EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000
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Overview of comments received on ICH E6 (R3) Guideline for Good Clinical Practice

EMA/CHMP/ICH/135/1995

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
ACRO	0	0		ACRO welcomes the approach to provide a flexible framework for clinical trial conduct. As service providers delivering clinical trials worldwide, ACRO members note that it is now usual practice for clinical trials to include one or more decentralized elements. This has also been reflected with guidance being released by EMA and FDA. This means that the contents of Annex 2 will be critical to the practice of the majority of trials. ACRO would therefore welcome the release of the draft of Annex 2 as soon as possible in order to understand ICH E6 (R3) in its entirety. ACRO would also ask for ICH members to expedite and harmonize guidance on topics which will be affected by the contents of Annex 2.	Publication of the draft of Annex 2 as soon as possible.
ACRO	0	0		The operational impact of ICH E6 (R3) is unclear at this time. As noted above, it is now usual practice for clinical trials to include one or more decentralized elements. This means that the contents of Annex 2 will potentially have a significant operational impact in terms of the change management require to implement ICH E6 (R3) across the industry. ACRO would therefore welcome the release of the draft of Annex 2 as soon as possible in order to understand the operational impact of implementation of ICH E6 (R3).	Publication of the draft of Annex 2 as soon as possible.
ACRO	0	0		ACRO welcomes the draft guidance which broadly seems to be in line with the policy aims, notwithstanding the absence of Annex 2 and the details therein (see separate comment). ACRO notes that companies will need to have clear implementation plan which includes embedding risk proportionality in company processes.	ACRO would welcome training by the ICH E6 R3 working group on how risk proportionality will be approached during inspections.

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AFI	0	0		The guidelines often refer to applicable local regulatory requirements: could a minimum 'essential records retention period' be proposed? 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	3.16	Considering the increasing use of RWE/RWD, can you give more insights on the requirements for accepting RWE/RWD in relation to GCP? For RWE/RWD, the computerized systems used to capture the data would not follow the same high principles as in a 'regular' clinical trial setting. What measures are required in terms of computerized sytsems validation for making RWE/RWD acceptable?	
Beate Kern, Department of Health Brandenburg, Germany	0			Service providers are playing an increasingly important role in studies. For this reason, service providers who are commissioned with a relevant scope of work should be indicated in the application and in the nationally prescribed study registers. (This information should be added to the CTIS database introduced in Europe).	Service providers who are commissioned with a relevant scope of work should be indicated in the application and in the nationally prescribed study registers.
Catalent Pharma Solutions	0	0	Appendix C	It would be helpful to clearly state which essential records are required before, during and after the study, like in the case of ICH E6(R2) sections 8.2 to 8.4, as it helps sponsors put the various documentation requirements in perspective (particularly for the start of trial, as these can be used as a go/no go checklist).	See "Comments and rationale"
CDISC TMF Reference Model	0	0	Appendix C	Appendix C contains a list of ESSENTIAL and POTENTIAL ESSENTIAL records. As a Trial Master File expert community, we strongly believe that this will cause confusion in an Industry where we have established a defacto standard for the contents of a trial master file. As there is a numbering system, we believe that some clinical trial professionals will start to follow the ICH numbering system, and 12 years of effort to harmonise will be compromised. In addition, stating that some are ESSENTIAL and some are only POTENTIAL ESSENTIAL may mean that only ESSENTIAL records are collected, where the POTENTIAL ESSENTIAL records are actually ESSENTIAL if they are relevant to the trial. The list is also missing many records types and would therefore not give the complete story of the conduct of the study and the quality of the data produced. It would also not meet the Inspection needs of today. We would like to see the list removed altogether (as shown by an informal vote at the TMF Summit in London in 2022), and for direction to be given that the points C.3.1 (a) to (bb) should be followed. We think this is an excellent framework for decision making but has some aspects needing clarification or adding - such as expanding the scope of evidence of oversight management and risk. This framework should also explain the Investigator TMF responsibilities; at the moment it is focussed on the Sponsor. It is understood that a non ICH document cannot be referenced in an ICH guide, but we would implore that the CDISC TMF Reference Model is referenced in the training.	1. Remove the list of ESSENTIAL and POTENTIAL ESSENTIAL records 2. Ensure that C.3.1 aligns with all the requirements throughout R3
Charles River Labs	0	0	4.2	Section 4.2 on Data Life Cycle Elements lacks wording regarding Retention and Archival of Records. This is not discussed elsewhere in the document.	Add a section to outline the archival and retention expectations.

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Charles River Labs	0	0	4.3	Section 4.3 on Computerized Systems lacks wording regarding decommissioning. This is not discussed elsewhere in the document.	Add section or wording on decomissioning.
Clinical Pharmacology and Pharmacovigilance Unit, University of Kinshasa	0	0	III	The investigators, monitors and auditors generally turn a blind eye when it comes to ascertaining that a given person is the "legally acceptable representative" or "legal guardian" for a given study participant. In practice, at least in settings with low administrative capabilities or attendance, it is almost impossible to demonstrate the status of “legally acceptable” representative. Orphans or children who left their biological parents for relatives with better living conditions, are not covered by any adoption certificate. The uncles/aunts/cousins/family friends automatically become the legal guardians, and this is accepted by society. For the sake of transparency and to streamline practice of what is acceptable, I propose to add the concept of “socially acceptable representative” in settings with poor civil service. A socially acceptable representative would be defined as "a person who, by the testimony of the head of the community and/or at least 3 adult members of the community, is known to be the guardian of the prospective study participant, without dispute whatsoever”. The witnesses here do not need to sign any document, not even on the informed consent form, a statement by the investigator in the participant’s records will be enough.	In addition to the concept of the "legally acceptable representative", I suggest to have the concept of "socially acceptable representative" in settings with poor civil service.
DARQA	0	0		In the principles (lines 56-57), it states "This guideline is intended to be media neutral;" it is clear that the requirements are intended to apply regardless of whether records are paper or electronic. Therefore it is superfluous to include "in writing or electronically" in lines 277 and 414. This may also cause confusion - why specify in these lines only and not throughout (inconsistent)?	Remove "or electronically" from these lines
DARQA	0	0		By adding the separate section 4 about data integrity, the overview of responsibilities of the Sponsor and Investigator is less clear and may lead to confusion.	
DARQA	0	0		Instructions regarding IEC documentation are not consistent throughout and may lead to confusion: - Table 1 item 1.4 says "IRB/IEC composition" / Lines 358-359 refer to "A list of IRB/IEC members and their qualifications" - are these the same? (composition vs member list - inconsistent terminology) - Line 1051 states that "(b) The sponsor <u>should</u> ensure that the following [documentation] is obtained..." ('should' or 'must'?), but in 429-430 it states "1.4.2 The IRB/IEC <u>may be asked</u> by investigators, sponsors or regulatory authorities to provide its documented procedures and membership lists." --> If the Sponsor must ensure the documentation is obtained, then the IRB/IEC "may" not be asked, but "must" or "will" be asked. - Lines 1055/1056 state that the sponsor must obtain "(aa) a statement that [the IRB/IEC] is organised and operates according to GCP and the applicable regulatory requirements" but in the essential records table (previous bullet point), only the composition is mentioned, not this statement.	Clarify requirements and use consistent terminology. Consider merging sections 1, 2.4 and 3.8 - by making IRB/IEC communication a shared responsibility between the Investigator and Sponsor (or allowing the option for one or the other to coordinate communications), it leads to duplication and discrepancy in the text. Having one section on IRB/IEC, including how Investigators and Sponsors communicate wtih them and what documentation is required (and who should have it available), would be clearer and would mitigate this risk.

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DARQA	0	0	Appendix C	The concept of 'essentiality' is not clearly defined.	Recommend to clarify that the question of 'essentiality' is not only related to whether or not records should be maintained in the TMF, but to whether or not they should be generated in the first place; if they are generated and and are therefore relevant to reconstructing the trial, they should be maintained.
DGPharMed e. V. (Deutsche Gesellschaft für Pharmazeutische Medizin)	0	0		We welcome the revision of ICH E6, especially against the background of constant advances in knowledge and experience as well as techniques in clinical research and pharmaceutical medicine. Not only the adaptations to the current situation should be mentioned, but also the scope of the topics addressed. Based on the experience with the R2 and the Addendum, it would be helpful to supplement the topics with examples of use cases or similar. For the first few years after the R2 became valid, there was clearly visible uncertainty among the stakeholders of clinical research as to how and in what way the specifications were to be implemented in practice. They waited a long time until sufficient cases from practice became known and then began, mostly hesitantly, with their own implementation. In order to prevent this delay in the future and to eliminate uncertainty from the outset when implementing R3, appropriate examples would be useful.	Please provide examples of use cases or similar to reduce uncertainity regarding interpretation of E6 (R3)
eClinical Forum	0	0	II	The eClinical Forum wishes to commend the authors on this section of E6 R3. The Principles are well written overall, accurately reflect procedural and technology changes from the original releases of E6 and are aligned to state-of-the-art in clinical trial conduct.	Not Applicable
eClinical Forum	0	0	4	We also strongly welcome the new section on Data Governance standards, which significantly contributes to avoiding redundancy between Sponsor and Investigator sections. This and other newly introduced concepts diminish the need to keep over- or under-interpreting GMP requirements for GCP, as was the historical QA practice.	Not Applicable
eClinical Forum	0	0	2	We recognize the significant effort brought in further clarifying Investigator responsibilities when it comes to systems, data and vendor oversight. Further suggestions for improvement can be found below.	Not Applicable
eClinical Forum	0	0	Appendix 3	Increasingly, clinical trial endpoints are acquired by independent originators, for whom there is no direct transfer or delegation of responsibilities (i.e., Central Laboratories, Central Readers, Data Monitoring Committees, Independent Review Committees etc.). Would there be a dedicated section or appendix to clearly define their responsibilities?	Recommend dedicated guideline on the modalities for establishing and eventually formally certifying systems, processes, devices and overall responsibilities for all those data sources. Would such provisions be eventually also applicable to Third Parties that are Investigative Site Delegates or have accepted transferred responsibilities by Sponsors?

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EUCROF	0	0		EUCROF appreciates the opportunity to provide comments for this important Guideline E6(R3) and recognizes the structural and content-related changes compared to E6(R2). Regarding the structural changes, we have the following general comments: 1. The purpose of the introduction of Chapter 4 (DATA GOVERNANCE - INVESTIGATOR AND SPONSOR) is understood, however some confusion is foreseen as to whether certain requirements are applicable to the sponsor, to the investigator, or to both. For example lines 1893 - 1896: 4.2.3 Review of Data and Metadata Procedures for review of trial-specific data, audit trails and other relevant metadata should be in place. It should be a planned activity, and the extent and nature should be adapted to the individual trial and adjusted based on experience during the trial. It sounds like a requirement for the sponsor, however it is not clear. On the other hand it is very unlikely that investigators will have procedures to review audit trails and other relevant metadata. Clarification would be welcome. 2. The terms in the GLOSSARY are not numbered any more. Numbering is easing the process of referencing. Please consider to introduce a numbering system for the terms.	
German Pharmaceutical Industry Association (BPI)	0	0	3.13.2	Terminology is not always clear and unambiguous, e.g. Section 3.13.2 (e) refers to "urgent safety issues", but section 3.13.3. refers to "Immediate Hazard". A further similar term used in the document is "incident" and "issue". Neither of the terms is explained in the glossary, differences are not clear, consequently required actions are not clear.	Align terminology / amend glossary.
German Pharmaceutical Industry Association (BPI)	0	0	0	Sometimes the document outlines if a term is explained within the glossary, however, this is not done for all terms that can be found in the glossary. It would be helpful and facilitate reading of the document if all terms that are listed in the glossary are marked respectively in the text. Furthermore, far more terms should be explained within the glossary for a better understanding.	Add reference to glossary to all terms within the document. Add further (new) terms to the glossary, e.g. immediate hazard / harm / incident/ issue / data governance / "verifying" versus "confirming" (e.g. for QC activities - which wording is used when?) /
Good Clinical Trials Collaborative, on behalf of supporting organisations	0	0	Submission	Thank you for the opportunity to comment on the draft ICH GCP E6(R3) guideline. This commentary has been prepared by the Good Clinical Trials Collaborative following consultation with a broad group of experts, and supported by (1) more than 50 medical societies and patient advocacy and research organisations, who form the Coalition for Reducing Bureaucracy in Clinical Trials and (2) the Biomedical Alliance in Europe (BioMed Alliance), a non-profit organisation representing 36 European research and medical societies uniting more than 400,000 researchers and healthcare professionals.	

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Good Clinical Trials Collaborative, on behalf of supporting organisations	0	0	OVERARCHING COMMENT	The new revision is a substantial improvement on previous versions. It is very positive to see the focus on Principles, rather than operational details. This is in line with the recommendations made in the G7 100 Days Mission to Respond to Future Pandemic Threats, which stated that, "*We should refocus regulatory guidelines on the fundamental scientific and ethical principles… whilst embracing flexibility and innovation… The Good Clinical Practice for clinical trials guidance should be revised to focus on what matters for the generation of actionable information about effects of an intervention, rather than what is easy to check but less relevant, placing an emphasis on principles and purpose rather than process*." However, further improvements are essential if the ICH E6 (R3) guideline is to have the intended beneficial impact on clinical trials.	
Good Clinical Trials Collaborative, on behalf of supporting organisations	0	0	OVERARCHING COMMENT	It needs to be made much clearer that Guidance is Guidance, rather than binding requirements or 'rules', and that the Annexes (just 1 in this version) are to be used as implementation guides rather than as detailed requirements.	It should be emphasised (e.g. in section I. Introduction) that it is acceptable to use an alternative approach to those specified in the Annex(es) providing that it satisfies the Principles of GCP (lines 35-265) and the applicable laws. Doing so will help ensure that the document lasts the test of time – advances in drug development, innovations in communications and information systems technology, novel or changing diseases and health conditions, and varying healthcare and societal contexts. It will foster innovation in trial methodology to the benefit of trial participants and the efficient generation of reliable clinical trial results.
Good Clinical Trials Collaborative, on behalf of supporting organisations	0	0	OVERARCHING COMMENT	There is a serious danger that for all the good intent of the authors of this revision, those charged with implementing it (including sponsors, investigators, auditors and inspectors) will fail to appreciate the context set by the Principles (lines 35-265) and apply the details set out in the Annex and associated Appendices rigidly 'reading from the back'. The most extreme examples of such over-interpretation are likely to be an excessive focus on Records, Data and Computer Systems (multiple pages) in the Investigator and Sponsor sections (sections 2 and 3) and on the Essential Records (the last 6 pages of the document) rather than on the much more thoughtful, balanced and risk proportionate approaches set out at the beginning (pages 1-6).	Some fairly simple but essential changes would substantially reduce the risk of over-interpretation and are detailed in the following commentary.
Good Clinical Trials Collaborative, on behalf of supporting organisations	0	0	Key theme	Key theme #1: Document structure and layout: Some simple changes are required to better orientate the reader and avoid confusion.	Suggestions follow.

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Good Clinical Trials Collaborative, on behalf of supporting organisations	0	0	Contextualising Annex with reference to principles	Add introductory text to emphasise the need to refer back to Principles and provide the rationale for what follows. These should be included at the start of Annex 1 and the start of each Section or major sub-section.	There are already a few good examples of such an approach in the current draft (e.g. at the start of Section 3 [Sponsor; lines 923-925] and Point 3.10 [Quality Management; lines 1103-1112]).
Good Clinical Trials Collaborative, on behalf of supporting organisations	0	0	Key theme	Key theme #2: There is a need for some re-organisation and grouping of the existing principles (Section II) to improve comprehension and impact; some further improvements to the Principles themselves (lines 78-265) such as the benefits of involving the perspectives of patients, healthcare providers and professionals in trial design; and consistent reference to the 'Principles of GCP' (rather than 'GCP') in the Annex(es). The Principles might be further improved by text explaining the rationale (we are happy to provide examples).	Suggestions follow.
Good Clinical Trials Collaborative, on behalf of supporting organisations	0	0	II. Principles of ICH GCP	Add statements in Introduction and at the start of the Annexes that guidance is guidance: State that this guideline is to intended to guide (rather than be a strict set of rules) and that it is acceptable to use an alternative approach to those specified in the Annex(es) providing that it satisfies the Principles of GCP (lines 35-265) and the applicable laws.	Note: For comparison, all FDA guidance documents currently include such a statement.
Good Clinical Trials Collaborative, on behalf of supporting organisations	0	0	II. Principles of ICH GCP	Be consistent in referring to the document as a guideline (as it is titled) rather than a standard: There are several places where the document is referred to as a "standard" (which implies that it is rigid and obligatory) rather than guidance (lines 2, 4, 9, 2167).	Reference to "standard" should be modified to "guideline" to be consistent with the document title ("ICH Harmonised Guideline") and encourage thoughtful implementation in line with the principles.
Good Clinical Trials Collaborative, on behalf of supporting organisations	0	0	Key theme	Key theme #3 Records, Data & Computerised Systems: The new draft has substantially increased text relating to records, data and computerised systems. In addition to being covered in Principles 9.4-9.5 (lines 217-228), the Investigator section now includes 2 pages (lines 831-911) on Records, the Sponsor section includes 5 pages (lines 1590-1785) on Data and Records, and there is an entire new Section 4 of 5.5 pages on Data Governance (lines 1813-2029) that applies to both Sponsors and Investigators. In places the new text is helpful in providing guidance, emphasising proportionality and fitness-for-purpose, and enabling flexibility to the context of the specific trial and changes in information technology in the future. In other places, the text is unduly rigid and enforces or encourages over-interpretation that will harm trial quality and adaptability.	See notes below for suggestions.

