptive and the message be left unnoticed. Preferences for which communication channel to use, at what time in the day or in the evening and for urgent communication in particular should be discussed prior to consenting to take part in the trial	
Good Clinical Trials Collaborative (GCTC), https://www.goodtrials.org/	137	144	3.1.1	The inclusion of text to promote engaging patients, patient advocacy groups and their communities in Section 3.1.1 (lines 137 to 144) is noted. However, the text falls substantially short of reflecting established best practice in clinical trials by describing an unduly limited set of potential areas for involvement and consultation.	The text in Section 3.1.1 should be revised to incorporate the relevant principle from the World Health Organization’s Guidance for Best Practices for Clinical Trials, as follows: “Patients, patient advocacy groups and their communities provide valuable contributions to the design, execution and interpretation of the results of clinical trials. Their early involvement can play a key role in: defining, refining and prioritizing research questions; assessing and increasing the acceptability and feasibility of the trial, selecting trial interventions and outcomes that are relevant and meaningful to the intended population; developing the trial design and procedures; optimizing the nature and delivery of information; and encouraging dialogue about access to health care interventions that prove effective. This activity is particularly important in trials that incorporate decentralised elements, pragmatic elements and/or RWD, where particular skills requirements, technologies or practical considerations may only be identified through such engagement.”
Lymphoma Coalition	137	144	3.1.1	The guideline missed a requirement to share trial outcomes or data usage details with participants post-trial.	Add: Sponsors should commit to providing participants with summaries of trial outcomes and explanations of how their data contributed to the study, unless explicitly waived by the participant.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Lymphoma Coalition	137	144	3.1.1	Ther guideline does not provide guidance on mitigating technology literacy gaps in decentralized trials using DHTs.	Add: Sponsors must assess participants' technological literacy during trial design and provide tailored training, user-friendly tools, or alternative methods (e.g., paper-based systems) to ensure equitable participation.
EUCROF	139	144	3.1.1	Early engagement with patient advocacy groups is mentioned but no reference to feedback loops for trial design improvements. Patient-centric approach is being disucssed widely.	Propose to reference Annex 1 section 3.1.3.
Trials@home	140	141		It is acknowledged that trials with decentralized elements do not use per definition DHTs. This could be reflected in Annex 2.	Consider adding "when" before the phrase "used in trials with decentralised elements" or alternatively "when used in clinical trials"
European Huntington Association	143	144	3.1.1	I believe it is unclear what this specialized training entails. Does it refer to technology training?	Prposed change: Clarify what this training refers to - "specialised training or the provision of technology).
EORTC	145	147	3.1.2	When non-commercial trials are concerned, they are usually designed and conducted by investifgators or network of investigators. In such case, healthcare providers and sponsors are the same entities/ persons	Consider specific wording for clarifictaion of responsibilities for non-commercial clinical trials
EFPIA consoldiated comment	149	149	3.1.2 (b)	The term "workflow" is unclear in this context. Suggest changing "workflow" to "routine practice" or specify what exactly is meant with routine workflow, e.g. clinical routine procedures	Develop protocols that incorporate the routine ~~workflow~~ **clinical practice** of healthcare
ESMO (European Society for Medical Oncology)	152	153	3.1.2.	Research nurses may also heLp in designing more confortable trials from the beginning. May of the procedures in the clinical trials are not always needed and they add more complexity specially for the patients logistics.	It may be useful to add that healthcare professionals should also garante that all the procedures added in the workflow are actually relevant and useful.
European Huntington Association	153	153	3.1.2	Healthcare professionals and/or investigators may have a key role in anticipating constraints and plan in advance effective ways to overcome these constraints.	Proposed change: Include another point "d) Identify potential constraints in trial implementation and proactively plan effective strategies to address them."
DARQA	154	159		"Sponsors are encouraged to engage with regulatory authorities". While this is an excellent suggestion: When more Sponsors indeed start to engage with authorities early, are authorities ready for this?	
EUCROF	154	154	3.1.3	IRBs/IECs should be added as well as in many countries, the sponsor is also in charge to submit to IRBs/IECs.	Change as follows: "Sponsors are encouraged to engage with regulatory authorities and IRBs/IECs, as applicable, especially …"
European Huntington Association	154	154	3.1.3	The term "Engaging" is used on the other entrances,so I believe it is more coherent to stick to it.	Proposed change: "Engaging with regular authorities should be done early, especially...." instead of "Sponsors are encouraged to engage with regulatory authorities early, especially…"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Good Clinical Trials Collaborative (GCTC), https://www.goodtrials.org/	154	156	3.1.3	The encouragement on lines 154-156 "to engage with regulatory authorities early, especially when designing and planning trials that use various operational approaches… and RWD sources" appears not to account for constraints on regulators' capacity to meet expectations for advice, either in relation to timeliness, resources or expertise. While constructive, timely dialogue with regulators is desirable, the current wording may risk generating demand that exceeds capacity and may also lead to a perception of increased risk or cost associated with decentralised/pragmatic elements or use of RWD sources. Some regulators who provide such scientific advice are already over-subscribed and have long turn-around times. Such guidance may also have adverse consequences such as creating: (i) Perception of additional risk (ii) Unreasonable additional cost (iii) Substantial additional delays (iv) Increasingly conservative approaches to avoid the above. For example, Sponsors may avoid sensible design choices (e.g. use of decentralised elements or use of RWD) if they believe that they would then necessitate lengthy or costly delays waiting for regulatory feedback.	Edit section 3.1.3 to read: "Sponsors may engage with regulatory authorities early, especially when designing and planning trials that use various operational approaches (including complex design elements and technological tools) and RWD sources. Early engagement will may help address the appropriateness of using such operational approaches and RWD sources in the design of their trial and will allow for timely identification of challenges and strategies for resolution."
Trials@home	154	159		The phrase "various operational approaches and data sources" could benefit from greater specificity, where appropriate. For example, in the context of recommending early engagement with regulators, one could argue whether this is always necessary.	Suggestion to rewrite line 155 to "especially when designing and planning trials that use complex design elements and technological tools, and RWD sources."