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Good Clinical Trials Collaborative, on behalf of supporting organisations	0	0	Remove excessive details in Investigator and Sponsor sections	Given the presence of Section 4 on Data Governance, much of the text on Records in the Investigator section (Point 2.12; lines 831-911) and Sponsor section (lines 1590-1785) is unnecessary, over-restrictive and/or lacks proportionality.	Examples given below.
Good Clinical Trials Collaborative, on behalf of supporting organisations	0	0	Table 1 - Essential Records for All Trials and Table 2 Potential Essential Records	By contrast with the preceding text on essential records, these tables are much more considered and helpful.	Proposed amendments to further help encourage proprotionality are listed below.
Good Clinical Trials Collaborative, on behalf of supporting organisations	0	0	Table 2, Row 2.8	Modify to "documentation of delegation of key activities…"	
Good Clinical Trials Collaborative, on behalf of supporting organisations	0	0	Table 2, Row 2.32	Modify to "documentation of ~~relevant~~ key communications and meetings"	
Good Clinical Trials Collaborative, on behalf of supporting organisations	0	0	Key theme	Key theme #5: Roles & responsibilities. The following changes are necessary to avoid a level of specificity that may restrict sensible arrangements or impose unreasonable / unworkable oversight obligations on individuals /organisations for activities or data sources outwith their control.	
Good Clinical Trials Collaborative, on behalf of supporting organisations	0	0	Key theme	Key theme #6: Other issues. A range of corrections and clarifications that will help improve the document and the way that it is interpreted and implemented	
Good Clinical Trials Collaborative, on behalf of supporting organisations	0	0	Blinding and Bias	The document rightly emphasises the need for reliable results. In the context of randomised trials, the reliability of the results is strongly influenced by proper randomisation processes (including the inability to predict treatment allocation), encouraging adherence to allocated treatment, maximising completeness of follow-up for study safety and efficacy outcomes, and evaluation of the occurrence or nature of study outcomes that can not be influenced by knowledge of treatment allocation (see www.goodtrials.org for more information on these and related principles). These critical-to-quality principles are largely absent from the current document yet can have a much bigger impact on reliability of results than the accuracy of individual data points or extent of documentation.	https://www.goodtrials.org/guidance

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Good Clinical Trials Collaborative, on behalf of supporting organisations	0	0	Review of Safety Information and Safety Reporting	Key sections related to review of safety information and safety reporting (Principle 1.2, Investigator section 2.7.2, and Sponsor section 3.13) do not adequately guide the user on effective, informative safety monitoring and reporting.	Examples of relevant, useful guidance can be found in the U.S. FDA's Guidance on Safety Reporting Requirements for INDs and BA/BE Studies (https://www.fda.gov/media/79394/download) and in the Good Clinical Trials Collaborative's guidance: https://www.goodtrials.org/the-guidance/guidance-overview/informative-and-relevant/#assessing.
Good Clinical Trials Collaborative, on behalf of supporting organisations	0	0	GENERAL	Minor improvements to support consistency, clarity etc.	Suggestions follow.
GQMA	0	0		Should the recommendations of the EMA expert group regarding Auxiliary Medicinal Products in Clinical Trials dated 2017 be taken into account for monitoring analoguous to section 3.11.4.5.3 Monitoring of Investigational Product Management? Auxiliary medicinal products mentioned in the protocol, at best prepared at site under specific conditions would also qualify for drug accountability, temperature monitoring etc. Furthermore, this would also apply to the management of auxiliary medicinal products analoguous to section 3.15 Investigational Product(s), section B 4 Trial Design, section B.7 Treatment and Interventions for Participants, and C.3 Essentiality of Trial Records (where applicable)	Insert a (brief) section on the monitoring and one section on the management of auxiliary medicinal products as specified in an approved protocol.
GQMA	0	0		Artificial Intelligence becomes more and more important also in the field of medicine.	Take this topic in this update into consideration as well.
Jazz Pharmaceuticals	0	0	0	Overall Jazz believes the proposed revisions and restructuring provide many helpful clarifications to the intent and application of this Guideline, and we support the changes.	
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	0	0		Add internal links to references "see section xxx" to facilitate navigation through the document and easily switch to the referenced section.	
Mandy Jackson National Clinical Trials Office Quality Working Group Ireland	0	0		Numerous reference to being 'Fit for purpose' e.g. computerised systems, data acquisition tools,non-trial-specific systems. Will guidance be provided on assessment of/criteria to apply to determine 'fit for purpose' or will it be individual responsibility?	
Medicines for Europe	0	0		Throughout the guideline (in various sections that allude to computerised systems and data, the term "responsible party" is used. It is however unclear who the "responsible party" is. Does this refer to a third party provided? On occasion the expression should be accompanied by "(sponsor or investigator)".	Please, either clarify the expression in each section or add this term in the glossary.
Medicines for Europe	0	0	General	Clarification on how the new recommendations in the guideline would be applied to ongoing clinical trials would be beneficial for sponsors as substantial new informations has been introduced in the revised guidance.	
Medicines for Europe	0	0	-	Further elaboration on the relevant requirements regarding monitor's qualification and selection is needed as such recommendation was removed in this version. (ICH E6. R2. Section 5.18.a)	

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Ollie Östlund	0	0		ICH E6 has a history of being applied by regulators and in legal requirements far beyond its actual scope, which has negatively impacted initiatives such as learning healthcare systems. While the new revision is an *immense* improvement in flexibility and proportionality, the crux of the matter remains: Either ICH E6 should be used *also* for clinical trials where the main purpose is not regulatory decision-making. In that case, ICH E6 must be explicitly developed to support also trials for purely scientific purposes and for systematic improvement of standard of care and development of clinical guidelines, including both explanatory and pragmatic trials. Otherwise, ICH E6 *cannot* be invoked in these situations. While the scope is clearly stated in the guideline, in the latter case ICH has a responsibility to very clearly state, in the guideline, that ICH E6 *should never be required* outside trials intended for specific regulatory decision-making, and may recommend that the scientific community develop their own guidelines.	
Ollie Östlund	0	0		The reworking of ICH E6 into a main document with additional annexes makes me wonder when a guideline will be an E6 annex and when it will be a standalone ICH guideline. Consider that the current flat document structure may be easier to navigate. Even the Q-S-E-M system may not be very useful.	
Ollie Östlund	0	0	Guideline title	Title: The phrase “Good clinical practice” is both pretentious and somewhat vague, and the origin is not clear to me. Several legal texts and guidelines have claimed to define “GCP” in different situations, such as ICH E6, 2005/28/EC and ISO 14155. In the ICH framework, E6 refers back to E8, which seems more fundamental. I recommend changing the title to the clear and descriptive “Unified scientific, ethical and quality standards for clinical trials intended for regulatory decision-making [in ICH member countries]”. This summarises the introduction, makes the scope and applicability explicit, and decreases the risk of misunderstanding the intent of the guideline.	Change title from "Guideline on good clinical practice" to "Unified scientific, ethical and quality standards for clinical trials intended for regulatory decision-making in ICH member countries”
Quotient Sciences	0	0	0	In general, there is insufficient consideration of the important differences between phase 1 healthy volunteer trials and later phase trials in patients. The draft guideline does not acknowledge the difference between phase 1 trials in healthy volunteers and later phase trials in patients. In particular, the requirements for public registration, diversity of trial populations and participant involvement do not apply to phase 1 healthy volunteer research in the same way that they do to research in patients. Further details are below. It is essential to clarify which aspects of the guideline are not applicable, or differently applicable, to healthy volunteer trials, to ensure clarity and compliance and to avoid unnecessary monitoring and auditing queries.	

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Quotient Sciences	0	0	0	Transparency Information about, and results of, phase 1 trials are highly commercially sensitive, and of negligible benefit to patients, the public and prescribing physicians. Prospective registration of phase 1 healthy volunteer trials with a minimal dataset only has been successfully implemented in the EU and UK to protect commercial confidentiality. The minimal dataset is published before the trial starts and publication of full trial details is deferred. The publication of trial results is even more commercially sensitive and sponsors must be able to control exactly how and when their results are published, so that they can mitigate commercial risk. There is currently no requirement for sponsors of phase 1 trials in the UK or US to publish their results - sponsors should be encouraged to post their results at the earliest opportunity when the commercial risk has diminished, to ensure that publication requirements do not undermine the commercial development of new medicines. The guidance should clearly distinguish between requirements for patient trials and those for phase 1 healthy volunteer trials. Also, for phase 1 healthy volunteer trials it should not be mandatory to actively provide results to participants. Phase 1 trials assess the safety, tolerability, pharmacokinetics and pharmacodynamics of new potential medicines. The results do not indicate whether the medicine will work in patients and technical data (e.g. pharmacokinetic parameters) are of no relevance or interest to the public. In addition, our long experience has shown that the vast majority of healthy volunteers have no interest in phase 1 trial results. A very basic summary should be made available to participants on request, but sponsors/investigators should not be obliged to provide results to all participants.	
Quotient Sciences	0	0	0	Diversity of trial populations A requirement to increase diversity among participants would not be appropriate for phase 1 healthy volunteer trials. Phase 1 trials are done early in development, in small groups of healthy adults, and aim to investigate safety, tolerability, pharmacokinetics and pharmacodynamics of potential new medicines. For safety reasons, to reduce variability in the results, and to ensure trials are completed in a timely manner, people who are not healthy are excluded. Pregnant or breastfeeding women are excluded for safety reasons, and many early trials exclude women of childbearing potential because there is little or no information available about the potential effects of the test medicine on the unborn child. Also, some protocols require specific populations, e.g. young men, elderly men and women, women of non-childbearing potential, or specific ethnic groups (e.g. Japanese), so that safety, tolerability, pharmacokinetics and pharmacodynamics can be compared among different populations. There are other reasons why populations may be restricted: e.g., investigation of skin reactions is most easily done in people with pale skin; and vegans/vegetarians are excluded from trials in which the FDA-recommended high-fat bacon- and egg-containing breakfast is used to test the effect of food on pharmacokinetics of the test medicine. It is in the interest of investigators of phase 1 healthy volunteer trials to allow as diverse a trial population as possible, to aid recruitment; however, trial populations often must be restricted for reasons of science and safety. It is ethical to restrict populations in these trials because participants get no medical benefit from taking part. The guidance acknowledges that certain trials, such as early phase trials, may not require a heterogeneous population, but it must go further and state that early phase trials, which carry no medical benefit, necessarily require restricted populations, for reasons of safety and science. While no group should be unnecessarily excluded, it should not be a requirement for investigators to take action to increase diversity among phase 1 healthy volunteer populations.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Quotient Sciences	0	0	0	Participant involvement Involving patients in the design, management and conduct of later phase patient trials can be beneficial to both patients and sponsors. But it's inappropriate to involve healthy volunteers in the design and management of phase 1 healthy volunteer trials, for various reasons: * Healthy volunteers are fit and well and do not have special needs that might not be fully understood by personnel designing or managing the trial (e.g. mobility, diet). * Looking after the needs of volunteers is central to the success of phase 1 trials and phase 1 units. We review the participant information sheet and protocol from the point of view of a participant and consider aspects of the design that may cause unnecessary discomfort or inconvenience, e.g, avoid discharge of volunteers late in the evening or prolonged fasting. * Phase 1 trial designs must comply with international guidelines and be appropriate to the safety profile, pharmacokinetics and pharmacodynamics of the IMP. The schedule of procedures and sampling is usually very intensive. We aim to minimise inconvenience, but we must ensure volunteer safety and data quality. So, for example, if we must interrupt volunteers' sleep to do procedures, or if volunteers must remain in bed or fast for prolonged periods, we ensure that we inform them of all the burdens and inconvenience of participation. It's in our best interest to do that because not doing so would risk a high withdrawal rate, which would increase the cost of the trial, extend its timelines and potentially lead to exposure of additional volunteers, which has ethical implications. While involving healthy volunteers in the design, management and conduct of individual trials is not appropriate, it is appropriate for phase 1 units to ask healthy volunteers for regular feedback on their documents, facilities and processes, and to respond to that feedback. The guidance should clearly distinguish between the requirements for the involvement of patients in the design, management and conduct of patient trials and a requirement for phase 1 investigator sites to seek feedback on partcipants' experience of their participant-facing documents, facilities and processes.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Richmond Pharmacology Dr Ulrike Lorch Dr Jörg Täubel Dr Thomas Ashdown Dr Edward Jackson Dr Thomas York	0	0		Richmond Pharmacology appreciates the opportunity to offer feedback on the ICH E6(R3) Good Clinical Practice Guidance. As an organization owned and managed by very experienced and distinguished Principal Investigators and Coinvestigators, we are experts in early phase clinical research. Many of the trials we perform are first-in-human (FIH), including healthy and patient participants, the latter often with rare diseases. The investigational medicinal products (IMP) researched in our trials are mostly biologicals and advanced therapies, including in-vivo genome editing therapy. The sponsors of our clinical trials are mainly based in all regions of the founding regulatory members of ICH. Our comments and proposals stem from three decades of continuous practical experience as early phase investigators. We fully support some of the aims of the ICH Good Clinical Practice revision, particularly the promotion of a proportionate risk-based approach. However, we strongly believe the ICH E6 Revision should recognise a distinction between experienced and inexperienced investigators, empower the experienced investigator and encourage less experienced investigators to develop. Our comments and proposals stem from three decades of continuous practical experience as early phase investigators. Most of our comments are general as we feel that the spirit of the guidance, regarding the role of the investigator, needs significant revision. We have provided a few specific points to illustrate our position.	We would appreciate the opportunity to participate in ICH guidance revisions early to provide an early-phase, investigator perspective. The ICH is traditionally a council of regulatory authorities and sponsors. Given that ICH guidelines significantly impact investigators and patients, the voice of these key stakeholders needs to be heard at the earliest opportunity. Investigators are an extremely diverse group, and many investigators may not even be aware that an ICH guideline is being revised. The ICH should endeavour to promote greater inclusivity at the earliest stages of guideline revision.
Richmond Pharmacology Dr Ulrike Lorch Dr Jörg Täubel Dr Thomas Ashdown Dr Edward Jackson Dr Thomas York	0	0		Successful clinical trials require the alignment of four key parties: the sponsor, the regulator, the investigator, and the patient. It is therefore unfortunate that the Expert Working Group for ICH E6 Revision (and other recent ICH revisions) comprises of just regulators and sponsors. We are deeply concerned that this guidance supports the concerning industry trend towards diminished investigator responsibility. Such an approach is likely to exacerbate a deep-rooted problem in clinical trials, the scarcity of experienced principal investigators. This is perhaps best illustrated by the alarming "one-and-done" investigator phenomenon, where investigators only ever participate in a single clinical trial [1]. Therefore, the investigator pool can be considered as two distinct groups; the experienced, professional investigator often operating in a specialised clinical trials unit and the occasional investigator, who participates in clinical research alongside their normal job, perhaps recruiting a few patients into a large multicentre trial. Recognising the distinction between these investigator types is crucial. Whilst greater sponsor control and influence may be necessary for part-time investigators, this can be oppressive for the skilled investigator and will contribute to greater burnout. The ICH GCP Guidance should recognise the experienced investigator.	Recognise the distinction between experienced and occasional investigators.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Richmond Pharmacology Dr Ulrike Lorch Dr Jörg Täubel Dr Thomas Ashdown Dr Edward Jackson Dr Thomas York	0	0		We feel the considered ICH GCP revision promotes a top-down, prescriptive relationship between the sponsor and the investigator. On the contrary, the relationship between the sponsor, the investigator, the regulator, and the patient should be collaborative. The benefits of a cooperative relationship are considerable for all parties. The Sponsor: Professional clinical trial units have a wealth of specialised clinical trial knowledge which can be an invaluable resource for the sponsor. It is not uncommon for a sponsor to be running its first clinical trial with a compound class that the investigator may have significant experience with. Specialist units are often highly proficient in protocol development and have developed systems and processes to ensure that they can run multiple clinical trials efficiently. This has direct benefits on study delivery, analysis shows that the study initiation phase is considerably faster when sponsor and investigator have an established relationship [2]. A recent survey showed that many investigators do not feel like their sites are taken into consideration when protocols are designed by sponsors [3]. Investigators would welcome greater protocol collaboration and the ICH GCP guidance should actively encourage this.	Promote the expertise of the experienced investigator.
Richmond Pharmacology Dr Ulrike Lorch Dr Jörg Täubel Dr Thomas Ashdown Dr Edward Jackson Dr Thomas York	0	0		The Patient: Patient safety is the foundation of all clinical practice, but it is perhaps in early-phase clinical research, where the risks and benefits are less certain, that this is most crucial. The investigator is ultimately responsible for the safety of the patient throughout the trial. Therefore, it is vital that the investigator has easy access to relevant safety information to maintain safe medical oversight. For experienced investigators, running multiple clinical trials, this should integrate into their established systems to avoid unnecessary bureaucratic burden. The investigator also acts the patients advocate throughout the clinical trial, carefully considering the impact any decisions may have on the patient. The Investigator: A collaborative relationship can engage the experienced investigator and help to retain the interested investigators. Research shows that experienced investigators have evolved strategies to overcome the same challenges that result in the "one-and-done" investigator phenomenon [4]. These strategies enable experienced investigators to conduct multiple clinical trials safely and efficiently. Respecting and integrating these strategies into clinical trials will help to reverse the industry shortage of experienced investigators. We appreciate that the revision has made some steps towards facilitating this, but we believe this should be encouraged with greater conviction. It is key that professionalism needs to be valued and supported. The ICH GCP Guidance must promote the experienced investigator.	Promote the expertise of the experienced investigator.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Richmond Pharmacology Dr Ulrike Lorch Dr Jörg Täubel Dr Thomas Ashdown Dr Edward Jackson Dr Thomas York	0	0		In addition to retaining experienced investigators, the training of new dynamic investigators is of paramount importance. One way of engaging new investigators is relevant, flexible, and practical training and certification by professional bodies. We are training a new generation of early phase investigators who will see many advances in clinical research. We wish to train and guide this next generation of investigators to safely respond to such advancements with flexibility and ingenuity. This is of particular importance given the changing nature of clinical trials with a move towards longer term follow up and decentralised trials. Training and accreditation should be practical and encompass a wide breadth of different clinical trials. The role of the investigator must remain attractive and those who wish to train towards becoming an experienced investigator should be incentivised. There is an abundance of evidence showing that certified professional investigators perform better, in terms of both quality and efficiency, which ultimately reduces costs and allows timely patient access to novel therapies [6]. Good Clinical Practice has always stated that investigators should be appropriately qualified "The investigator(s) should be qualified by education, training and experience to assume responsibility for the proper conduct of the trial". It is difficult to ascertain how this is upheld given that the majority of investigators fulfil the "one-and-done" criteria. Furthermore, just 6% of annual clinical trial spending is directed towards professional investigators, with the majority awarded to part-time investigators [6]. We believe the revision of the ICH GCP guidance is an excellent opportunity to promote the next generation of professional, experienced, clinical trials investigators.	Promote and incentivise the next generation of professional, experienced, clinical trials investigators.
Richmond Pharmacology Dr Ulrike Lorch Dr Jörg Täubel Dr Thomas Ashdown Dr Edward Jackson Dr Thomas York	0	0		Referenced Articles: [1] One and done: Reasons principal investigators conduct only one FDA-regulated drug trial - PubMed (nih.gov). https://pubmed.ncbi.nlm.nih.gov/29740635/ [2] Why Would Investigators Leave After Only One Clinical Trial? - PSI CRO (psi-cro.com). https://www.psi-cro.com/investigators-leaving-clinical-trials/ [3] Sponsors Still Not Leveraging Site Experiences, Feedback, Survey Shows | CenterWatch. https://www.centerwatch.com/articles/26629-sponsors-still-not-leveraging-site-experiences-feedback-survey-shows [4] Continued investigator engagement: Reasons principal investigators conduct multiple FDA-regulated drug trials - ScienceDirect. https://www.sciencedirect.com/science/article/pii/S2451865419302650 [5] One and done: Reasons principal investigators conduct only one FDA-regulated drug trial - PubMed (nih.gov). https://pubmed.ncbi.nlm.nih.gov/29740635/ [6] Research Projects Show Credentialed Principal Investigators and CRCs Perform Better | 2018-07-02 | CenterWatch. https://www.centerwatch.com/articles/12556-research-projects-show-credentialed-principal-investigators-and-crcs-perform-better	
SHIONOGI	0	0	throughout the entire guideline	to ensure consistency throughout the entire guideline	suggest to replace 'trials' with 'clinical trials' througout the entire document, where applicable to ensure consistency and avoid misunderstanding
SHIONOGI	0	0	throughout the entire guideline	In the draft guideline there are a couple of examples where the term 'patient' or 'patients' is used. Should this be replaced participant(s) to avoid that healty volunteers are being excluded.	suggest to replace the word 'patient' and 'patients' with 'participant' and 'participants'

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
SHIONOGI	0	0	Glossary & Annex 4	Missing definition on Artificical Intelligence (AI). AI becomes more and more important in clinical trials. There should be some reference to the use of AI in clinical trials, including how to ensure audit trails, in the guideline	Suggest to add AI, including audit trail, in Annex 4 and glossary
SHIONOGI	0	0	Glossary and 2.3	Lacking definition of and reference to Site Management Organization (SMO) which are used more and more in clinical trials. Since SMOs may be contracted by clinical sites to perform trial related tasks, it may be useful to add SMO to the glossary with a similar reference to Service Provider as for CRO and to add in section 2.3 as an example of a service provider.	suggest too add SMO to the glossary and in section 2.3
SHIONOGI	0	0	4.3	Missing definition on Serious Breach (of protocol and/or GCP/regulatory requirements) and requirements from the sponsor to report these to the regulatory authorities as per local requirements. MHRA, EMA as well as other regulatory authorities have specific requirements of the prompt reporting of a 'serious breach'.	suggest to add a definition on serious breach and a section in Annex 3 on the sponsor requirements for reportign serious breaches.
SHIONOGI	0	0	Annex 2 and glossary	Lacking definition as well as lacking responsibilities for the investiagtor related to Urgent Safety Measures. There is only the requirement for the sponsor to report urgent safety issues to the IRB/IEC and/or regulaotry requriements and investigators without undue delay (3.13.2 (e)). However, an Urgent Safety Measure is initiated by the investigator to ensure the participant's safety.	Please add responsibilities for the investigator in Annex 2 as well as a definition in the glossary for Urgent Safety Measures or issues
SHIONOGI	0	0	throughout the entire guideline	there is no reference to auxilary medicinal products used for the needs of a clinical trial as described in the protocol, but not as an investigational products.	It is recommended to consider to add the term auxilary medicinal products in the glossary and in Annex 3, under 3.15 or a new section
SHIONOGI	0	0	4.3	Recommended to have instructions that the sponsor is responsible to ensure the investigator's responsibility that the electronic data (e.g. ePRO data saved on a CD-rom) should be accessible during an inspection e.g. that both the equipment and the software to read the data are available. If systems are decommisioned the investigator should notify the sponsor.	See column H35

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Swedish Monitors attending NORM meeting 2023	0	2832	The whole document	This revision is unfortunately not very easy to read and follow. It lacks the clarity that revision 2 had. Reading it, it feels like a lot of information has been included, that might more belong in a different guideline. As monitors, we are the ones that will try to assist sites as well as Sponsors when implementing and applying GCP and make it work in practice. Working in a lot of smaller academic studies, we come in contact with both Investigators and Sponsors with little or no previous experience, and we feel that this revision of the guideline for GCP will not be as easy to follow as previous version(s). As this guideline is more difficult to follow, we fear it might generate "guide to the guideline"-documents to be able to clarify for site(s)/ Investigator(s)/ Sponsor(s) what to do and how to interpret the text, where the guideline is now trying to be broad and cover everything instead of being specific. And if that is the case - that everyone needs to write their own guides on how to follow/interpret the guideline, we're in trouble.	Clearer headings, and shorter more bullet-point like instructions.

2. Specific comments on text

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Ludger Wienbrede	2	3		"Good Clinical Practice (GCP) is an international, ethical, scientific and quality standard for the conduct of trials that involve human participants." Since ICH GCP was published in 1995 it was never clear what this statement effectively means. Does it mean that ICH E6 contains all standards of GCP? Then the statement should read: "Good Clinical Practice (GCP) is an international, ethical, scientific and quality standard for the conduct of trials that involve human participants and that is completely described in this ICH GCP Guideline." Or does GCP refer to the standards of this E6 guideline plus someting in addition? In this case, the "someting in addition" should be unambiguously named as well. Otherwise, it would be at anybody's caprice to decide whether or not something is according to GCP. For example, it is not clear what line 361ff means "The IRB/IEC ... should comply with GCP.": Does it mean that it should comply with E6? Or comply with E6 and something more (in this case: what exactly is this something more?) Note that according to line 175, compliance with the trial protocol and applicable regulatory requirements is not necessarily included in compliance to GCP. This means: If GCP is more than ICH GCP, that more is not in the protocol and the regulatory requirement, but somewhere else. Should the vague definition cover the following?: If GCP inspectors from different countries invent their own rules, this is also GCP, because it meets the definition of lines 2 and 3. This is what happens with the ever expanding concept of essential documents. ICH GCP presented a list of distinct items, suggesting is was only a minimum, and inspectors and auditors took as an opportunity to inflate the concept of essential, which was a misfortune for trialists who could never quite keep up with handlimg the growing universe of essential documents.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Ludger Wienbrede	6	8		Comment on style: Change: The term “trial conduct” in this document includes processes from planning to reporting, including planning, initiating, performing, recording, oversight, evaluation, analysis and reporting activities as appropriate. To: The term “trial conduct” in this document includes planning, initiating, performing, recording, oversight, evaluation, analysis and reporting activities as appropriate. --- Consider to delete "planning", since planning can be very far away and quite separated from what most people would regard as "trial conduct". Better use "preparation" or "set up". Actually, very little if anything in this E6 text describes processes that most people would call "planning". Also something like "approval" should be added, since E6 features the operation of ethics committees.	
EUCROF	8	8	I. INTRODUCTION	Trial conduct should also include archiving. See also Principles: II.9.6	…, performing, recording, oversight, evaluation, analysis, reporting and archiving activities as appropriate.
Association for Clinical Data Management (ACDM)	12	13	Introduction	Appreciate driving consistency across and between the Guidelines	No Action
Fergus Sweeney	13	14	I	"These include fostering…"	should read "This includes fostering…"
EFPIA Consolidated Comments	20	23	I	1. Footnote is not clear so propose to make this a glossary term. 2. It is not clear that this guideline applies only to interventional clinical trials in ICH regions only	1. glossary term instead of footnote for investigational product. 2. This guideline applies to interventional clinical trials of investigational products requiring regulatory approval of the clinical trial in the ICH regions. This guideline may also be applicable to other interventional clinical trials of investigational products that are not intended to support marketing authorization applications in accordance with local requirements.
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	20	21	I	"The guideline applies to interventional clinical trials of investigational products that are intended to be submitted to regulatory authorities" This wording is misleading because it is not clear what the intention of the submission is.	Suggestion: "The guideline applies to interventional clinical trials of investigational products that are intended to support marketing authorisation application."
Ludger Wienbrede	20	21		Comment on meaning: "This guideline applies to interventional clinical trials of investigational products that are intended to be submitted to regulatory authorities." What is this supposed to refer to? Are the clinical trials submitted to regulatory authorities or are investigational products submitted to regulatory authorities? Both meanings makes no sense. If this is refer to the submission of applications for authorisations the text should read appropriately. Moreover, the term "interventional" is not well-defined and requires clarification in the Glossary section. It could mean: Anything more than obervation like a fly on the wall, e.g. if questionaires are used that are not the standard practice this is already interventioanal. Ot is could mean: Study-specific blood collections are still non-interventional as long as the use of the investigational product is according to standards practice.	
SHIONOGI	20	20	I Introduction	typo / grammar	suggest to replace 'interventional clinical trials of investigational products' with 'interventional clinical trials with investigational products'