European Huntington Association	155	156	3.1.3	I believe providing more concrete examples of these various operational approaches would be helpful.	Proposed changes: Clarify these examples "(including complex design elements and technological tools)"
EORTC	156	159	3.1.3	reference is being made to agree with authorities for the the sources of RWD. This is confusing, all trials largely use existing RWD. Should not it be referred rather to the method of accessing to data in a decentralised manner	Across the document, ensure dichtomy between RWD and the methods through whci these data will be collected in a decentralised manner
Lymphoma Coalition	160	188	3.2	The section lacks a requirement to consider patient-relevant endpoints, particularly quality of life (QoL) measures.	Add: The selection of endpoints should include patient-reported outcomes (PROs) to capture quality-of-life measures and treatment burden, ensuring clinical relevance to patients.
EUCROF	162	164	3.2	"Additional consideration may need to be given to the protocol and/or protocol-related documents when utilising various operational approaches and/or data sources so that all parties involved in the trial conduct are adequately informed." This sentence only covers trial conduct but not trial assessment. The assessment by regulatory authorities and IRB/IEC, as applicable, is not addressed.	Change to "Additional consideration may need to be given to the protocol and/or protocol-related documents when utilising various operational approaches and/or data sources (decentralised or pragmatic elements or the use of RWD, as applicable) so that all parties involved in the trial assessment and conduct are adequately informed.
EFGCP	164	164	3.2	New Text addition. Rationale: case studies and examples will support widespread adoption and innovative approaches	Addition: "Regulators are encouraged to publish guidance and information (to the extent possible), on those operational approaches for complex designs, technological tools and RWE sources that have been considered acceptable in given trial designs."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
INNODIA (INPACT: INNODIA People with Type 1 Diabetes Community)	164		3.2	**Data Standardization Gaps in Decentralized and Real-World Data (RWD) Trials**:The guidance does not require sponsors to harmonize data collection across different digital health technologies (DHTs), leading to inconsistencies in safety assessments and trial endpoints.	Ensure protocols define how different data sources are standardized, particularly for continuous monitoring tools.
Trials@home	165	169	3.2.1	See my previous comment on lines 45-48, section 2.1 Whereas design elements and data sources should be adequately described why should the appropriateness of their use be justified? Shouldn't we then also ask to justify why in conventional trials we sometimes burden participants with collect of data which is already available in RWD sources or why we ask for participants to come to site, instead of possibly decreasing their burden by performing a visit remotely.	Recommendation would be to delete everything after 'The specific design elements and data sources should be adequately described in the protocol'
ESMO (European Society for Medical Oncology)	170	174	3.2.2.	To avoid inconsistency of data it should be predefined what data are collected from which source and how.	Could add the following" It should be clearly stated (in protocol/protocol related documents).
Miroslava Calegari	170	174	3	The current text acknowledges variability but does not suggest specific solutions to mitigate inconsistencies. Standardization in data collection methods ensures that differences in trial sites, timing, or remote participation do not introduce bias into results. Addressing data standardization is especially critical for trials using real-world data or digital health technologies (DHTs), as these sources often lack uniform reporting mechanisms. Ensuring data standardization enhances regulatory acceptance and trial reliability, especially in multi-site and decentralized trials.	Since data may originate from different sources or various practice settings (e.g., sources with different timing of data collection), there may be data variability within and/or between data sources/settings. The impact of such data variability should be considered in the trial design and discussed in the protocol or protocol-related documents (e.g., statistical analysis plan). To ensure consistency, sponsors should define standardized methodologies for data collection, harmonization, and validation, particularly for trials incorporating real-world data (RWD), digital health technologies (DHTs), and decentralized monitoring tools.
Trials@home	170	172	3.2.2	"Should be considered" -> If the effect of setting is unknown, should this preclude flexibility in location?	
EFPIA consoldiated comment	171	174	3.2.2	Recommend to consider data harmonisation early to enable pooling from multiple data sources/settings. Suggest to add this text. Potentially change the order to have variability last in 3.2.2	**Data harmonisation should be considered early in order to enable analysis of data captured from different settings, if relevant.**
EUCROF	175	177	3.2.3	It could be that other individuals, like healthcare professional or data managers need to be trained as well, when RWD sources are used. This should be added.	Change as follows: "The design elements and data sources should be considered when determining the need for appropriate training and technical support to be provided to the investigator, investigator site staff, healthcare professionals, sponsor personnel (e.g., data managers) and participants (see Annex 1, section 2.3.2)."
EFGCP	176	176	3.2.3	Need to add in Study Staff before investigator to cover vendors	Insert "study staff" before Investigator, for example when using a CRO/specialist vendor.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA consoldiated comment	178	182	3.2.4	There is a lack of clarity on what “emerging abnormalities” , how they are identified and by whom. This term has not been used in the Principles and Annex 1 nor in other regulatory documents / guidelines. To change to a well defined / commonly used term across guidelines, such as safety concerns or other terms defined in regulatory documents or provide more clarity, such as examples, on what emerging abnormalities are, how they are identified and by whom.	The protocol and, where applicable, protocol-related documents should describe how safety information will be collected from the variety of data sources (e.g., by DHTs, in- person or remote visits), how emerging ~~abnormalities~~ **information** potentially related to participants’ safety will be identified and made available to the investigator and what actions should be taken by the investigator in these instances.