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
SHIONOGI	20	20	I Introduction	The footnote 1 'For the purpose of this guideline, the term “investigational products” should be considered synonymous with drugs, medicines, medicinal products, vaccines and biological products' is still confusing	Suggest to replace with '…..should be considered synonymous with a pharmaceutical form of an active ingredient of drugs, medicines, medicinal products, vaccines and biological products or a placebo being tested or used as a reference in a clinical trial'
Fergus Sweeney	21	23	I	The sentence commencing "This guideline may also be applicable…" assumes to apply this guideline to actors beyond the scope of ICH. ICH scope is clinical trials of investigational products intended to be submitted to regulatory authorities. Whilst academic researchers have been able to comment at intervals on the draft text in preparation and this has been very helpful, since they also represent views of investigators, the Annex 1 text is still essentially focused on trials conducted by the pharmaceutical industry and the CROs it employs, it is complex and detailed, demanding significant resource that academia is often not funded for. To apply Annex 1 in all its detail, beyond industry led MA related trials is overreach. The text can certainly be a source but academia may have different, equally valid approaches. It is to the detriment of public health such trials are restricted due to a rigid, industry style approach to trial conduct. It will perpetuate the cirticism already long levelled at ICH and which were among the drivers of GCP rennovation.	If ICH chooses still to have text extending its scope it should state that "The principles may be applied to clincal trials of interventional medicinal products that are not intended to suport marketing authorisations". Or "The principles may be applied to clincal trials of interventional medicinal products that are not intended to suport marketing authorisations, for which the detailed guidance may also serve as a reference but alternative approaccches to the. details in Annex 1 are acceptable." or delete this sentence.
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	21	23	I	"This guideline may also be applicable to other interventional clinical trials of investigational products that are not intended to support marketing authorisation applications in accordance with local requirements." According to ICH E6 (R2), the guideline can be applied to all clinical trials where the safety and well-being of participants could be affected (this would include studies of psychotherapies or surgical methods), and also to non-interventional studies. This should not be changed with R3. The possibility to apply ICH E6 (R3) to these studies helps to ensure patient safety and data integrity. Also, the planned Annex 2 of ICH E6 (R3) should include pragmatic elements and real-world data sources. Therefore, this guideline should not exclude all non-interventional studies from the beginning.	Suggestion: "The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects."
Swedish Monitors attending NORM meeting 2023	21	23	I Introduction; Guideline Scope	The sentence "This guideline may also be applicable to other interventional clinical trials…" is unclear. Is "may" the best wording here? All intervetional clinical trials (marketing or not) should follow GCP.	Change "may" to "should" or similar.
SHIONOGI	22	22	I Introduction	typo / grammar	suggest to replace 'interventional clinical trials of investigational products' with 'interventional clinical trials with investigational products'
Fergus Sweeney	28	29	I	The sentence " The principles outlined on this…" coudl be better worded	Suggest reword to "The principles outlied in this guideline may be satisfied using alternative approaches which ensure the principles are upheld. The principles should be applied to fit the intended purpose of the clincal trial."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
DGPharMed e. V. (Deutsche Gesellschaft für Pharmazeutische Medizin)	35	77	II	Should principles also consider environmental impact of trials (travel, shipments, waste, resources)	Add environmental impact of trials (travel, shipments, waste, resources)
Good Clinical Trials Collaborative, on behalf of supporting organisations	35	77	II. Principles of ICH GCP	The introductory text on Principles of ICH GCP (lines 35-77) is very strong, setting out exactly the right tone and emphasis.	
Good Clinical Trials Collaborative, on behalf of supporting organisations	35	77	II. Principles of ICH GCP	This text is very strong and should remain unaltered. It provides guidance, context, and rationale and encourages thoughtful application of the rest of the document.	
SHIONOGI	36	37	II Principles of ICH GCP	term of 'new medicines or uses of existing medicines' seems not to be alligned with the footnote 1 in I Intoduction. It may be interpreted that 'medicines' are not including drugs, vaccines, medicincal and biological products.	suggest to add a footnote that 'medicines' are synonymous for drugs, medicines, medicinal products, vaccines and biological products
Ludger Wienbrede	40	40		Comment on style: The sentence "Trials with inadequate design and/or poorly conducted trials may place participant safety at risk and yield inadequate or unreliable evidence and are unethical." should be rephrased to "Trials with inadequate design and/or poorly conducted trials may place participant safety at risk and/or yield inadequate or unreliable evidence and, therefore, are unethical." (inclusion of the terms "/or" and "therefore"). This improved linguistic presentation endorses the ethical concept that underlies the ICH GCP guideline by providing a stringent reasoning.	
EFPIA Consolidated Comments	41	41	II - Principles of ICH GCP	We suggest deleting the following statement as the text does not seem appropriate or necessary for the guideline.	evidence, are unethical and do not make best use of resources. They waste resources and the efforts and time of investigators and participants.
EUCROF	41	41	II. PRINCIPLES OF ICH GCP	Sponsors should be included.	They waste resources and the efforts and time of sponsors, investigators and participants.
Fergus Sweeney	41	41	II	Add to sentence "They waste resources…". It is also about impact on health and decision making.	Add to end of sentence "They waste resources…". The following "….and can lead to poor decision making based on unreliable results."
EUCROF	42	43	II.	"The principles of GCP are designed to be flexible and applicable to a broad range of clinical trials" "Broad range" somehow also says "not all of them". The statement should be more precise.	The principles of GCP are designed to be flexible and applicable to all clinical trials of investigational products.
Fergus Sweeney	44	44	II	suggest reword	"…planning to address the specific…"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUCROF	47	48	II.	"...the setting in which the clinical trial is being conducted, and the type of data being collected." Record retention should be added	...the setting in which the clinical trial is being conducted, the type of data being collected, and the type of records being retained.
Fergus Sweeney	50	51	II	More should be added on efficient approaches as a follow-on to the first sentence. This is a major issue with broad impact. The rest of the paragraph should be a new following paragraph starting "Innovative digital approaches…" which are an important new aspect of this guidance and not only an example of efficiency.	Following the first sentence "The principles are intended…design and conduct." Add "Efficient approaches ensure focus on critical trial aspects. By focusing on the critical aspects the sponsor can spare resources to enable larger, better powered, more effective trials to be conducted and cokmpleted, or enable additionlal trials to take place which would not otherwise have been possible. This efficiency is very important to patient and public health objectives." Start a new paragraph with the text from line 51 onwards but deleting "For example" so new paragraph starts "Innovative digital health technologies...."
Ludger Wienbrede	50	55		Comment on style: Consider to reduce the marketing speech in this section. E.g. "wearables and sensors" might be a good idea to collect data but they do not "expand the possible approaches to trial conduct". "innovative digital health technologies" "will aid in keeping clinical trial conduct in line with advancing science and technological developments": Yes, but this is tautological and/or trivial. Consider to delete lines 51 - 55. The statement "The use of technology in the conduct of clinical trials should be adapted to fit the participant characteristics and the particular trial design. This guideline is intended to be media neutral to enable the use of diferent technologies for the purposes of documentation." already says it all, without advertising anything.	
DGPharMed e. V. (Deutsche Gesellschaft für Pharmazeutische Medizin)	54	54	II	Add that wearables, sensors and health technologies can reduce patient burden.	Add that wearables, sensors and health technologies can reduce patient burden.
EFPIA Consolidated Comments	56	58	II	Technology is not only used for documentation, also data collection, data processing.....	This guideline is intended to be media neutral to enable the use of different technologies for the purposes of communication with stakeholders, data collection, processing, analysis, documentation, maintenance and archiving.
EFPIA Consolidated Comments	59	65	II	Ensuring that partiticpants are not excluded because of digital technology also needs to be considered, for example trials in the elderly may not be suited to collecting data on participants smartphones. Should caregivers be considered too?	The use of innovative clinical trial designs and technologies may help include diverse patient populations, as appropriate, and enable wider participation. The design of the trial, to ensure appropriate quality and meaningful trial outcomes, may be supported by the perspectives of stakeholders; for example, patients, caregivers and/or healthcare providers. Their input can increase the likelihood of meaningful trial outcomes, which are relevant to both trial participants and future patients. This input will also guide decisions on the feasibility of data collection and assure that participants in the trial are not unduly burdened or digitally challenged.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Jazz Pharmaceuticals	59	77	II	Prior to final protocol submission, sponsors should be required to conduct thorough patient/potential participant interviews or caregiver interviews that must be conducted with 10% of the expected number of enrolled participants. Sponsors should incorporate these comments and concerns into trial designs and/or protocol amendments to the greatest extent possible/reasonable. i.e., 30 participants/caregivers must be interviewed before initiating a trial or finalizing a protocol for an expected enrollment of 300. The interview should contain the following questions (for discussion): o What motivates participant/caregiver to participate in the trial? o What major concerns are there? o What technical or logistical concerns does the participant/caregiver anticipate? o What have been the primary difficulties in managing a particular condition, and does the participant/caregiver have any suggestions for mitigating these issues?	
ACRO	60	62		ACRO welcomes the emphasis on stakeholder engagement to help with feasibility and protocol design to decrease study burden. We would recommend that the guidance is explicit about the need for this engagement to be at the protocol development stage, rather than later in the process. The risks of later engagement include lack of meaningful impact and perception as a "tick-box" exercise. ACRO also welcomes the acknowledgement that the use of innovative clinical trial designed and technologies may help include diverse patient populations. However, ACRO would welcome further emphasis in the draft of the importance of ensuring diversity of patients in order to ensure that trial outcomes are relevant to a wider set of patients, in line with principle 1.4.	To add "feasibility" and to add "for diverse communities" to line 61: "The design of the trial, to ensure feasibility, appropriate quality and meaningful trial outcomes for diverse communities, may be supported by the perspectives of stakeholders; for example, patients and/or healthcare providers."
ACRO	60	65		ACRO welcomes the recognition of the benefits of patient involvement in the design of trials. However, ACRO would like to see the guidance to be more explicit on patient and public involvement and the need for involvement to be as early as possible. This is because, in the absence of harmonized guidance on when to consider patient and public involvement, it is likely that there will be a heterogeneity of requirements. This will potentially bring operational challenges due to different requirements. However, more critically, it may be that the patient and public voice is excluded from certain jurisdictions, due to regulators in other jurisdictions being more explicit in their requirements. Examples include creating committees made of patients (and/or their caregivers) who have experience with a given disease and with clinical trials to review protocols and provide comments on how to lessen the subject burden.	ACRO recommends adding guidance to involve patients and public as early as possible and prior to finalization of the protocol where possible, whilst acknowledging that involvement can also occur later on.
Association for Clinical Data Management (ACDM)	60	65	Principles of ICH GCP	This position aligns with the FDA draft guidance on DHT (line 101-103 "remote data acquisition may also address challenges associated with centralized trials, such as the burden of traveling to the trial site . . ."	No Action
FVR-Finnish Vaccine Research	60	60		include pragmatic trial as one option	The use of innovative clinical trial designs and technologies may help include diverse patient populations, as appropriate, and enable wider participation, e.g. in pragmatic trials.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Good Clinical Trials Collaborative, on behalf of supporting organisations	60	62	II. Principles of ICH GCP	Address awkward syntax: "The design of the trial, to ensure appropriate quality and meaningful trial outcomes, may be supported by the perspectives of stakeholders; for example, patients and/or healthcare providers."	Suggested text: "To ensure appropriate quality and meaningful trial outcomes, the design of the trial may be supported by the perspectives of stakeholders; for example, patients and/or healthcare providers and professionals."
Ludger Wienbrede	62	65		"Their input can increase the likelihood of meaningful trial outcomes, which are relevant to both trial participants and future patients. This input will also guide decisions on the feasibility of data collection and assure that participation in the trial does not become unduly burdensome for those involved." - Consider to replace "can" and "will" by "may", since nobody knows if it always does.	
Fergus Sweeney	65	65	II	Suggest reword "unduly" to "unecessarily".. Trials may be burdensome, especially compared to normal care and this can be essential to their objectives and to patient benefit.	suggest " become unecessarily burdensome…"
Fergus Sweeney	65	66	II	wording on perspectives of investigators and trial staff should also be included, their experience of conducting trials is essential to a good, proportionate and operationally feasible design.	add a new sentence as of line 65: "The perspectives of potential investigators and trial staff should be sought and are important to ensuring the design of good, proportionate and operationally feasible protocols and processes."
Unicancer	66		II Principes of ICH GCP	66 "Clinical trials should be designed to protect the rights, safety and well-being of participants and 67 assure the reliability of results" Also taking into account the best study design for optimal efficacy of the drug tested.	Clinical trials should be designed to protect the rights, safety and well-being of participants and assure the reliability of results. Clinical trials should be designed for an optimal efficacy of IMP.
Fergus Sweeney	68	68	II	Risk analysis can be very detailed and lead to many minor risks that can be accepted, even when those risks are related to critical factors. The suggested wording is to reinforce a proportionate, risk based approach.	suggest to add "..significant …" to read "..and the significant risks that threaten…"
Association for Clinical Data Management (ACDM)	70	73	Principles of ICH GCP	This is an important concept, I often see sponsors designing unnecessary complexity into trials because they want to adopt processes, even if those processes do not add value	No Action
EFPIA Consolidated Comments	72	73	II	It is recommended that this be expanded to data collection tools.	Trial designs and processes should be operationally feasible and avoid unnecessary complexities.
Ludger Wienbrede	75	76		Consider to delete "These principles are applicable to trials involving human participants." as it is redundant. Line 3 already states that this guideline applies to trials that involve human participants.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA Consolidated Comments	78	264	II	The sub-section numbering of section II overlaps with the sub-section numbering in section III. Section III contains quite some cross-referencing of sub-sections	Please consider numbering the principles differently to avoid confusion (for example P1., P1.1, P1.2, etc., just like in the Appendices A1., B1., and so on)
Good Clinical Trials Collaborative, on behalf of supporting organisations	78	265	II. Principles of ICH GCP	The principles themselves (lines 78-265) are generally good, although would be improved by some presentational changes and modifications.	Detailed suggestions follow.
Good Clinical Trials Collaborative, on behalf of supporting organisations	78	264	II. Principles of ICH GCP	Regroup the Principles: The order of the 11 Principles appears haphazard, making them difficult to learn, follow or implement. The use of some simple subtitles and re-ordering along the following lines would make a substantial improvement to their comprehension	Suggested grouping and order: Ethical Clinical Trials - Principle 1 – Rights and Well-being - Principle 2 – Informed, Voluntary Consent - Principle 3 – IRB/IEC Informative and Relevant Clinical Trials - Principle 4 – Scientifically Sound - Principle 9 – Generate Reliable Results Context Appropriate Clinical Trials - Principle 7 – Risk Proportionate Well designed and conducted, by qualified people - Principle 6 – Quality - Principle 8 – Protocol - Principle 5 – Qualifications - Principle 10 – Roles and Responsibilities Good Manufacturing Practice (GMP) standards - Principle 11 - GMP
Good Clinical Trials Collaborative, on behalf of supporting organisations	78	264	II. Principles of ICH GCP	Involving perspectives of patients and healthcare professionals/providers: Although the introductory text (lines 61-62) mentions the benefits of involving these perspective, there is no mention of such involvement in the principles themselves (Principles 1-11).	The following text could be added as point 6.4 under Principle 6 (lines 162-176): *"Perspectives of members of the community (e.g. patient group, geographical location or demographic characteristics) from which trial participants are to be drawn and those of healthcare organisations and professionals who care for them should be sought as appropriate to inform trial design and conduct."*
Good Clinical Trials Collaborative, on behalf of supporting organisations	79	79	II. Principles of ICH GCP	Refer to Principles of GCP throughout: There are many places (particularly in Annex 1) that refer to compliance with "GCP". These should all be changed to compliance with "the Principles of GCP" to ensure that the correct emphasis and encourage thoughtful implementation. (Examples are on lines 79, 175, 589, 1018, 2126, 2246, 2571, 2669, and 2696 – there may be other instances too.)	Change "consistent with GCP" to "consistent with the Principles of GCP" for consistency with objectives of the guideline.
Ollie Östlund	79	80	II.1.	E6 seems to *define* "GCP". It seems strangely recursive for it to state that trials should follow "GCP and regulatory requirements".	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA Consolidated Comments	85	87	II.1.2	While focused on safety, there are other considerations that should be reviewed for impact on participants (e.g. efficacy, operational considerations, etc). It is recommended that reference to "safety" be deleted at the end of line 85.	The safety of the participants should be reviewed periodically as new safety information becomes available, which could have an impact on the participant or the conduct of the trial.
Ludger Wienbrede	85	87		Consider the use of the relative pronoun: The safety of the participants should be reviewed periodically as new safety information becomes available, which could have an impact on the participant or the conduct of the trial. Means: ... as any type of safety infomation becomes available, whether it could have an impact or not. Whereas (preferred wording): The safety of the participants should be reviewed periodically as new safety information becomes available that could have an impact on the participant or the conduct of the trial. Means: ... safety infomation becomes available that could actually have an impact.	
Quotient Sciences	85	87	1.2	'Periodic' review is not suitable for short-term phase 1 trials. Data need to be reviewed on an ongoing basis, and at appropriate milestones (e.g., at dose escalation meetings).	Please edit as follows: 1.2 The safety of the participants should be reviewed periodically on an ongoing basis as new safety information becomes available, which could have an impact on the participant or the conduct of the trial.
Fergus Sweeney	86	86	II.1.2	reword	"…could have an impact on participant safety or…"
Good Clinical Trials Collaborative, on behalf of supporting organisations	90	91	Principle 1 (1.3)	The current statement that a "trial should be initiated and continued only if the anticipated benefits justify the known and anticipated risks" would seem to rule out many trials in Healthy Volunteers (who will gain little or no benefit) or infectious disease Challenge Trials (where participants are differently given an infection prior to be given an investigational treatment or comparator).	
Mithra Pharmaceuticlas SA PV	90	91	1.3	consider also newly identified risks detected during the trial (so not anticipated or known at the start of the trial)	known, anticipated or newly identified risks
ACRO	92	98	1.4	ACRO would welcome further emphasis in the draft of the importance of considering a diversity of study sites in order to ensure accessibility and availability of the trial to patients from diverse communities.	To add: "Consideration should be given to ensuring diversity of location and type of study sites in order to support representation of the anticipated study population."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA Consolidated Comments	92	98	Principle 1.4	We need to be more clear on why we need to have the different participant populations and the circumstances when this is not needed without always generalising across the broader population.	When designing a clinical trial, the scientific goal and purpose should be carefully considered so as not to unnecessarily exclude particular participant populations. The participant selection process should be representative of the anticipated population who is likely to use the medicinal product in future clinical practice to allow for generalising the results across the broader population, unless there is a good medical or scientific justification for doing otherwise (e.g., early phase, proof of concept trials, bioequivalence studies). Certain trials (e.g., early phase, proof of concept trials, bioequivalence studies) may not require a heterogeneous population.
Ludger Wienbrede	92	94		"When designing a clinical trial, the scientific goal and purpose should be carefully considered so as not to unnecessarily exclude particular participant populations." - Why are the scientific goal or the purpose relevant for exclusion of particular populations? What might actually be relevant for exclusion are the enrolment critera, the type and location of study sites, some trial procedures, schedule and duration of visits, endorsements, recruitment methods, etc.	
Ollie Östlund	92	98	II.1.4	ICH methodologists have probably done some salvage to this already, since the first sentence is good and "certain trials" are excluded. However, generalisation of trial results are *never* based on representability even in phase 3, although this is a very persistent misunderstanding. Generalisation is a complicated methodological problem, and principles belong in a speciality guideline like E10 or E9, not here. With the terminology of Schwartz and Lellouch [DOI: 10.1016/0021-9681(67)90041-0], generalisation by representative patient selection is used in "pragmatic" trials estimating programmatic effectiveness. With few exceptions, and in accordance with legal requirements, drug trials aim to estimate biologic efficacy, that is, they are "explanatory". This is reflected in things like attempting to optimise treatment adherence, which would not be done in a pragmatic trial: Here it is clear that the aim is not to be representative of clinical practice, where adherence is mostly unmonitored. For a thorough discussion of the role of representability in clinical trials, se Stephen Senn's textbook "Statistical issues in drug development". For a published regulatory perspective of value, see Gedeborg, "Pragmatic clinical trials in the context of regulation of medicines" DOI: 10.1080/03009734.2018.1515280.	"Careful consideration should be given to how the trial results will be generalised. In general, generalisation of trial results will not be based on recruiting a representative population, and trials will usually not have sufficient power to show heterogeneity of treatment effects."
Quotient Sciences	92	98	1.4	As noted above, the draft guidance acknowledges that certain trials, e.g., early phase trials, may not require a heterogeneous population, but it needs to go further and acknowledge that it is appropriate to exclude groups of people from phase 1 healthy volunteer trials for reasons of safety and science.	Please edit as follows: 1.4 When designing a clinical trial, the scientific goal and purpose should be carefully considered so as not to unnecessarily exclude particular participant populations. TWherever possible, the participant selection process should be representative of the anticipated population who is likely to use the medicinal product in future clinical practice to allow for generalising the results across the broader population. Certain trials (e.g., early phase, proof of concept trials, bioequivalence studies) may not require a heterogeneous population. Indeed, early phase trials in healthy volunteers, which carry no medical benefit, usually require restricted populations, for reasons of safety and science.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Ludger Wienbrede	94	97		"The participant selection process should be representative of the anticipated population who is likely to use the medicinal product in future clinical practice to allow for generalising the results across the broader population." - Consider to delete "to allow for generalising the results across the broader population" because the anticipated population might actually be narrower than the broader population.	
EUCROF	95	95	II. 1.4	"… who is likely to use the medicinal product in future …" Medicinal product should be replaced with investigational product	… who is likely to use the investigational product in future …
Fergus Sweeney	95	95	II.1.4	reword	"…anticipated population which…"
SHIONOGI	95	95	1.4	…who is likely to use the medicinal product in future….. Medicinal product may be confusing and not interpreted as including, vaccines, biological products, medicines and drugs.	Suggest to ensure consistency of use of terms throughout the guideline or have a footnote added to explain what medicinal products are
EUCROF	98	98	II. 1.4	"Certain trials (e.g., early phase, proof of concept trials, bioequivalence studies) may not require a heterogeneous population." To be more precise, include "allow for"	Certain trials (e.g., early phase, proof of concept trials, bioequivalence studies) may not require or allow for a heterogeneous population.
Fergus Sweeney	98	98	II.1.4	reword	"…may not require such a heterogeneous…"
Ludger Wienbrede	98			"Certain trials (e.g., early phase, proof of concept trials, bioequivalence studies) may not require a heterogeneous population." - However, would a bioequivalence studies not be the best way to compare a medicinal product between heterogenous participants? Therefore, it cannot be claimed that bioequivalence studies do in any case do not require a heterogeneous population.	
Ipsen	99	105	II. PRINCIPLES OF ICH GCP	Suggest rewording the last clause of the sentence "however, the practical interactions and the delivery of medical care and decisions can be carried out by appropriately qualified healthcare professionals in accordance with applicable regulatory requirements." It is not clear what is meant by practical interactions and is the medical care and decisions also trial related in which cause the PI is responsible for the care and decision? If this added clauses is meant to cover decentalised trials, the wording should be made clearer.	
Jazz Pharmaceuticals	99	105	II.1.5	What is the definition of the term "qualified"? Who will be the arbiter of that definition? Will this be a term on which sponsors will need to provide justified interpretation? Could additional or clearer guidance be provided in the Guideline?	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	99	102	I 1.5	Link between investigator and clinical trial is missing. Such a link can be found for example in section 2.7.1 "qualified physician, a qualified dentist…. who is an investigator or a sub-investigator for the trial".	Suggestion: "A qualified physician or, when appropriate, a qualified dentist (or other qualified healthcare professionals in accordance with local regulatory requirements) who is an investigator or a sub-investigator for the trial should have the overall responsibility..."
Quotient Sciences	99	105	1.5	The draft guidance says that practical interactions and the delivery of medical care and decisions can be carried out by appropriately qualified healthcare professionals. What are 'appropriately qualified healthcare professionals'? In a phase 1 setting, practical interactions and medical procedures are carried out not only by physicians and nurses but also by clinical trials technicians/associates - typically life science graduates who have been trained in clinical procedures. Technicians/Associates are not registered healthcare professionals, but are appropriately qualified and experienced to do clinical procedures, such as monitoring blood pressure and recording ECGs. Please clarify that phase 1 clinical trial staff such as Technicians/Associates who are not registered healthcare professionals may carry out practical interactions and delivery of medical care.	Please add text in bold: 1.5 A qualified physician or, when appropriate, a qualified dentist (or other qualified healthcare professionals in accordance with local regulatory requirements) should have the overall responsibility for the trial-related medical care given to, and medical decisions made on behalf of, participants; however, the practical interactions and the delivery of medical care and decisions can be carried out by appropriately qualified healthcare professionals or other appropriately trained staff (e.g., clinical technicians) in accordance with applicable regulatory requirements.
Ludger Wienbrede	103			"… however, the practical interactions and the delivery of medical care and decisions can be carried out by appropriately qualified healthcare professionals in accordance with applicable regulatory requirements" should be reworded to "… however, the practical conduct ..."	
Association for Clinical Data Management (ACDM)	106	108	Principles of ICH GCP	Like this as again supports driving consistency	No Action
Fergus Sweeney	106	106	II.1.6	overinterpretation of data privacy requirements and imprecise wording on these are having a stifling effect on research and legitimate data use. It is mportant that data reported in clinical trials is ultimately traceable. This requires use of indirect identifiers such as codes. It is data that can directly identify the participant that need great care. Participants have a right to expect their direct identity is protected, adn their data are not misused but they also have a real right to expect that their data can be used and is used to improve public health and life for people with their condition. They altruistically participate in trials with a clear expectation that their data will be well used for future good.	reword to "…that could directly identify participants…"
EFPIA Consolidated Comments	115	118	Principle 2.1	1. We recommend additional language regarding assent to be provided by minors. Refer to lines 330 - 332 (section 1.1.7) 2. It would be helpful to include information about updates of ICFs during the trial. Consider reconsenting for individual risk-benefit participation in a clinical trial (e.g. a participant included with deviations but received medication already).	1. In the event a minor is a participant, assent should be collected from the individual, as appropriate. 2. Freely given informed consent should be obtained and documented from every participant prior to clinical trial participation and re-consenting during the clinical trial, when applicable.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Fergus Sweeney	117	117	II.2.1	The principes will be very directly applied. It is essential that they are inclusive of different populations. It is important to direclty inlucde minors and adults incapable of providing consent. They are a hugely important part of the population and need trial results more that many others, so it is essential to directly include them.	reword to "…provide consent including minors and adults incapable of providing consent,…"
Ollie Östlund	117	119	II.2.1	This seems to make enrolling unconscious patients in emergency situations impossible, and so goes against point 2.3. Importantly, what constitutes a legally acceptable representative varies by country, and local ethics requirements for emergency trials may not rely on them. Further clarification on what extra requirements, if any, E6 puts on top of local legal research ethics requirements should be given. There are already two parallel systems in the EU for consent in trials on the, often unimportant, basis of them involving drugs or not, and it should not be complicated further unless motivated.	
DGPharMed e. V. (Deutsche Gesellschaft für Pharmazeutische Medizin)	123	123	II.2.2	Elaborate that "understandable" has to be considered for each patient population.	Elaborate that "understandable" has to be considered for each patient population.
Association for Clinical Data Management (ACDM)	125	130	Principles of ICH GCP (2.3)	For future reference the FDA guidance on DHT includes additional recommendations for clinical and privacy risks to be documented in consent (Section F part 3). Appreciate the support for eConsent	No Action
CARVALHO Carla	125	130	2.3	Access to the medical dossier of participating subjects by the sponsor for verification of the data collected in the case report form in regards to the source data should be authorized by the subjects. This should be clearly reflected in the statement in order to avoid to collect by the sponsor pseudo-anonimized copy of the medical dossier of the participating subjects for additionnal monitoring or sponsor's decision. If a pseudo-anonmized copy of the medical dossier (partly) is taken, this should be clearly reflectly in the informed documents and authorized by the participating subjects.	The informed consent process should take into consideration relevant aspects of the trial, such as the characteristics of the participants, the trial design, the anticipated benefit and risk of medical intervention(s), the setting and context in which the trial will be conducted (e.g., trials in emergency situations), and the potential use of technology to inform participants (or their legally acceptable representatives), the process to maintain the confidentiality of the subject's data by the sponsor during the data collection, the possibility to copy any part of the medical dossier and obtain informed consent.
PPD	125	130	II. PRINCIPLES OF ICH GCP	In response to the use of "risk of medical interventions", R3 should incorporate the idea of "burdens" here as referenced in 2.8.1 (b) - lines 597-602. Consideration should be given by the sponsor to understanding the "real world" burdens which each protocol brings to participants prior to forming the consent language. Also focus on line 178 in 7.0 to add word burden here as well	The informed consent process should take into consideration relevant aspects of the trial, such as the characteristics of the participants, the trial design, the anticipated benefit and risk of medical intervention(s), the setting and context in which the trial will be conducted (e.g., trials in emergency situations, potential burdens), and the potential use of technology to inform participants (or their legally acceptable representatives) and obtain informed consent.
Fergus Sweeney	127	127	II.2.4	reword	"…anticipated risks and benefits…". Plural

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Fergus Sweeney	131	131	II.2.4	Clinical trials conducted in situations of emergency for the individual patient are crtical to emergency care. They have been restricted in the past as they were not openly enabled. This is essential in the principles and not only in the Annex I. A new section II.2.4 is needed to avoid that such trials are inhibited by the application of the principles.	Add new section II.2.4 "In exceptional cricunstances, where a trial is investigating urgent treatment of a patient unable to consent due to their condition (e.g. major trauma) and where time does not enable a legally acceptable representative to be identified or become available, the trial and treatment may proceed, in accordance with a protocol approved by the IRB/IEC and regulatory authority. The consent of the patient or their legally acceptable representative should be sought as soon as possible."
Ludger Wienbrede	132	138		In many countries, clinical trials require authorisation by a competent authority. This should be reflected here. Unlike the Declaration of Helsinki, ICH E6 is not only directed to medical doctors but also to sponsors and persons out of the medical profession. Moreover, for some issues of review, e.g. the quality of the investigational medicinal product, ethics comittees might be not sufficiently qualified. Some ethics committees would not conduct a review of the quality of the medicinal product, even if there no authority that does that. Finally, the review of the issues that have traditionally been reviewed by ethics committees in the past 50 years, might also be reviewed by other institutions, e.g. authorities. Half a century ago there were good reasons to introduce the approval by an ethics committee. Nowadays, such a review might not be sufficient or appropriate any more. If ICH GCP regards the ethics committee process as part of the "conduct of clinical trial" as the definition of lines 2 and 3 state, the authority procedures should also be part of ICH GCP.	
AFI	137	138	3.2	Periodic review of the trial by the IRB/IEC should also be conducted in accordance with applicable regulatory requirements	Concerns regarding this periodic review. Not clear how the IRB/IEC should conduct this review and the action to be taken, especially in the light of the EUCTR 536/2014 regulation.
German Pharmaceutical Industry Association (BPI)	137	138	3.2.		Which is the basic of the „periodic review" by the EC? E.g. the annual safety report, SUSAR-reports and/or reports of serious breaches. So far we do not send extra reports to the EC.
Kotagiri Srinivasa Rao	137	138	3.2	Periodic review of the trial by the IRB/IEC should also be conducted in accordance with applicable regulatory requirements.	It is better to provide the timeline eg. Yearly once
Medicines for Europe	137	138	section 3.2	Not applicable for short term phase I studies	For long-term studies periodic review of the trial by the IRB/IEC should also be conducted in accordance with applicable regulatory requirements
Quotient Sciences	137	138	3.2	The guidance refers to periodic review of the trial by the REC in line with applicable regulatory requirements. In some jurisdictions, periodic review is covered by guidance, not law. For example, future arrangements for REC periodic review in the UK are likely to be covered in guidance.	Please add text in bold: Periodic review of the trial by the IRB/IEC should also be conducted in accordance with applicable regulatory requirements or local guidance.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Good Clinical Trials Collaborative, on behalf of supporting organisations	141	141	Principle 4	Delete “robust and” from “robust and current scientific knowledge and approaches”. The evidence available is not always robust – for example at the beginning of the COVID-19 pandemic, very little was known about the detailed pathophysiology, the role of particular pharmacological pathways, etc. It was precisely because of these uncertainties that randomised trials were needed to distinguish between treatments that people thought might work (often based on weak data) and those that actually do so (based on the results of trials). Where such trials were not done, patients were exposed to the harms of widespread use of unproven and potentially hazardous treatments, damaging individual and public health.	Delete “robust and” from “robust and current scientific knowledge and approaches”.
Ludger Wienbrede	145	149		The "the current understanding of the underlying biological mechanism" should be linked with an "and should reflect" not with a ";" otherwise the linkage is not clear. In addition, clinical trials should be allowed even if the underlying biological mechanism is unknown as long as the trials are safe. Trials like that of James Lind and the Medical Research Council trial on Streptomycin are still useful and should still be allowed.	
SHIONOGI	148	148	4.3	The term 'treatment' in the sentence 'the underlying biological mechanism (of both the condition and the treatment)' is limited and may not include vaccines that are developed to prevent the occurrence of a certain condition or disease.	Suggest to replace treatment with 'treatment or vaccine'
ACRO	150	152	4.3	ACRO notes the inclusion of a requirements for a periodic review of current scientific knowledge and approaches to determining whether modifications to the trial are needed. In order to adopt a proportionate approach to conducting and documenting the periodic review, ACRO would welcome additional clarification on this.	Addition of "appropriate": "There should be appropriate periodic review of current scientific knowledge and approaches to determine whether modifications to the trial are needed, since new or unanticipated information may arise once the trial has begun"
GQMA	154	154	II.5	Auditors and monitors do not 'conduct' a clinical trial, but do review trial documentation and processes. The wording "Clinical trials should be designed and conducted by qualified individuals." might be misleading here.	Change to: "Clinical trials should be designed and handled by qualified individuals."
Ludger Wienbrede	154			Change "Clinical trials should be designed and conducted by qualified individuals" to "Clinical trials should be designed, approved and conducted by qualified individuals". Qualification of personnel of ethics commmittees and competent authorities is also important.	
Quotient Sciences	154	160	5.1	Please include nurses in the list, as they play a key role in clinical trials.	5.1 Individuals with different expertise and training may be needed across all phases of a clinical trial, such as physicians, scientists, nurses, ethicists, technology experts, trial coordinators, monitors, auditors and statisticians. Individuals involved in a trial should be qualified by education, training and experience to perform their respective task(s).

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Association for Clinical Data Management (ACDM)	156	160	Principles of ICH GCP (5.1))	This is a particular issue with the increased use of third party vendors, many of the tech vendors do not understand the need for evaluating and documenting qualifications of their staff.	Could you add any vendors including technology vendors to this
CARVALHO Carla	156	160	5.1	Even if the list of roles identified is not exhaustive, since data managers are deeply involved in the set-up of the electronic case report form/clinical database as well as preparation of the data for analysis, it's recommended to identify such role.	Individuals with different expertise and training may be needed across all phases of a clinical trial, such as physicians, scientists, ethicists, technology experts, trial coordinators, monitors, auditors, data managers and statisticians. Individuals involved in a trial should be qualified by education, training and experience to perform their respective task(s).
EFPIA Consolidated Comments	156	160	Principle 5.1	Should Data Managers be included? Need to have consistency check on the roles	Individuals with different expertise and training...monitors, auditors, data managers/scientists and statisticians
European Association of Hospital Pharmacists (EAHP)	156	158	II 5.1	Hospital pharmacists should be added among the experts listed in section II 5.1.	Individuals with different expertise and training may be needed across all phases of a clinical trial, such as physicians, hospital pharmacists, scientists, ethicists, technology experts, trial coordinators, monitors, auditors and statisticians.
GQMA	158	160	II.5.1	Analogous to section III.2.1.1, any personnel involved in clinical trials should prove the qualification.	Change to: "Individuals involved in a trial should be qualified by education, training and experience to perform their respective task(s) and should provide evidence of such qualification." Would be applicable to section III.3.11.2.1b as well.
Good Clinical Trials Collaborative, on behalf of supporting organisations	159	159	Principle 5 (5.1)	Change from “qualified by education, training and experience” to “qualified by education, training and/or experience” to recognise that appropriate individuals may satisfy requirements for their trial-specific role with one or a combination of these.	Change text as proposed.
Ludger Wienbrede	165			The sentence "Quality of a clinical trial is considered in this guideline as fit for purpose." is incomprehenisble or at least meaningless. This is to be rephrased to reflect the author's intention or to be deleted. Verbiage that does not contribute to a sound understanding of principles or which fails to provide clear guidance should be omitted.	
Mandy Jackson National Clinical Trials Office Quality Working Group Ireland	165	165		Quality of a clinical trial is considered in this guideline as fit for purpose	Could statement be clarified
Fergus Sweeney	166	166	II.6.1	"..amount of information.." is not a good determinant of quality, the use in a principle could drive excess data collection. suggest "scope of information.."	Reword to "The quality and scope of information…" or "The quality of information generated…"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Fergus Sweeney	171	172	II.6.2	It is very important to avoid absolute terms such as "all" and "maximise", they are the opposite of a proportionate approach and will drive a race to the bottom of irrelevant and unfeasible detail. These words should be deleted and the sentence rephrased	reword to "Quality by design involves fosussing on the design of (key) components of the trial in order to support the likeliehood of trial success (i.e. that the trial will answer the research question)."
Good Clinical Trials Collaborative, on behalf of supporting organisations	173	173	Principle 6 (6.2)	After "to maximise the likelihood of trial success (i.e. that the trial will answer the research question" add "and that the rights, safety and wellbeing of participants are maintained". This better reflects the definition of trial success.	Change text as proposed.
Alasdair Breckenridge[†], Jeffrey K. Aronson, Terrence F. Blaschke, Dan Hartman, Carl C. Peck, Bernard Vrijens	174	176	6.3	We welcome this review and propose two additions. In an article published in 2017 in Nature Reviews Drug Discovery, the authors delineated the adverse implications of poor medication adherence in clinical trials. They proposed that regulators should tackle the problem by requiring that all applications for marketing authorization of medicinal products should include an informed response to the question "What reliable method was used to measure patient adherence in this trial?" and that trialists should be required to include objective methods of measuring patient adherence in their trial designs. Ref: Breckenridge A, Aronson JK, Blaschke TF, Hartman D, Peck CC, Vrijens B. Poor medication adherence in clinical trials: consequences and solutions. Nat Rev Drug Discov. 2017 Mar;16(3):149-150. doi: 10.1038/nrd.2017.1. Epub 2017 Feb 3. PMID: 28154411. We therefore propose adding a requirement to reflect this, after the text at section 6.3 (see next column).	Modification of section 6.3: Strategies should be implemented to avoid, detect and address serious non-compliance with GCP, the trial protocol and applicable regulatory reqirements to prevent recurrence. Specifically, trialists shoud be asked to include in their design a reliable method that they will use to measure patient adherence in the trial.
Association for Clinical Data Management (ACDM)	174	176	Principles of ICH GCP (6.3)		Please reference ICH Q9