François Houÿez, Eurordis	178	186	3.2.4	The trial own data base can extract data from electronic health records and from other systems; including manual entry by the investigator(s). With Digital Health Technologies, large quantities of data can be sent to the investigator(s) by the trial participants. To reduce the workload for investigator(s), devices might sent the data directly to the Trial Data Base, with nno supervision by the investigator(s). If the case, automated alert systems should be in place in the Trial Data base to inform the investigator(s) of abnormal values being enterred in the Trial Data Base, when applicable	
Ipsen	178	178	3.2.4	It would be helpful to add examples after the statement "protocol-related documents" to provided clarification/expectations of where such details should be recorded based on study design.	Add examples of "protocol-related documents"
Trials@home	178	182	3.2.4	See my previous comment on line 126-130, section 2.5. Also, we should not forget that in a traditional clinical trial the participant is most of the time at home out of sight of the investigator so we could again argue that the sample principles apply there	Proposed change would be 'The protocol... should descrive how safety information will be collected and from which data sources'
Trials@home	183	185		These sentences reflect on decision making regarding (the way of) trial participation. Safety information that is obtained remotely and provided to the investigator could also trigger additional safety monitoring actions (e.g., need for a visit; in-person of via teleconference) and trial protocols could also describe how/when this is triggered and escaleted.	Suggestion to add that the triggers for different ways of following up on this safety information should be described in the trial protocol.
Fondazione per la ricerca farmacologica Gianni Benzi onlus (FGB) for the European Rare Diseases Research Alliance (ERDERA)	187	188	3.2.5	The protocol should describe also the modalities of the informed assent process in case of trials with children	Modalities of the informed consent and assent process (e.g., remote or in-person) should be described in the protocol.
Trials@home	187	187		Here, 'remote' and 'in-person' are presented as opposites/mutually exclusive. However, remote visits (i.e., conducted outside the invesitgator's location) can be in-person (e.g., with site study staff or local HCPs), using teleconference calls, or via a telephone call. In other words, in-person visits can be remote or on-site.	Annex 2 should not present "remote" and "in-person" as opposites (when remote is defined as "outside the investigator's location").
Trials@home	190	192	3.3	"...in accordance with **local regulatory requirements**." How to proceed in case there is no local legal base (regultory requirement) about conducting certain DC elements e.g. shipment to patient's home?	There was at least one case where due to lack of legal basis, local authorities would not allow certains procedures. In such case could it be suggested to consider a higher level available regulation such as national or regional (e.g. EU) regulation?
UNICANCER	190	192	3.3.	Communication with the IEC: various operational approaches and data sources being used (sponsor): Same comment	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
UNICANCER	190	192	3.3.	Communication with the IEC: various operational approaches and data sources being used (sponsor): Communication with the regulatory authority should also be considered	Unicancer recommendation is to add a section "Regulatory authority"
EUCOPE	193	196	3.4	In situations where RWD are used, the sponsor should ensure that appropriate consent or permission for the use of the data has been obtained in accordance with applicable regulatory requirements.	clarify "appropriate consent and permission" if it is the broad ICF or Consent for Secondary Use of Data. Which is the meaning of permission? the patient permission or the EC/AC/Garante permission?
EUCROF	193	196	3.4	Mentioning the use of personal data when using RWD would emphasize the importance of the appropriate consent. Also, please see comment under section 2.2.	Add sentence: "This is especially important in situations where RWD are not used in an anonymized way but as personal data (e.g., psydonymized data)."
European Huntington Association	193	196	3.4	I believe it's important to clarify that consent or permission may need to be obtained not only from the participants but also from other individuals involved in the collection of RWD, such as healthcare professionals or family members not directly involved in the trial.	Proposed change: Clarify who may/should provide appropriate consent or permission in the paragraph "In situations where RWD are used, the sponsor should ensure that appropriate consent or permission for the use of the data has been obtained in accordance with applicable regulatory requirements."
Fondazione per la ricerca farmacologica Gianni Benzi onlus (FGB) for the European Rare Diseases Research Alliance (ERDERA)	193	196	3.4	Reference to secondary data use could be added to improve clearness. The informed consent and the presence of possible accessibility conditions should be considered for the secondary use of data, as well as the ethics approval, if required by the applicable local law. Moreover, it shouldbe considered that the informed consent is not the only one legal basis for the processing of personal data.	In situations where RWD are used, the sponsor should ensure that appropriate consent or permission or ethics approval, if required by the applicable local law, for the secondary use of the data has been obtained in accordance with applicable regulatory requirements. In addition, the sponsor may rely on legal bases other than informed consent.
INNODIA (INPACT: INNODIA People with Type 1 Diabetes Community)	193		3.4	**Patient Privacy Protections are Unclear in Cross-Border Trials:** The guidance does not clearly state how participant data should be protected when transferred across jurisdictions with differing privacy laws (e.g., GDPR in the EU vs. HIPAA in the US).	Sponsors should ensure compliance with regional and international data protection laws and transparently communicate how data is used and protected.
Lymphoma Coalition	193	196	3.4	This section does not mention patient autonomy in data-sharing decisions. Patients should have clear information about how their data is used, with an opt-out mechanism.	Add: Participants should have the option to review and control how their data is used throughout the trial and after its completion.
Association for Clinical Data Management (ACDM)	195	196	3.4	Data Privacy regulations, local regulations and GDPR should be also considered	Recomendation to include reference to GDPR
EFPIA consoldiated comment	197	253	3.5	On section 3.5 Data Considerations the guidance provide aspects that should be considered on RWD, EHR, etc... but from my point of view it is missing to emphasize some elements that should be aligned with Annex 1 such as: computerized system validation requirements, accesibility to audit trail, user access management... These elements should be fit for purpose in terms of GxP compliance and Annex 2 should help the reader apply the relevant requirements in Annex 1 to data sources not under their control but which need proportionate assessment before use in the trial. Include text to refer to Annex 1 Data Governance and computerized systems sections, for example relevant parts of Annex 1 Section 3.16.1(x)vi to ix.	This section should be read in conjunction with Annex 1, Data Governance, Section 4 and Section 3.16.1(x)vi to ix.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUCROF	197	253	3.5	The section on Data Considerations does not explicitly address how to ensure the reliability of RWD. Some examples of RWD validation would be helpful, for example in section 3.5.1.(b).	Provide guidance on methods to validate and ensure the quality of RWD used in the trial.
Lymphoma Coalition	197	245	3.5	This section lacks data transparency principles, particularly regarding patient access to their own trial data.	Add: Participants should have access to their own clinical data collected during the trial in a comprehensible format upon request, including insights from wearables and real-world data sources. Sponsors must outline this process in informed consent materials.
AFI	200	253	3.5.1	RWD section does not take in consideration different types of data and approaches to collect them. It seems that considerations reported are still too high leading to have own interpretation. It would be appropriate to redefine the context.	
Association for Clinical Data Management (ACDM)	200	206	3.5.1	Maybe more specific to detail that Real World Data to be used on clinical research to be used for example in interventional trials… Some learning may be needed from sites on how this data need to be populated if the purpose is also clinical research.	
INNODIA (INPACT: INNODIA People with Type 1 Diabetes Community)	200		3.5.1	**Real-world data (RWD) collection**: RWD collection may introduce biases. Healthcare record completeness for T1D varies across regions—some systems do not track insulin adjustments or CGM use consistently.	Sponsors should validate RWD quality and ensure missing data is addressed using standardized imputation methods.
Medicines for Europe	200	251	3.5.1	RWD: more specific examples and case studies are missing to illustrate best practices and potential pitfalls	Specific examples and case studies will be beneficial
Teva Pharmaceuticals	200	251	3.5.1.	RWD: more specific examples and case studies are missing to illustrate best practices and potential pitfalls	Specific examples and case studies will be beneficial
Breakthrough T1D	201	202	3.5	In addition to real world data and pragmatic elements, well recognized data sets such as those generated by natural history protocols is another resource that can help improve the design of clinical trials. Also, a virtual placebo/synthetic comparison arm releases participants for trial interventions, which is critical in diseases such as type 1 diabetes where investigators struggle to recruit patients. Synthetic control arms can accelerate the development of critical therapies in diseases with high unmet medical needs.	Include datasets generated by natural history protocols that follow regulatory guidance as another example to electronic healthcare records (EHR), claims data and registry data.
Miroslava Calegari	201	205	3.5.1	The original text lacks guidance on handling missing or inconsistent data, which is a major concern in trials incorporating RWD. Defining interoperability measures between different health data platforms is crucial for ensuring data consistency. Transparency in how third-party data providers curate RWD is necessary to maintain regulatory compliance and trust in trial results. Proposed change is ensuring transparency and interoperability in RWD use aligns with regulatory expectations for data reliability.	A variety of RWD sources may be used in clinical trials (e.g., EHRs, claims data, registry data). The sponsor should apply special considerations to these data sources depending on the data collection and acquisition process and if the data are primary or secondary, since the sponsor may have different levels of control over what and how data elements are collected. Sponsors should establish clear data management strategies, including methods for addressing missing or inconsistent data, ensuring interoperability between different digital platforms, and mitigating potential biases that arise from diverse data sources. Additionally, when third-party data providers are involved, transparency on how datasets are curated and processed should be ensured.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUCROF	203	204	3.5.1	"… and if the data are primary or secondary, …". It is not totally clear what primary and secondary data are and it could be mixed up with data for primary and secondary objectives.	Change as follows: "… if the data are gained through primary data collection or through secondary use of a data source, …"
Association for Clinical Data Management (ACDM)	206	206	3.5.1	Approval for the study and ICF consent, in order to know since when you are able to collect the data from these sources needs to be also considered.	Recomendation to include recomendations on how systems should be adapated on data collection as per ICF
EORTC	209	213	3.5.1	This section is confusing: in the context of pragamtic trials for instance, investigators ask a question in routine practice. The procol must adapt to RWD and not the other way around. The defintion of RWD are data which are collected with no interference with routine clinical work-ups, otherwise they are no longer RWD. This is criticla to ensure external validity	Ensure clarity of the wording and what is meant as far as data collection is concerned, according to protocol or protocol to be flexible enough to adapt to real-life. Collection of RWD should be collected with no specific protocol ask but just as they are generated in clinical practice, otherwise they no longer are RWD. This is otherwise contradictory to section 3.1.2.b lines 149-151
EUCROF	212	213	3.5.1	"…therefore, the protocol schedule may not match with those available from the RWD." In clinical trials with planned use of RWD, the protocol should not mandate a strict visit schedule but take into account that participant's visit intervals will show a high variety and will not follow a strict visit schedule like in RCTs. The protocol should be written in such a way that it allows for variations in the schedule. However, the protocol should address how to handle such variations from a "theoretical schedule" that would be considered ideal and would be required to be followed in an RCT.	The point should be switched to considerations as to how to handle deviations from a "theoretical visit schedule".
Medicines for Europe	212	213	3.5.1	The text "therefore, the protocol schedule may not match with those available from the RWD" could be amended to clarify, what does a "protocol schedule" refer to.	The following change is suggested: "therefore, the protocol schedule **of clinical trial** may not match with those available from the RWD".
François Houÿez, Eurordis	214	220	3.5.1 (a.iii	Missing data can also be due to large populations of participants moving to different healthcare systems, including different countries for refugees, eg people living with a rare disease who left Ukraine and stelled in EU MS. Maybe a specific paragraph should be added on data transferability rather than missing data, when agile clinical centres succesfully continued to monitor trial participants from the new location.	
ESMO (European Society for Medical Oncology)	221	223	3.5.1	Clear decription of quality ensurance in registries / from RWD needed.	To consider a RWD source as adequate a level of quality control is needed. This might in part be covered in 3.5.1. c
Trials@home	221	223	3.5.1	Is this different from all other types of data collected in a clinical trial. Would this not fall under the same requirements?	Suggest to make reference to Annex 1
Association for Clinical Data Management (ACDM)	224	225	3.5.1 a (v)	Consent for the participants to be considered to use these kind of data in clinical research need to be considered as well.	Recomendation to include reference on participants consent on the use of their data
EFPIA consoldiated comment	224	225	3.5.1 (v)	It is not clear why RWD in (v) "De-identification methodologies used to protect the provacy and confidentiality of trial participants". Should it not be just any patients. RWD does not mean the data from the clinical trials	(v) "De-identification methodologies used to protect the privacy and confidentiality of **patients ~~trial participants~~".**
EUCOPE	224	225	3.5.1	The term "de-identification" refers to the process of removing or altering information that can directly or indirectly identify a person? or perform the anonymized process?	clarify de-identification methodology

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
François Houÿez, Eurordis	224	225	3.5.1 (a.v	For the de-identification, should the information materials at the consent phase inform on the residual risk of identification?	