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
WestRock Corporation	174	176	6.3	In an article published in 2017 in Nature Reviews Drug Discovery, the authors delineated the adverse implications of poor medication adherence in clinical trials. They proposed that regulators should tackle the problem by requiring that all applications for marketing authorization of medicinal products should require an informed response to the question "What reliable method was used to measure patient adherence in this trial?" and that trialists should be required to include objective methods of measuring patient adherence in their trial designs. *Breckenridge A, Aronson JK, Blaschke TF, Hartman D, Peck CC, Vrijens B. Poor medication adherence in clinical trials: consequences and solutions. Nat Rev Drug Discov. 2017 Mar;16(3):149-150. doi: 10.1038/nrd.2017.1. Epub 2017 Feb 3. PMID: 28154411.* Indeed, medication adherence in clinical trials has been a recognized global regulatory priority for many years. In its Guidance documents, the U.S. Food and Drug Administration has repeatedly encouraged the use of digital health technology, such as "Smart Packaging", as an innovation to both encourage medication adherence ("[sic] so that nonadherent patients can be encouraged to perform better") and to inform product development. *FDA-2012-D-1145, Guidance Document: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products, Guidance for Industry, (March 2019) No. FDA-2021-D-1128, Draft Guidance Document: Digital Health Technologies for Remote Data Acquisition in Clinical Investigations, Guidance for Industry, (December 22, 2021).*	We propose to add a qualifier to indicate that strategies deployed should be "validated subject-centered strategies" with a reference to one such validated strategy, and to add improvement of "patient medication adherence" as a key goal. We also propose to add a question of "What reliable method was used to measure patient adherence in this trial?"after the text at section 6.3. "Modification of section 6.3: Validated subject-centered strategies such as smart packaging should be implemented to improve patient medication adherence, and avoid, detect, and address serious non-compliance with GCP, the trial protocol and applicable regulatory requirements to prevent recurrence. Specifically, trialists should be asked to include in their design a reliable method to measure patient adherence in the trial."
WestRock Corporation	174	176	6.3	Smart Packaging has been shown to capture robust and highly reliable dosing history data through electronic medication event monitoring, and this type of indirect method for estimating when and how much drug is ingested has been validated in the scientific literature. Vrijens B, Tousset E, Rode R, Bertz R, Mayer S, Urquahart J.; J Clin Pharmacol 2005 Apr;45(4):461-7; Savic RM, Barrail-Tran A, Duval X, Nembot G, Panhard X, Descamps D, et al.; Clin Pharamcol Ther 2012 Oct 3; Rubio A, Cox C, Weintraub M. Prediction of diltiazem plasma concentration curves from limited measurements using compliance data. Clin Pharmacokinet 1992; 22:238-46. Further, from an adherence improvement perspective, the use of Calendared Blister Packaging (specifically Westrock's Adherence Platform) has been validated to improve both medication adherence and associated health outcomes. Zedler BK, Kakad P, Colilla S, Murrelle L, Shah NR. Does packaging with a calendar feature improve adherence to self- administered medication for long-term use? A systematic review Clinical Therapeutics 2011; 33(1): 62-73; Zedler BK, Joyce A, Kakad P, Harpe SE, A Pharmacoepidemiologic Analysis of the Impact of Calendar Packaging on Adherence to Self-Administered Medications for Long-Term Use Clinical Therapeutics 2011:33(5): 581–597; Dupclay L, Eaddy M, Jackson J, Raju A, Shim A. Real-world impact of reminder packaging on antihypertensive treatment adherence and persistence. Patient preference and adherence. 2012; 6:499-507. doi:10.2147/PPA.S31417; Bosworth H, Brown J, Danus S, Sanders L, McCant F, Zullig L, Olsen M. Evaluation of a Packaging Approach to Improve Cholesterol Medication Adherence Am J Manag Care. 2017 Sep 1;23(9):e280-e286.	We propose to add a qualifier to indicate that strategies deployed should be "validated subject-centered strategies" with a reference to one such validated strategy, and to add improvement of "patient medication adherence" as a key goal. We also propose to add a question of "What reliable method was used to measure patient adherence in this trial?"after the text at section 6.3. "Modification of section 6.3: Validated subject-centered strategies such as smart packaging should be implemented to improve patient medication adherence, and avoid, detect, and address serious non-compliance with GCP, the trial protocol and applicable regulatory requirements to prevent recurrence. Specifically, trialists should be asked to include in their design a reliable method to measure patient adherence in the trial."
Good Clinical Trials Collaborative, on behalf of supporting organisations	175	175	Principle 6 (6.3)	Change "compliance with GCP" to "compliance with the Principles of GCP" for consistency with objectives of the guideline.	Change text as proposed.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Good Clinical Trials Collaborative, on behalf of supporting organisations	176	176	Principle 6 (6.3)	Change from “to prevent recurrence” to “to address the consequences (e.g. to participant safety) and prevent recurrence”, which better focuses the principle on the purpose and goals of such strategies.	Change text as proposed.
PPD	178	191	II. PRINCIPLES OF ICH GCP	The need to include burdens should occur	7. Clinical trial processes, measures and approaches should be implemented in a way that is proportionate to the risks and burdens to participants and to the importance of the data collected. 7.1 Trial processes should be proportionate to the risks and burdens inherent in the trial and the importance of the information collected. Risks in this context include risks to the rights, safety and well-being of trial participants as well as risks to the reliability of the trial results. 7.2 The focus should be on the risks and burdens to participants beyond those associated with standard medical care. The risks relating to investigational products that have a marketing authorisation when used in the clinical trial context may differ from the routine care of patients and should be taken into consideration.
Ludger Wienbrede	186	187		The sentence "The focus should be on the risks to participants beyond those associated with standard medical care." should be modified to: "The focus should be on the risks to participants beyond those associated with standard medical care or beyond those associated with deviating from standard medical care." The original wording implies that a clinical trial always only might include risks that go beyond standard medical care but in cases where, e.g. the standard medical care is halted or modified due to trial design reasons, a risk may emerge from such deviation from standard medical care. This needs to be highlighted in order to avoid misconception of this point.	
Quotient Sciences	186	189	7.2	This point specifically relates to patient studies and does not apply as written to health volunteer trials. The wording should be expanded and clarified to include both.	Please edit as follows: The focus should be on the risks to participants. In patient trials, this focus should be on risks beyond those associated standard medical care. The risks relating to investigational products that have a marketing authorisation when used in the clinical trial context may differ from the routine care of patients and should be taken into consideration.
EFPIA Consolidated Comments	190	191	Principle 7.3	Reference to E8 and Critical to quality factors would be appropriate here to help guide the use of them in practice.	Risks to the critical to quality factors should be managed prospectively and adjusted when new or unanticipated issues arise once the trial has begun. See ICH E8 general considerations for clinical studies.
EUCROF	190	190	II. 7.3	"Risks to critical to quality factors should be managed prospectively…" is diffucult to read	Critical to quality factors should be quoted for better readability: Risks to 'critical to quality factors' …