AFI	226	235	3.5.1 a (vi), b, c	Taking into consideration that data sources for RWE may belong from system used by site for clinical practice, it seems in conflict that the Annex 2 is implying a different approach (e.g. validation of tools).	Recommendation is to align the approach considering the primary use of the data source (clinical practice, etc….)
European Huntington Association	226	227	3.5.1	I believe it is important to also include technological devices and digital assessment tools, as they are increasingly used as measures in studies and trials.	Proposed change: "The validation status of tools used for the acquisition of RWD (e.g., registries, digital assessment tools), as appropriate." instead of "The validation status of tools used for the acquisition of RWD (e.g., registries), as appropriate. "
EFGCP	227	227	3.5.1	Suggest additional point to cover issues with data sources	(vii) Deviation Documentation when data discrepancies, errors or issues arise consequential to the data source(s)
ESMO (European Society for Medical Oncology)	228	232	3.5.1	The sponsor should ensure the fitness for purpose of RWD, which can be described by their reliability and relevance. The term reliability includes accuracy, completeness and traceability; the term relevance includes the availability of key data elements (e.g., exposure, outcomes, covariates) to answer the specific trial question with the specific method.	we may want to make a more explicit reference to the need for reporting quality standards e.g., ESMO is working towards a RWD Quality Assessment tool, deliverable by Q3 2026
François Houÿez, Eurordis	228	232	3.5.1 (b	For pragmatic trials in particular, different trial site might use different measurement tools, different assays, different imaging devices etc. To maintan the pragmatic characteristic of the trial, no standardisation can be imposed.	The sponsor should ensure the fitness for purpose of RWD, which can be described by their reliability and relevance. The term reliability includes accuracy, completeness and traceability; the term relevance includes the availability of key data elements (e.g., exposure, outcomes, covariates) to answer the specific trial question with the specific method. For pragmatic - multi-centre trials in particular, data variability by trial site should be closely monitored.
Fondazione per la ricerca farmacologica Gianni Benzi onlus (FGB) for the European Rare Diseases Research Alliance (ERDERA)	232	232	3.5.1	When assessing fitness for purpose, special consideration should be given to rare diseases, as included in the EMA document "Data Quality Framework for EU medicines regulation: application to Real-World Data" EMA/503781/2024	While RWD should be fit for purpose rather than tailoring the study purpose to fit the RWD source, it is important to recognize that in some cases, the metrics and characterization of RWD may reveal limitations that necessitate adjustments to the study design (iterative process). For instance, if a rare disease is insufficiently captured in an RWD source, but a broader yet relevant concept is well represented, the study may focus on that broader concept. Conversely, in causal studies, if key confounders are not adequately captured, an alternative RWD source may be required to ensure the study's validity.
Association for Clinical Data Management (ACDM)	233	238	3.5.1	Ensure access to audit trail, user access management - More information should be provided on how these systems would be GxP compliance as per Computerised Systems section in Annex 1.	Recomendation to include reference from Annex 1, section on Computerized System Validation: These decentralized elements should be GxP compliance or validated in a way that we ensure traceability of the data
EORTC	233	238	3.5.1	This does not differ from any other clinical trial or data collection method. Unclear why this statement is needed	To be removed, not specific

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
European Huntington Association	233	238	3.5.1	I believe the section's readability will improve with a rearrangement of the content.	Proposed change: Move the paragraph "c) The RWD used in a clinical trial (e.g., data acquired during clinical practice, RWD from a third party) may be owned or controlled by entities other than the sponsor. In such cases, the sponsor should have agreements with those entities in place that allow regulatory authorities to access the source records and data for the purpose of conducting regulatory inspections in accordance with applicable regulatory requirements." as item (vii) on the previous list of considerations (lines 207-227), under a point called "RWD ownership"
Good Clinical Trials Collaborative (GCTC), https://www.goodtrials.org/	233	238	3.5.1 (c)	Section 3.5.1(c) states: "The RWD used in a clinical trial (e.g., data acquired during clinical practice, RWD from a third party) may be owned or controlled by entities other than the sponsor. In such cases, the sponsor should have agreements with those entities in place that allow regulatory authorities to access the source records and data for the purpose of conducting regulatory inspections in accordance with applicable regulatory requirements." It is reasonable to require the sponsor to keep available an unmodified, certified copy of the data as provided by the RWD system so that the source can be reviewed by inspectors. However, sponsors are unlikely to be able to insist on provision of an auditing right on those who provide RWD (e.g. the NHS in the UK, US Medicare, a hospital EHR provider, a national death register). This is likely to be particularly problematic if the source of information is sensitive for additional reasons (e.g. a health system providing care for current or former military or government personnel) or if the regulatory inspector is from a different country. The current language could have a detrimental impact on the reliability of the trial results and the ability to assess the safety and efficacy of medicines. For example, there may be a circumstance where information about a patient (such as their date and cause of death) is known in one system (e.g. the records for a hospital that is not enrolling participants in the trial) but is not used for the trial because the sponsor chooses not to link to that source because they cannot secure the necessary audit rights. If RWD can only be used where source records and data are made routinely available for inspection, it will likely severely limit the range of RWD sources that are available for trials and reduce appetite for their use when they are available due to perception of increased regulatory compliance risk.	Amend the current text to reflect a more pragmatic requirement, as follows: "The RWD used in a clinical trial (e.g., data acquired during clinical practice, RWD from a third party) may be owned or controlled by entities other than the sponsor. In such cases, an unmodified, certified copy of the data as provided by the RWD system should be available for the sponsor to share for the purpose of conducting regulatory inspections in accordance with applicable regulatory requirements." [Note: Similar language to that we propose here is already included in U.S. FDA Guidance on the Use of Real-world evidence to support regulatory decision-making for medical devices.]