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
FVR-Finnish Vaccine Research	190	191	7.3	Is there a grammatical error in the sentence? Beginning of the sentence difficult to understand for a non-native English speaker.	Risks critical to quality factors should me managed prospectively and adjusted when new or unanticipated issues arise once the trial has begun
Ludger Wienbrede	190			This makes no sense: "Risks to critical to quality factors should be managed prospectively …" This should be deleted or replaced by a meaningful statement.]	
Medicines for Europe	190	190	7.3	to' needs to be deleted	Risk to critical to quality factors
Quotient Sciences	190	190	7.3	The wording could be improved. Please refer to 'risks to factors critical to trial quality' or use italics ('risks to *critical to quality* factors') or hyphenation ('risks to critical-to-quality factors') to improve clarity.	Please edit as follows: Risks to critical to quality factors critical to trial quality should be managed prospectively and adjusted when new or unanticipated issues arise once the trial has begun.
Sunnikan Consulting	190	191	II 7.3	unintelligibility linked to the following : "Risks to critical to quality…"	A "to" to be removed
Swedish Monitors attending NORM meeting 2023	190	190	II Principles of ICH GCP; 7.3	The sentence starting "Risks to critical to quality factors should be managed prospectively..." seems to have too many "to" or some word missing. By removing the first "to" the sentence makes sense. See strikethrough.	"Risks to critical to quality factors should be managed prospectively..."
Fergus Sweeney	191	191	II.7.3	reword	Suggest ""…prospectively and they or their management adjusted…"
Ludger Wienbrede	196	197		"A well-designed trial protocol is fundamental to the protection of participants and for the generation of reliable results." This should be deleted because it is obvious and simplified and therefore misleading. If you have a perfect protocol but the medicinal product is defective or if the investigators are not qualified the perfect protocol is useless. If you leave the statement here you could as well add "review of the protocol by an ethics committee is fundamental to the protection of participants", "<xxx> is fundamental to the protection of participants". Many things are fundamental, why is the protocol presented as being especially fundamental?	
Unicancer	196	196		this paragraph should be moved to section 5. Section 8 is dedicated to description	
Ludger Wienbrede	198	199		"The scientific objectives of any trial should be clear and explicitly stated in the protocol." This should be deleted because it is obvious. If you leave the statement here you could as well add "The inclusion criteria of any trial should be clear and explicitly stated in the protocol", "The sample size of any trial should be clear and explicitly stated in the protocol", etc. It is nonsense to repeat here what is already stated in Annex B, especially if no consequences of this statement or justification for this statement are presented here.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA Consolidated Comments	200	201	8.3	The clinical trial protocol as well as the plans or documents for the protocol execution (e.g., statistical analysis plan, data management plan, monitoring plan) should be clear, concise and operationally feasible. They also need to be consistent.	Suggest including:"...should be clear, concise, consistent and operationally feasible"
EUCROF	200	202	II. 8.3	"8.3 The clinical trial protocol as well as the plans or documents for the protocol execution (e.g., statistical analysis plan, data management plan, monitoring plan) should be clear, concise and operationally feasible." Supplement with more information and change order of plans to match chronology better. Add also some manuals, in order to make clear what could be understood under "documents".	The clinical trial protocol as well as the functional plans or documents for the protocol execution (e.g., monitoring plan, safety plan, data management plan, statistical analysis plan, laboratory manual, investigational product manual) should be clear, concise and operationally feasible.
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	200	202	II 8.3	The upcoming ICH M11 guideline should be added as a reference here.	
Unicancer	202		8.3	Better to have all document available before to start the study	should be clear, concise, operationally feasible and available before the start of the trial.
EFPIA Consolidated Comments	206	208	Principle 9.1	Standard of care also needs to be considered as it provides for data which might not exactly meet the timelines but is acceptable without creating unreliable results. So this would allow for the consideration of different types of data sources. Propose to ensure this is covered in annex 2 and training. This has been classified as minor but could be major if it is misinterpreted.	The quality, type and amount of the information generated in a clinical trial should be sufficient to provide confidence in the trial's results and support good decision making.
Fergus Sweeney	206	206	II.9.1	as also in II.6.2 "..amount of information.." is not a good determinant of quality, the use in a principle could drive excess data collection. suggest "scope of information.."	Suggest Reword to "The quality and scope of information…" or "The quality of information generated…"
Good Clinical Trials Collaborative, on behalf of supporting organisations	206	208	Principle 9 (9.1)	This text repeats (near verbatim) the second sentence of Principle 6 (6.1).	One or the other could be deleted.
GQMA	207	207	II.9.1.	Providing 'confidence' in trial results might not be enough by applying quality and amount of the information generated in a clinical trial.	Change to: "The quality and amount of the information generated in a clinical trial should be sufficient to provide confidence and ensure reliability in the trial's results and support good decision making."
Good Clinical Trials Collaborative, on behalf of supporting organisations	209	213	Principle 9 (9.2)	With Principle 9 (9.4): these points are repetitive and one or other could be deleted with no loss of meaning.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Ludger Wienbrede	209	213		"Systems and processes that aid in data capture, management and analyses, as well as those that help ensure the quality of the information generated from the trial, should be fit for purpose, should capture the data required by the protocol and should be implemented in a way that is proportionate to the risks to participants and the importance of acquired data." This has to be re-worded as is sticks together elements that do not match. E.g. "Systems and processes that aid ... management and analyses ... should capture the data required by the protocol ...": Well, systems that aid management and analyses do not themselves capture data. You might state that systems and processes should be proportionate to the risks to participants and the importance of acquired data, but if you state "Systems and processes ... should be implemented in a way that is proportionate to the risks ..." then this conveys that the original systems and processes are quite complicated and extensive, but you might implement them in a sloppy way, as long as this does not put participants at risk.	
PPD	209	213	II. PRINCIPLES OF ICH GCP	There is inconsistency in the use of "systems" and "computerised systems". If these terms are not synonymous, they should be included in the glossary. "System" could mean a process.	Define System in Glossary Define Computerized System in Glossary
EUCROF	215	216	II. 9.3	It is not clear what key trial objectives are. Only primary objectives or primary and secondary objectives?	Trial processes should support the trial objectives defined in the protocol.
Association for Clinical Data Management (ACDM)	217	219	Principles of ICH GCP (9.4)	Like the expectation are 'Fit-for-purpose' - realistic approach.	No Action
EFPIA Consolidated Comments	217	219	Principle 9.4	1. Computerised systems are not always at a trial level, so how should these CTQs be identified on a trial basis? 2. validation of the computer system demonstrates the fit for purpose of that system.	Computerised systems (including digital health technologies) used in clinical trials should be fit for purpose (e.g. through risk-based qualification or validation) and factors critical to their quality should be addressed in their design or adaptation for clinical trial purposesto ensure the integrity of critical trial data.
Good Clinical Trials Collaborative, on behalf of supporting organisations	217	219	Principle 9 (9.4)	See above.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Quotient Sciences	217	219	9.4	Section 9.2 states that data/quality systems and processes should be fit for purpose and *implemented in a way that is proportionate to the risks to participants and the importance of acquired data* . We welcome this, as systems used in routine clinical practice may have limitations but still provide reliable data. Even state-of-the-art medical and laboratory equipment and systems may not meet the highest standards with respect to data integrity – e.g. they may not support individual log-ins or may not fully comply with 21 CFR part 11 with respect to electronic signatures, even though they are maintained, serviced and demonstrated to be fit for purpose. Also, systems used in experimental pharmacology to investigate exploratory objectives (e.g. intragastric pH measured via a portable device, flow cytometry, polysomnography, electroencephalography, ambulatory blood pressure/ECG monitoring, and wearable devices to monitor sleep patterns) may employ systems that are not designed specifically for use in clinical trials, but nevertheless produce useful data to support decisions on future drug development. They may not meet the highest standards with respect to security and audit trail but may be implemented with appropriate and proportionate safeguards (eg manual logs, saving data in protected folders) and provide valuable additional information. The guidance doesn't go far enough in clarifying that suitable clinical and laboratory equipment and systems that meet the highest standards with respect to data integrity (e.g., individual log-ins, full compliance with 21 CFR part 11 requirements for electronic signatures, full audit trail) may not exist. A pragmatic approach needs to be taken with respect to use of systems used in routine clinical practice and systems used in experimental pharmacology that do not meet the highest standards of data integrity but are implemented with appropriate risk mitigation and are maintained, serviced and demonstrated to be fit for purpose. We recommend that the phase of the trial and its objectives be key factors in assessment of risk and that early clinical pharmacology studies be acknowledged as employing systems that might not be considered suitable for measuring a primary endpoint in a pivotal trial but that are used in a way that allows appropriate control of data integrity. Clarification should be added to Section 9.4.	Please add text in bold: 9.4 Computerised systems used in clinical trials should be fit for purpose, and factors critical to their quality should be addressed in their design or adaptation for clinical trial purposes. 'Fit for purpose' means that the features of the system are appropriate to the importance of the data and risk to participants, taking into account the phase and objectives of the trial. Thus, a system used to capture exploratory outcome measures in a phase 1 trial may not have all the features necessary for a system that captures primary outcome measures in a phase 3 efficacy trial (e.g. security, full audit trail) but may be implemented with appropriate and proportionate risk mitigation based on a risk assessment of the importance of the data and risks to participants.
Society of Quality Assurance (SQA)	217	217	9.4	It is recommended to clarify the expectations for 'fit for purpose'. In most cases, fit for purpose is demonstrated through risk-based qualification or validation. Providing such clear guidance is likely to remove ambiguity around usage of systems and this should also include tools used in data capture and analysis (e.g. spreadsheets and web portals).	"Computerized systems (including tools) used in clinical trials should be fit for purpose (e.g. through risk-based qualification or validation)....."
EFPIA Consolidated Comments	220	224	Principle 9.5	The word 'efficient' is very subjective, is not verifiable and does not hold meaning in this context.	Clinical trials should incorporate efficient and well-controlled processes for managing records through appropriate management of data integrity, traceability and protection of personal information, thereby allowing the accurate reporting, interpretation and verification of the clinical trial-related information.
Good Clinical Trials Collaborative, on behalf of supporting organisations	223	224	Principle 9 (9.5)	Change "verification of the clinical trial-related information" to "verification of the key clinical trial-related information" to emphasise the need for this to be done in a manner that is proportionate to the criticality of the information and avoid over-interpretation / excessive practice.	Change text as proposed.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
DGPharMed e. V. (Deutsche Gesellschaft für Pharmazeutische Medizin)	225	228	II.9.6	Are certified digital copies of paper records acceptable?	Clarify if certified digital copies of paper records are acceptable
Dr. C. Wilsher	225	228	9.6	Why does it only state "regulatory authorities" here, when other sections of this draft guidance say there should be direct access for monitors, auditors, IEC/IRB and RA? See section B11. This R3 draft principle could be used as an excuse to deny access to others (see section B11) as it is not an explicit principle of the new GCP. Suggest adding language to be consistent with B11.	Clinical trial-related records should be retained securely by sponsors and investigators for the required period of time and should be available to regulatory authorities, monitors, auditors, and IEC/IRB, upon request to enable reconstruction of the trial conduct and results in order to ensure the reliability of trial results
Fergus Sweeney	225	228	II.9.6	it is retaining the records that supports reliability of results,	Suggest ""…retained securely….period of time, in order to support the reliability of trial results…enable reconstruction of the trial conduct and results."
GQMA	225	228	II.9.6	In line with section C.2.2 also service providers are responsible for archiving trial data and documents as per GCP.	Change to: "Clinical trial-related records should be retained securely by sponsors, investigators, and delegated service providers for the required period of time and should be available to regulatory authorities upon request to enable reconstruction of the trial conduct and results in order to ensure the reliability of trial results."
Good Clinical Trials Collaborative, on behalf of supporting organisations	227	228	Principle 9 (9.6)	Change "to enable reconstruction of the trial conduct and results in order to ensure the reliability of trial results" to "to enable evaluation of the key elements of trial conduct and results." The word 'reconstruction' is already over-interpreted by many, is an impossible goal (there are many factors that are never recorded anywhere and which are largely irrelevant), and in any case even if one could 'reconstruct' what happened it does not necessarily follow that doing so will ensure the reliability of trial results. The suggested revision retains the ability to 'evaluate' and assess what happened and focuses attention and effort on the aspects that are most important.	Change "to enable reconstruction of the trial conduct and results in order to ensure the reliability of trial results" to "to enable evaluation of the key elements of trial conduct and results."
EFPIA Consolidated Comments	229	231	Principle 9.7	Needs to be written as a requirement and needs to say investigational product as opposed to drug.	To ensure the transparency of clinical trials in drug investigational product development the includes registration of said trials on publicly accessible and recognised databases and the public posting of clinical trial results should be undertaken in accordance with applicable regulatory requirements.
Ludger Wienbrede	229	231		"The transparency of clinical trials in drug development includes registration on publicly accessible and recognised databases and the public posting of clinical trial results." This statement should be deleted as it appears not to belong to this E6 guideline. First: It is a definition and therefore should rather be moved to the glossary section. Second: The term "transparency" is only used here, nowhere else in the E6 guideline. Therefore it makes no sense to define it (neither here not in the glossary section). Third: The statement does not demand transparency and no other part of the E6 guideline does. Therefore, this statement is useless and out of place in this E6 text.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	229	231	9	Further claification is needed on whether the trial registration on public domain and public posting of clinical trial results would include all types of clinical trials including phase 1 healthy volunteer subjects, PoC studies and other early phase studies as well. Currently, clinicaltrials.gov (public domain) does not mandate trial registration of phase I studies with healthy volunteer subjects. From our perspective, the requirement should not include Phase I studies, since these studies are done during the development phase of a product and this information shall be confidential. So, additional clauses to this principle are needed as all clinical trial results may not be relevant.	The transparency of clinical trials (for Phase II-IV) in drug development includes registration on publicly accessible and recognised databases and the public posting of clinical trial results
Quotient Sciences	229	231	9.7	Transparency requirements need to acknowledge that information about and results of phase 1 trials are highly commercially sensitive, and of negligible benefit to patients, the public and prescribing physicians. Prospective registration of phase 1 healthy volunteer trials with a minimal dataset only has been successfully implemented in the EU and UK to protect commercial confidentiality. The minimal dataset is published before the trial starts and publication of full trial details is deferred. Publication of trial results is even more commercially sensitive and sponsors must be able to control exactly how and when their results are published, so that they can mitigate commercial risk. In many countries (e.g. UK, USA), there is no legal requirement for sponsors of phase 1 trials to publish their results. There is little benefit to patients, the public and prescribing physicians in doing so - the only people likely to benefit are commercial competitors. Thus, sponsors should be encouraged to post their results at the earliest opportunity when the commercial risk has diminished, to ensure that publication requirements do not undermine the commercial development of new medicines. The guidance should clearly distinguish between requirements for patient trials and those for phase 1 healthy volunteer trials. It should be possible to defer publication of full trial details and trial results until a time when the commercial risk has subsided.	Please add text in bold: 9.7 The transparency of clinical trials in drug development includes registration on publicly accessible and recognised databases and the public posting of clinical trial results. For phase 1 healthy volunteer trials, full registration of trial details and posting of results may be postponed until after the commercial sensitivity of the data has diminished, in accordance with applicable regulatory requirements and local guidance.
Good Clinical Trials Collaborative, on behalf of supporting organisations	233	234	Principle 10	The headline principle is a good one – that roles and responsibilities should be clear and documented appropriately. But this should be reworded from "Roles and responsibilities…" to "Key roles and responsibilities…" in order to ensure that this is applied proportionately.	Reword "Roles and responsibilities…" to "Key roles and responsibilities…"
Good Clinical Trials Collaborative, on behalf of supporting organisations	233	245	Principle 10	See comments above. Changes are required to emphasise focus on "key" roles & responsibilities (rather than excessive details) and to ensure that roles and responsibilities for delivering or organising the delivery of particular activities can be pre-agreed and documented by the Sponsor and Investigator in order to best deliver an efficient, high quality trial and facilitate participation. The principles should be clear that the responsibility for oversight of the delivery of that activity then falls to the organisation (Sponsor or Investigator) that is tasked with organising it.	Reword to emphasise: "Responsibility for performance of an activity resides with the organisation arranging the service."
eClinical Forum	236	238	II 10.1	This states the sponsor or investigator can transfer any or all duties or functions (hereafter referred to as activities). But does not state to whom. This is inconsistent with 998-1001.	Either combine with III 3.6.7 or refer to the other clause.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA Consolidated Comments	236	245	10	We recommend that it be clarified that delegated personnel must be qualified/trained.	The sponsor may transfer or the investigator may delegate some or all their tasks, duties or functions (hereafter referred to as activities) to appropriately trained and qualified personnel they retain overall responsibility for their respective activities.
EUCROF	236	241	II. 10.1	It is not clear why the word "Delegation" cannot be used for investigators and sponsors. In principle, the same mechanism is happening: somebody who is responsible delegates a task to somebody else, but remains responsible. It is about task allocation. The fact that the US is using "Transfer of Obligations" for sponsors should not dominate the wording in this international guideline.	
Fergus Sweeney	236	236	II.10.1	reword	"..or the investigator/insitution may delegate.."
Good Clinical Trials Collaborative, on behalf of supporting organisations	236	243	Principle 10 (10.1 and 10.2)	These points should be amended to include the following principle: "Responsibility for performance of an activity resides with the organisation arranging the service." The current wording is not appropriate and would be almost impossible to follow in some instances. For example, in some trials it may make very good sense (on grounds of quality, consistency, convenience to participants, etc) for the Sponsor to organise a third party pharmacy (e.g. to do direct-to-patient drug distribution) or third party laboratory or imaging facility. These are roles that might normally reside with the Investigator (e.g. Annex 1; clause 2.10.1). It is not reasonable or practical to expect the Investigator to be held responsible for the performance of that central pharmacy or other facility (which they didn't select, don't have a contractual relationship with, and may have no other interactions with).	Change text as proposed.
GQMA	236	238	II.10.1	As per section II.10.2 and II.10.3 the sponsor or investigator cannot delegate all their activities, but have to retain the oversight over the trial. The sentence in section II.10.1 is somewhat contradictory and "but they retain overall responsibility for their respective activities" could be misunderstood.	Change to: "The sponsor may transfer or the investigator may delegate most tasks, duties or functions (hereafter referred to as activities), but they retain overall responsibility for the delegated activities."
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	236	238	II 10.1	The changed wording regarding the responsibilities of sponsor and investigator is a bit unclear and perhaps misleading. Compared to R2 it seems there is a transfer of responsibilities to the investigator and the sponsor has no longer any responsibility here. See also III 2.3.1 "ultimate responsibility": The term "ultimate responsibility" suggests that the sponsor is no longer responsible here.	
Society for Clinical Research Sites	236	243	10.1 & 10.2		The wording in lines 238 and 241 should be changed from "responsible" and "responsibility" to "accountable" and "accountability". Common definitions differentiate the meaning of "responsible" (as germane to the obligation to perform the task and/or comply with the rule) and "accountable" (as ownership of the results). In the case of the principle, the delegated individuals would be responsible for completing the tasks and/or complying for the rules, but the delegating authority (be it the sponsor or investigator as applicable) would remain accountable for their delegate's performance.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
The GCP Unit at Odense University Hospital, OPEN	236	238	10.1	Why two different words for sponsor: transfer and investigator: delegate? It must be possible for investigators to transfer tasks (e.g. lab, handeling IMP) to other departmentes or organisations. Delegation documented on a delegation log) is according to DKMA reserved to persons in the investigators own department	Define transfer and delegate in GLOSSARY Use "transfer or delegate" for both sponsor and investigator
Good Clinical Trials Collaborative, on behalf of supporting organisations	237	238	Principle 10 (10.1)	To be read in accordance with context of comment above: Delete “but they retain overall responsibility for their respective activities”.	Change text as proposed.
Association for Clinical Data Management (ACDM)	239	243	Principles of ICH GCP (10.2)	So what exactly does this mean. If Sponsor outsources they retain responsibility and must oversee what they have outsourced. If an investigator outsources at their site the investigator retains responsibility and must oversee. What about Sponsor outsourcing on behalf of the investigator - Sponsor retains responsibility and must oversee. Investigator must oversees what they are responsible for?	The verbiage is not clearly understood. Could the section 'Where activities have been transferred or delegated to service providers, the responsibility for the conduct of the trial, including quality and integrity of the trial data, resides with the sponsor or investigator, respectively'. be written to clearly state what investigator is responsible for and what sponsor is responsible for.
Fergus Sweeney	239	243	II.10.2	reword	..or the investigator/insitution should…"
Medicines for Europe	239	243	10.2	If service providers are arranged by other service providers (for example, CRO arrange a EDC/IWRS or central imaging vendor and use their own agreement) on behalf of sponsor, then the service providers which arrange another service provider (as 3rd party vendor) should maintain appropriate responsibility - oversight and supervision of trial related activiteis performed by the service provider (as 3rd party vendor) unless sponsors involve a evaluation, selection, qualification and agreement of the service providers (3rd party vendor) from the planning stage.	Proposed to add the below languages: When a service provider arrange another service provider (3rd party vendor) and delegate trial related activities to the service provider, then agreement between two providers should clearly document roles, activities and responsibilities in an agreement between two service providers. Also the service provider which transfer trial related activities to other 3rd party should maintain appripriate oversight and supervision of the trial related activities as per agreement.
Quotient Sciences	239	243	10.2	The word 'respectively' does not make sense in this sentence. Does responsibility lie with the transferring/delegating party? If so, please make the suggested change. If not, please clarify	Please add text in bold: Where activities have been transferred or delegated to service providers by the sponsor or investigator, the responsibility for the conduct of the trial, including quality and integrity of the trial data, resides with the sponsor or investigator, respectively.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Society for Clinical Research Sites	239	243	10.2	There is a fundamental issue with the way this section is written that will codify current issues that prevent the decentralization of clinical trials. Specifically, the statement "Where activities have been transferred or delegated to service providers, the responsibility for the conduct of the trial, including quality and integrity of the trial data, resides with the sponsor or investigator, respectively" is not strong enough to address the current disconnect between the contracting entity and the supposed responsible entity. An example of this issue arises when the sponsor contracts a service provider (such as a technology service provider or a health care provider not affiliated with the investigator/site), yet the investigator is deemed responsible for the actions/inactions of these sponsor-connected service providers.	We believe the guidance should be clear that the entity selecting the service provider and doing the contracting should be the responsible entity. If the sponsor chooses and contracts with a service provider to conduct visits outside of a local investigator's site and/or to provide technology required for participant use, the sponsor, not the local site investigator, is taking on the coordination of investigators at different sites participating in a multicenter trial. By definition in the glossary, this would be a "coordinating investigator". Thus, the sponsor as coordinating investigator bears the responsibility of investigator oversight for that service provider's conduct of the trial, including quality and integrity of the trial data. To the corollary, if the investigator/site is the one that selects and works with the service provider, then the investigator bears that obligation. The guidance should be clear in this point so that all parties understand that while they will have to cooperate with each other for study success, it is unambiguously the responsibility of the entity that selects and contracts with the service provider to provide that oversight.
Ipsen	240	243	10.2	Could examples of activities which may be transferred or delegated to service providers by investigator/institution be provided?	
Good Clinical Trials Collaborative, on behalf of supporting organisations	242	243	Principle 10 (10.2)	Delete "resides with the sponsor or investigator, respectively." and replace with "resides with the organisation (sponsor or investigator) which has agreed to be responsible for arranging the service or activity."	Change text as proposed.
Medicines for Europe	243	243	10.2	it might make sense to add institution; probably applicable to other sections	Where activities have been transferred or delegated to service providers, the responsibility for the conduct of the trial, including quality and integrity of the trial data, resides with the sponsor or investigator/institution, respectively.
Fergus Sweeney	244	224437	II.10.3	reword	"..responsibility for the quality of their respective activities."
Ludger Wienbrede	244	245		"The sponsor or investigator should maintain appropriate oversight or supervision of the aforementioned activities, respectively." While section 3.9 describes to some degree what sponsor oversight might be, the E6 guideline is silent about what investigator supervision should be. The E6 guideline should explain what investigator supervision is.	
The GCP Unit at Odense University Hospital, OPEN	244	245	10.3	Two words Oversight ans supervision are used. What is the difference? If none - be consistent. In E6 R2 oversight is related to sponsor and supervision to investigator. This is not the case in R3.	Define oversight and supervision in GLOSSARY. Be consistent