Medicines for Europe	235	238	3.5.1	Generally, the sponsor does not make agreements with data holders directly. In our opinion, the statement needs to be amended to allow also agreements between a service provider and data holder, not only between the sponsor and data holder.	The following amendment of the text is suggested: "In such cases, the sponsor **needs to ensure that** ~~should have~~ agreements **are** ~~with those entities~~ in place that allow regulatory authorities to access the source records and data for the purpose of conducting regulatory inspections in accordance with applicable regulatory requirements."
ESMO (European Society for Medical Oncology)	239	240	3.5.1	Data hacking is a reality in these days. I think a risk plan should be as well clarified in case of data leaks	Add what steps should be taken in case of data leaks.
ESMO (European Society for Medical Oncology)	239	245	3.5.1.(d)	The same consideration as above.	The following could be added in the last sentence (lines 244-245):", as well as predefined rules/guidelines on how data inconsistencies between different sources will be solved in systematic and consistent manner".

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Fondazione per la ricerca farmacologica Gianni Benzi onlus (FGB) for the European Rare Diseases Research Alliance (ERDERA)	240	242	3.5.2	Data linkage can also be valuable for small populations. Therefore, it may be worth including it among the examples.	(e.g., linking data from EHRs and claims databases, linking an RWD source to a mortality database to confirm outcomes, or linking datasets to address questions requiring large sample sizes, such as those related to rare diseases).
Association for Clinical Data Management (ACDM)	242	244	3.5.1 d)	Worth to mention that data may be not de-identified … or different identifiers need to be consider	
Medicines for Europe	242	243	3.5.1	Adequate measures to sufficiently protect data privacy and reliability of trial results when data are linked, can not be responsibility of the sponsor only.	The following change is proposed: "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 reliability of trial results **should be ensured by data holder or by the entity conducting the formal analysis**."
Fondazione per la ricerca farmacologica Gianni Benzi onlus (FGB) for the European Rare Diseases Research Alliance (ERDERA)	244	245	3.5.2	We deem it is important to emphasise that the inclusion of linkage information between datasets is more important for specific populations, such as rare disease patients, where the risk of re-identification is highest.	If data are to be linked, this should be pre-specified in the protocol or protocol-related documents, especially if the data belong to people affected by rare diseases, as the risk of re-identification is increased.
Miroslava Calegari	247	251	3	Device-based variability (e.g., different brands of continuous glucose monitors or wearable ECGs) can lead to inconsistent trial results. The guideline mentions security risks but does not validate the quality of remote data collection. Establishing equivalency between in-person and remote assessments would improve the reliability of digital health technologies in clinical trials. Strengthening validation measures for remote data collection improves data quality and consistency across decentralized trials.	Remote data collection in clinical trials that incorporate decentralized and pragmatic elements (e.g., the use of remote visits and DHTs, such as wearables, or the extraction of data from EHRs) requires special attention to be paid to data security vulnerabilities (see Annex 1, section 4.3.3), including cybersecurity and data privacy (see section 3.7). Additionally, sponsors should implement measures to validate remote data collection methods, ensuring that device-based variability does not impact trial consistency. Where applicable, sponsors should define equivalency standards between in-person and remote assessments to mitigate data integrity concerns.
Trials@home	248	249	3.5.1	Is this different from all other types of data collected in a clinical trial. Would this not fall under the same requirements?	Suggest to make reference to Annex 1
GQMA	250	250	3.5.2 (a)	A section 4.3.3 of Annex 1 is referenced here. The currently available Annex 1 draft version of 19-May-2023 does not have a section with that number.	Please check this reference.
European Huntington Association	252	253	3.5.2	I believe this item is too vague and would be clearer if a separate list were created to outline the considerations for remote clinical trial data collection.	Proposed change: Clarify the item "b) Some of the RWD considerations in section 3.5.1 may also apply to remote clinical trial data collection (e.g., DHTs including wearables)."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Trials@home	252	253	3.5.2	"Data Considerations: Some of the RWD considerations in section 3.5.1 may also apply to remote clinical trial data collection (e.g., DHTs including wearables)." This statement lacks clarity on the RWD considerations that may also apply to remote clinical trial data collection and is therefore too open to interpretation. Risk-averse companies may take this to mean all the RWD considerations apply which will hinder DHT use.	Propose to delete this statement as it adds no value without more clarity and specificity on which RWD considerations also apply to remote clinical trial data collection
ESMO (European Society for Medical Oncology)	254	276	3.6.	In decentralized trials, if medication is applied at home - clear mechanisms for accountability need to be in place.	Under 3.6.3 the recommendation needs to be stronger
EUCROF	254	276	3.6	The entire section applies to situations with primary data collection (entire trial or part of the trial) and this should be mentioned. The question arises, for example, if a comparator arm is created using existing data sources (e.g., registries), does the term investigational product also apply to the comparator product(s)? This/these product(s) was/were administered under normal clinical practice.	Please explain the frame to which section 3.6 applies.
François Houÿez, Eurordis	254	276	3.6	As for annex 1, it is essential to remind sponsors on the importance to make provisions for accessing the product at the end of the trial as per: Declaration of Helsinki § 34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process	
Teva Pharmaceuticals	254	276	3.6.	The guideline appears to suggest administrative management tasks be completed by investigators, which may be difficult for them to complete. A section places certain administrative management responsibilities on the sponsor.	It is recommended that ICH reconsider the feasibility of placing any of these responsibilities on investigators.
Ipsen	258	267	3.6.1	Is the expectation that the asseemsnt of the IMP approach should be documented ?	Please clarify section to improve understanding
Association for Clinical Data Management (ACDM)	268	270	2.6.2	Protocol should be also considered	Recomendation to include as per protocol
DARQA	268	271		In 3.6.2 there is a reference to 2.3.1. Where it relates to ensuring data privacy, suggest (also) to refer to 3.7.	
François Houÿez, Eurordis	268	271	3.6.2	When sending the investigational product to the participant, the sponsor can identify the person. Maybe only the investigator (or a delegated helathcare professional) should be responsible for sneding the IMP to the participants. Some national regulations prevent a pharmaceutical company from communicating directly with patients.	
Trials@home	268	269	3.6.2	"...in accordance with **local regulatory requirements**." How to proceed in case there is no local legal base (regultory requirement) about conducting certain DC elements e.g. shipment to patient's home?	There was at least one case where due to lack of legal basis, local authorities would not allow certains procedures. In such case could it be suggested to consider a higher level available regulation such as national or regional (e.g. EU) regulation?

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUCROF	277	286	3.7	While data privacy and confidentiality are emphasised in decentralised clinical trials (DCTs), the guideline does not provide specific guidance on key data protection principles, such as participant access to their own data.	It is recommended that decentralised elements and technologies explicitly incorporate data protection measures, including participant data access rights.
Miroslava Calegari	277	285	3	The current text does not explicitly state participants' rights to access, correct, or delete their data, nor does it outline cross-border data compliance. Given the increasing use of digital health technologies (DHTs) and real-world data (RWD), data protection and transparency are critical. Participants should have clear information on how their data will be used, who has access to it, and how they can exercise control over their personal information. This is particularly important for cross-border trials, where regulations like GDPR (in Europe) and HIPAA (in the US) have different requirements for data handling. Without explicit guidance on how participant data protection should be managed, there is a risk of inconsistent practices that could impact trust in clinical research and compliance with legal frameworks.	Sponsors must implement security safeguards, including cybersecurity, to protect the privacy and confidentiality of trial participants' personal information. In addition, sponsors must define and communicate participants' rights regarding their data—including access, correction, and deletion—while ensuring compliance with applicable data protection laws (e.g., GDPR, HIPAA).
Breakthrough T1D	278	285	3.7	The international nature of clinical trials and the variety of data protection levels across the globe is still a major burden to sponsors. This makes it challenging to comply with the requirements set in this Annex 2 and other regulatory documents relating to the topic (GDPR and other similar variations for instance). For a full benefit of the principles laid down in this Annex 2, it may relevant, at least for RWD and remote data collection, to consider a parallel workstream to provide more streamlined and harmonized guidance on these data protection requirements. This could be discussed by the regulators at the ICRMA level.	
Lymphoma Coalition	278	286	3.7	Participants are not given explicit rights to control secondary uses of their data post-trial.	Add: Participants shall be informed of their right to withdraw consent for future use of their data beyond the trial's scope, and sponsors must establish processes to honor such requests in compliance with applicable regulations.
Lymphoma Coalition	278	286	3.7	Participants are not informed about anonymization methods or re-identification risks.	Add: Participants shall be informed of the anonymization techniques applied to their data and potential re-identification risks, particularly when linking datasets from multiple sources.
Medicines for Europe	278	279	3.7	Security safeguards, including cybersecurity, can not be responsibility of the sponsor only. Data governance is regulated by the data holders, while the entity conducting the formal analysis (e.g. service provider) should ensure proper security safeguard in the analysis.	The following change is suggested: "Sponsors, **service providers and data holders** should ensure security safeguards, including cybersecurity, are in place to protect the privacy and confidentiality of personal information of trial participants.
Association for Clinical Data Management (ACDM)	285	286	3.7	Additionally, Principles of data minimisation (as per GDPR) should be followed. Data minimisation: data is adequate, relevant and limited to what is necessary. (purpose limitation)	Recomendation to include reference to GDPR
EUCROF	285	286	3.7	"The sponsors should address the risk of potential disclosure of personal information from a data breach when data from DHTs and/or RWD are used." This requirement should not be limited to DHTs and/or RWD but should be requested in general.	Change as follows: "The sponsors should address the risk of potential disclosure of personal information from a data breach when primary data collection and/or RWD are used, including the risks of international data transfer and use of DHT."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Fondazione per la ricerca farmacologica Gianni Benzi onlus (FGB) for the European Rare Diseases Research Alliance (ERDERA)	285	286	3.7	A data breach response plan could be foreseen to clearly define how the sponsor will address the risks of potential disclosure of information from a data breach.	The sponsors should set up a data breach response plan to address the risk of potential disclosure of personal information from a data breach when data from DHTs and/or RWD are used.
Ipsen	285	286	3.7	Question: Should we understand that use of DHTs/RWD have an inherent risk of data leaks so this should be mentioned in the Informed Consent?	Please clarify section to improve understanding
Medicines for Europe	285	286	3.7	Sponsor is usually not the developer of DHT or is usually not a data holder, which means that risks are difficult to be addressed by the sponsor only.	The following change is proposed: "The sponsors, **service provider or data holder** should address the risk of potential disclosure of personal information from a data breach when data from DHTs and/or RWD are used."
EFPIA consoldiated comment	287	295	3.8	The terminology used here is "appropriate" whilst for the investigator oversight (section 2.4) the risk propotionality is emphasized: activities should be "proportionate to the risks to trial participant safety and data reliability, and the importance of the data being collected" which is in alignment with Annex 1. consider to align	Sponsors should ensure that there are processes in place to provide appropriate **and proportionate** level of oversight
ESMO (European Society for Medical Oncology)	287	295	3.8	In decentralized trials, sponsor oversight is complicated - especially if non-trial personell takes over responsibility for trial patients. Mechanisms need to be in place that protect sponsors / sponsor delegated persons from misconduct of non delegated personel and delegated personel in remote settings.	Needs to be added. Misconduct of remote, non delegated personel impacting the Sponsor is legally hard to decipher, perhaps then focus on protecting the PIs and subInvestigators?
Medicines for Europe	287	295	3.8	Sponsor Oversight – Further clarification and expectations when utilizing decentralized clinical trial. Should sponsor implement additional audit strategies to ensure data integrity and subject protection when traditional monitoring is reduced?	Clarify if sponsor should implement additional audit strategies to ensure data integrity and subject protection when traditional monitoring is reduced.
Lymphoma Coalition	288	295	3.8	The guideline does lacks a requirement to disclose sponsor conflicts of interest, especially when using third-party RWD.	Add: Sponsors must disclose potential conflicts of interest (e.g., financial ties to third-party data providers) to IRBs/IECs and participants to ensure transparency and mitigate bias in trial design or data interpretation
Trials@home	288	290	3.8	This sentence makes it sound as if it is an all-or-nothing approach, where you either do a conventional trial or use many different data sources, operational approaches and service providers, whereas in practice one might often utilize one RWD source only or one additiona service provider	Proposal is to change the first part of the sentence 'sponsor oversight can be more complex **if several** data sources....'
UNICANCER	289	289	3.8.	and the number of service providers involved : add sites	and the number of sites and service providers involved
EFPIA consoldiated comment	294	295	3.8	Annex 2 text: Sponsor oversight includes, but is not limited to, quality control and assurance measures specifically customised to the clinical trial and its critical to quality factors and identified risks. There should be appropriate oversight of service providers including maintenance of their essential records. The comment is whether the wording should include 'but limited to' for the service providers as well, so that the wording would be: There should be appropriate oversight of service providers including, but not limited to, maintenance of their essential records.	There should be appropriate oversight of service providers including, **but not limited to,** maintenance of their essential records.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUCROF	296	310	3.9	It should be mentioned that regulatory requirements shall be fulfilled within the applicable regulatory frame which might differ between primary data collection in interventional trials and the secondary use of data integrated into an interventional trial. For those data, Pharmacovigilance rules for marketed products apply/have applied when generating the data.	
Lymphoma Coalition	296	310	3.9	The section does not require to inform participants of safety findings that may impact their continued participation. Likewise, it does not discuss how patient-reported safety concerns (e.g., side effects or long-term toxicity concerns) are incorporated into decision-making.	Add: Investigators shall promptly inform participants of significant safety findings relevant to their continued participation, ensuring they can make informed decisions about their involvement in the trial. Patient-reported safety concerns should be systematically collected and analyzed to guide ongoing trial monitoring and potential protocol adaptations.
EORTC	297	304	3.9.1	It should be differentiated: decentralised trials could rely on variety of sources while pragmatic trials rely on the standard routine examination and reporting. In addition, it should be added that in case of pragmatic trial, the intensity and frequency of safety examination should be aligned with routine practice and proportionated to the risks. (selective safety reporting applicable to pragmatic/de-escalation trial is recommended in the ICH guideline E19 on a selective approach to safety data collection in specific late-stage pre-approval or post approval clinical trials.). Through out the document, it seems that there is a confusion between the methods and sources to collect data , possibly in a decentralised manner and pragmatic trials/ elements	Clarify the document by dichtomising between sources of data and methods to collect data
Good Clinical Trials Collaborative (GCTC), https://www.goodtrials.org/	297	304	3.9.1	The current text relating to safety assessment and reporting in 3.9.1 (particularly lines 300 to 304) may exacerbate the issue of excessive uninformative communication of safety information. Requiring that the sponsor "should ensure that safety information is appropriately captured and made accessible to the investigator in a timely manner" fails to distinguish between the need to capture data that can inform an overall assessment of the safety of the intervention and information that is relevant to the immediate clinical management of participants under the investigators' care. The risk of important safety information being missed increases when the investigator is overwhelmed with unfiltered safety reports from all sources of information – as the current text may encourage – which can dilute the ratio of relevant, actionable information that requires timely response to the 'noise' of routine safety data that may require randomized comparison to assess causality.	Amend the text on line 301 so that the sentence reads: "The sponsor should ensure that safety information is appropriately captured and that the investigator is made aware of information that is relevant to the safety of their participants in a timely manner according to the protocol." For further recommendations on improving safety assessement and reporting within the European context, please refer to The Coalition for Reducing Bureaucracy in Clinical Trials at https://bureaucracyincts.eu/.
FVR – Finnish Vaccine Research	298	300	3.9.1	See the comment above on row 16 (section 2.5) about safety follow-up and assessment	For example, some trials may capture information via remote visits, DHTs, EHRs, **registers,** in-person visits or a combination thereof.
EFPIA consoldiated comment	299	299	3.9.1	Healthecare professionals other than investigational site personnel to be added as example of source of safety information	....For example, some trials may capture information via remote visits, DHTs, EHRs, in-person visits, **by healthcare professionals** or a combination thereof.....
EUCROF	300	305	3.9.1	The section does not reference Annex 1, for example 2.12.3 and 3.16.1 (k)	Add reference to Annex 1, 2.12.3 and 3.16.1 (k).

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUCROF	302	304	3.9.1	The medical decision making should be supplemented with appropriate safty reporting. Besides, the term "actionable" is not really clear.	Change sentence as follows: "The safety information should be provided in an operationally feasable manner described in the clinical trial protocol and that provides the investigator with an overview on the health status of the trial participant to allow for medical decision making and safety reporting according to regulatory requirements." In addition: Some examples of this „operationally feasible manner" would increase clarity. For example „only AEs leading to hospitalization" or „only AESIs based on a list in the protocol", etc.
FVR – Finnish Vaccine Research	302	304	3.9.1	"The safety information should be provided in an actionable manner that provides the investigator with an overview on the health status of the trial participant to allow for medical decision making." We think that "related to IP or other trial-related procedures" should be added. Or is the intention that an investigator in a kidney drug trial should take medical decisions for the study subject after hip fracture, i.e. decide whether to operate or treat conservatively?	The safety information should be provided in an actionable manner that provides the investigator with an overview on the health status of the trial participant to allow for medical decision making **related to IP or other trial-related procedures.**
Association for Clinical Data Management (ACDM)	307	307	3.9.2		Recomendation to include example of protocol-related documents like safety monitoring plan
EUCROF	307	307	3.9.1	For clarity	Add: „trial" to the „design elements", i.e.: "This approach should take into account the trial design, the trial design elements and the varitey of data sources."
European Huntington Association	307	308	3.9.2	I believe that the management of clinical trials with decentralized and/or pragmatic elements should also account for unexpected events and ensure that changes in real-world settings do not affect the trial's validity and reliability.	Proposed change: Include another point that covers unexpected events in the text "This approach should take into account the trial design, the design elements and the variety of data sources."