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Good Clinical Trials Collaborative, on behalf of supporting organisations	250	250	Principle 11	Modify “in accordance with the product specifications and the trial protocol” to “in accordance with the product specifications, the trial protocol, and applicable regulatory requirements".	Change text as proposed.
Catalent Pharma Solutions	252	253	II	Please add "and regulatory requirements" to the end of point 11.1 as regional regulatory requirements related to manufacutring of investigrational products should be considered, in additional to GMP standards.	11.1 Investigational products used in a clinical trial should be manufactured in accordance with applicable GMP standards and regulatory requirements
Good Clinical Trials Collaborative, on behalf of supporting organisations	252	264	Principle 11 (11.1 to 11.6)	These points can be deleted. GMP is a separate guideline. The lead principle requires compliance with GCP. There is no need to or benefit from repeating some of the requirements from GMP in this document.	Change text as proposed.
CARVALHO Carla	254	255	11.2	Some pharmacy are using pneumatic system for the distribution of investigational products (e.g., marketed products used as a comparator) inside of the hospital (e.g., bevacizumab as a comparator prepared for infusion at the pharmacy and shipped via the pneumatic system to the patient's infusion area). Even if such product is marketed, such pneumatic system should maintained the integrity of the investigational products and this should be demonstrated.	Measures should be in place to ensure that the investigational product provided to trial participants retains its quality (e.g used of pneumatic system for the distribution of investigational products from the preparation area to the patient's administration area should not alter the quality of the investigational product).
EFPIA Consolidated Comments	254	255	11.2	It is not clear what is meant by measures	Measures should be in place to ensure It should be ensured that the investigational product provided to trial participants retains its quality.
CARVALHO Carla	256	257	11.3	Several products in oncology requires a reconstitution step at the site level. This is not clearly reflected in the statement.	Investigational products should be prepared and used in accordance with the protocol and relevant trial documents.
AFI	261	262	11.5	Investigational product labelling should follow applicable regulatory requirements.	Please, clarify what is meant by "regulatory requirements". The labelling should be done according to the product status (if already approved for MA or not) and not following the regulatory requirements to avoid huge discrepancies.
EFPIA Consolidated Comments	263	264	11.6	Consideration of how the product is handled throughout its lifecycle. Propose to change the following: *Adequate measures to ensure that the investigational product is handled and shipped appropriately should be implemented.*	Adequate measures to ensure Appropriate investigational product is handling, shipping, return, destruction or alternative disposition of the investigational product should be ensured should be implemented.
EUCROF	263	264	II. 11.6	"Adequate measures to ensure that the investigational product is handled and shipped appropriately should be implemented." Storage and disposition should be added, if applicable	Adequate measures to ensure that the investigational product is handled, shipped, stored and disposed, if applicable, appropriately should be implemented.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Beate Kern, Department of Health Brandenburg, Germany	265		II.	Addition of a 12th principle: The processes, measures and approaches of the clinical trial should be implemented in such a way that the environmental impact/pollution is kept as low as possible.	Addition of a 12th principle: The processes, measures and approaches of the clinical trial should be implemented in such a way that the environmental impact/pollution is kept as low as possible.
Fergus Sweeney	266	266	Annex 1	III. Annex 1. This should start on a new page, and have a short introductory paragraph. At present it is not sufficiently separate from the principles, and lacks a context setting paragraph.	new page and paragraph see below for some content of paragraph
Fergus Sweeney	266	266	Annex 1	The wording at right should be added to an introductory paragraph which can also inlcude a wider context relating to the principles and later annexes.	Include in an introductory paragraph to Annex 1: "This Annex 1 is guidance indicating ways in which the principles of GCP can be achieved. Alternative approaches which ensure that the principles are upheld can also be used."
Good Clinical Trials Collaborative, on behalf of supporting organisations	266	266	III. Annex 1	Sections I and II each start on a new page (as do the Glossary and each of the appendices), but Section III (Annex 1) flows straight on from Principle 11.	Start Annex 1 on a new page for consistency, readability and to promote the principles as a distinct and important section.
Ollie Östlund	267	437	III.1	It may not be possible for a sponsor to demand that a particular IEC follows ICH guidelines. I guess you have considered this. The guideline could give some guidance as to how ICH E6 demands are expected to be implemented in local ethics review systems.	
Fergus Sweeney	269	269	1	reword the IRB/IEC rveviews the ethics of a trial. Whilst its review should of course be ethical in its own right, that is not the point of the sentence.	reword as "The IRB/IEC is responsible for the review of the ethics of the trial"
Fergus Sweeney	273	273	1.1.1	there is no need for absolutes "all" does not add any meaning and should be deleted	"…and well-being of participants."
Sandoz AG, Switzerland	273	274	1.1	Under Responsibility of EC, about vulnerable subjects has been removed compared to GCP R(2) version	Can have a better clarity of the review process when the trial include vulnerable subjects.
FVR-Finnish Vaccine Research	276	302	1.1.2	This is confusing and should clearly describe the IRB/IEC review before the trial conduct, and then, separately the continuing review (1.1.4) and updates to required safety information (1.1.2. g) 1.1.2. d describes information provided to study "participants". Should this be the target population?	Any other information to be provided to the trial target population
Fergus Sweeney	278	278	1.1.2.b	the IRB/IEC will not review "any" amendments. Absolutes are not necessary and in this case can drive truly disproportionate submissions to IRB/IEC of changes they are not required to review - absolutes are not needed delete "any". For example nonsubstantial amnedments are not reviewed	"protocol and amendents"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EAHP	284	286	III 1.1.2	Besides the Investigator's Brochure also the Pharmacy binder, the safety data sheet and the information on IMP compounding need to be included.	Investigator's Brochure or current scientific information, such as a basic product information brochure (e.g., Summary of Product Characteristics (SmPC), package leaflet or labelling), the Pharmacy binder, the safety data sheet and the information on investigational medicinal product compounding, as appropriate, including their updates;
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	284	286	III 1.1.2	The assessment of the trial products used in a clinical trial is in the EU primarily the responsibility of the authorities. We doubt that it is really feasible (practically and technically) for the ECs to take note of and evaluate every change of the IB/SmPC.	Suggestion: Delete "including their updates"
eClinical Forum	288	289	III 1.1.2(d)	This states that the IRB should review (d) any other information to be provided to the trial participant(s), including a description of the media through which such information will be provided; Any other information is relatively broad. It should be information pertinent to the trial.	Revise the paragraph to state " and other pertinent information that could affect the rights, safety and well-being of participants".
eClinical Forum	288	289	III 1.1.2(d)	Text in existing R2 talks about what is given to the IRB and the patient -- we believe this list to be still valid.	Align with list in R2
EFPIA Consolidated Comments	288	289	1.1.2 (d)	It should be clarified that not all information provided to participants should be provided to the IRB/IE, only information that informs a decision about participation is required. This is consistent with the EU Clinical Trials Q&A v6.5 Q1.24, and, as such, excludes questionnaires, patient diaries, cards, ePR), etc	any other information to be provided to the trial participant(s) before their decision to participate, continue or abstain from participation in the clinical trial, including a description of the media through which such information will be provided;
Quotient Sciences	288	289	1.1.2 (d)	This should apply to written information or information delivered via audio/visual systems (e.g. videos) that is used to inform the volunteer about the trial. Clearly, the investigator will provide information to participants during the informed consent discussion, and will answer volunteers' questions, and that verbal information cannot be reviewed by the REC. Please clarify that this requirement applies to written and audio/visual information provided to participants.	Please add text in bold: (d) any other participant-facing written information or audio/visual information to be provided to the trial participant(s), including a description of the media through which such information will be provided.
Society for Clinical Research Sites	288	289	1.1.2		We believe that the requirement not be "any other information…" but "any other informed consent materials…" as there is a substantial amount of other information that is immaterial or generally out of scope for IRB/IEC oversight not being germane to human subject protections. For example, the participant may be required to complete tax forms, routine hospital admission forms, notices of privacy practices at the health clinic and others that are independent of the study and not under the control of the IRB/IEC. The term "informed consent materials" is used in other sections of this draft guidance (e.g. Annex I Items 2.8.2, 2.8.11, 2.8.12, 3.13.1and Appendix C's Table 2) for similar purposes.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA Consolidated Comments	291	292	1.1.2 (e)	Verbiage in Section e is as follows "advertisement for participant recruitment (if used) and information on the recruitment process" . In addition to the advertisement, it would be valuable for the IRB to review/understand how the advertisement will be provided to participants (e.g., print, tv, radio, social media) Suggest adding as part of the review of information on the recruitment process to understand strategy for adversiting to recruit participants and for diversity/inclusivity.	suggested rewording - " (e) advertisement for participant information (if used) including the mechanism for adverstising (e.g. print, tv, radio, social media) and information on the recruitment process. "
Fergus Sweeney	294	294	1.1.2.f	the term compensation here refers to compensation for the participants time or travel or other expenses, not compensation for injury, which is part of insurance/liability	add "…for reasonable expenses or time commitment."
Society for Clinical Research Sites	299	300	1.1.2		Please specify if it is only the Principal Investigator's information to be submitted or if the intent is for the IRB/IEC to see qualifications of all sub-investigators the PI has delegated study tasks to. If it is the latter, then it seems the intent is that the IRB/IEC, not the investigator/institution, is the final authority on deciding which sub-investigators an investigator can delegate study tasks to.
CARVALHO Carla	304	306	1.1.33	The IRB/IEC reviews the protocol and also the expertise of the physician responsible for the conduct of the study at a site level. In some centers in the United States of America, the IRB review the resume of the physician before the submission of the study and do not verify at each initial submission of a new study that this physician has the adequate expertise/qualification to conduct this new study. The objective of the proposed change is to avoid this gap.	The IRB/IEC should review a proposed clinical trial as well as the qualification of the proposed principal investigator within a reasonable time and document its reviews clearly identifying the trial, the documents reviewed and the dates for the following
EFPIA Consolidated Comments	304	306	1.1.3	What is the expectation for reasonable time?	The IRB/IEC should review a proposed clinical trial within a reasonable time, ideally in parallel with the Health Authority review/assessment or in accordance with regulatory requirements.
Unicancer	305		1.1.3	Important to have the date and version number	the documents reviewed (including version and date)
Fergus Sweeney	306	306	1.1.3	reword	"..dates of.."
Fergus Sweeney	308	308	1.1.3.a	IRB/IEC may apply conditions to their opinion	"….opinion, with conditions if applicable"
Unicancer	308		1.1.3	approval/favourable opinion dated by the EC actually the problem is that the date of the favourable opinion could be the date of the letter, the date of the meeting or the reception date of the letter.	(a) dated approval/favourable opinion

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
DGPharMed e. V. (Deutsche Gesellschaft für Pharmazeutische Medizin)	316	317	III.1.1.4	This raises the question if more than an Annual Report is expected to be submitted to an IEC and how capacities for the review are to be allocated. That could cause major workload to IECs and will raise costs for clinical trials – and potentially hampering academic research.	Define which time intervals are considered appropriate to the degree of risk
EFPIA Consolidated Comments	316	317	1.1.4	Expectation of a minimum frequency can be guiding. Therefore, add back in annual review as included in R2.	but at least once per year.
FVR-Finnish Vaccine Research	316	317	1.1.4	Continuing review by the IRB/IEC should be reserved for selected trials with potentially considerable risks to participants. IRB/IEC resources are probably not adequate for all trials.	The IRB/IEC should conduct continuing review of trials with considerable potential risks to participants (risk-based approach).
German Pharmaceutical Industry Association (BPI)	316	317	1.1.4.	see also line 137	
IFCT	316	317	1.1.4	not applicable in France	
Medicines for Europe	316	317	1.1.4	Since preparation of interim reports enabeling periodical reviews is rather time consuming, their frequency should be known in advance.	The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to participants. Intervals should be pre-defined and communicated with sponsor.
Sandoz AG, Switzerland	316	317	1.1.4	Removed frequency of EC review on ongoing trial	It is better to have the review frequency on ongoing trial atleast once in a year as per GCP (R2) as there is no local regulatory frequency period in India.
EFPIA Consolidated Comments	330	332	1.1.7	Clarification regarding role of IRB/IEC needed as they are not responsible for the eligibility of each participant: Original Text: 'If minors are to be included in a trial, the IRB/IEC should review the assent information considering the age, maturity and psychological state of the minor, as well as applicable regulatory requirements' Also consider the other vulnerable populations. See 2.8.14	Suggest to change to: 'If vulnerable participants (e.g. minors) are to be included in a trial, the IRB/IEC should review the suitability of the consent or assent (minors) information, considering factors such as the age, maturity and psychological state of the minor participant, as well as applicable regulatory requirements'
EUCROF	330	332	III. ANNEX 1, 1.1.7	"1.1.7 If minors are to be included in a trial, the IRB/IEC should review the assent information considering the age, maturity and psychological state of the minor, as well as applicable regulatory requirements." Wording is misleading	If minors are to be included in a trial, the IRB/IEC should review the assent information considering the age, maturity and psychological state of the minor, as well as applicable regulatory requirements. as well as whether applicable regulatory requirements are complied with.
Fergus Sweeney	330	332	1.1.7	Consider whether assent should also be discussed as appllicable for adults who are incapacitated but still capable of listening and responding to information	reword if considered appropriate to include incapacitated adults

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA Consolidated Comments	338	339	1.1.8	This should address childcare, compensation for time away from work for participant or caregiver, etc. as other rationale for reimbursement as this would support enhanced accress for more diverse patient populations	Reasonable reimbursement of participants for travel, and lodging and other relevant expenses such as childcare is not typically coercive.
EUCROF	338	339	III. 1.1.8	"Reasonable reimbursement of participants for travel and lodging is not typically coercive." Would be good to emphasise that reimbursement for travel and lodging should be offered on a prorated basis as well and not all at once at the end of the trial.	Reasonable reimbursement of participants for travel and lodging is not typically coercive, but should also be offered on a prorated basis.
EFPIA Consolidated Comments	341	344	1.1.9	"information regarding payment to participants…set forth in the informed consent material and any other information to be provided to participants."	information regarding payment to participants…set forth in the informed consent material and or any other information to be provided to participants.
Medicines for Europe	341	344	1.1.9	As seperate information materials regarding payments (information regarding payment to participants, methods, amounts and schedule of payment to trial participants) can be submitted together with informed consent materials for IRB/IEC approval and provided to trial participants, flexibility on where such information should be provided would be reasonable.	The IRB/IEC should ensure that information regarding payment to participants, including the methods, amounts and schedule of payment to trial participants, is set forth in the informed consent material and or any other information to be provided to participants.
Quotient Sciences	341	344	1.1.9	The primary reason given by healthy participants in phase 1 trials for volunteering for clinical research is payment. A subgroup of the HRA Phase 1 Advisory Group met in March 2023 to discuss payments for participants who do not complete phase 1 trials, and it was agreed that it was not appropriate to advertise in the ICF the payments that volunteers would receive for completing only part of a trial, for various reasons. For example: * investigators tend to exercise discretion and pay volunteers more generously than pro rata if volunteers have been withdrawn owing to side effects * it is not possible to cover all possible circumstances * it might encourage participants to withdraw before completing a trial (because they feel that they have earned enough), and that might necessitate exposure of additional volunteers to an experimental medicine, which has ethical implications, and would slow the progress of the trial.	Please add text in bold: The IRB/IEC should ensure that information regarding payment to participants, including the methods, amounts and schedule of payment to trial participants, is set forth <u>appropriately</u> in the informed consent material and any other information to be provided to participants.
Fergus Sweeney	343	343	1.1.9	Avoid use of absoutes. "any" does not help here	"…material and other information …"
GQMA	346	375	III.1.2	Due to the use of the word 'should' the Composition, Functions and Operations of IECs is only a recommendation. This could result in less qualified IECs, e.g., in countries with weak regulatory supervision.	Use 'shall' instead of 'should' throughout the section.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Quotient Sciences	347	347	1.2.1	The wording could be improved for clarity.	Please add text in bold: 1.2.1 The IRB/IEC should consist of a reasonable number of members who collectively have the qualifications and experience to review and evaluate the science, the medical aspects and the ethics of the proposed trial. It is recommended that the IRB/IEC should include:
Ludger Wienbrede	348	355		"It is recommended that the IRB/IEC should include: (a) at least five members; (b) at least one member whose primary area of interest is not in medical sciences; (c) at least one member who is independent of the institution/investigator site." This should be more than a recommendation, it should be a requirement. Otherwise you would find ethics committes consisting of two persons working in the same institution as the investigator, sharing a similar status and background, be good friends with the investigator. This would undermine any meaningful review of the clinical trial.	
EUCROF	351	355	III. 1.2.1	More clarity as to whether a lay person and/or patient representative is required would be welcome. Somebody whose primary interest is not in medical sciences could be a laywer or ethicist. In some countries these professions do not qualify as lay persons. Is, according to ICH GCP, a lay person required or not?	
DGPharMed e. V. (Deutsche Gesellschaft für Pharmazeutische Medizin)	355	355	III.1.2.1	Consider adding further “independencies” (religious or political offices etc)	Consider adding further “independencies” (religious or political offices etc)
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	355	358	III 1.2.1	The IRB/IEC requires only one member (as a minimum) who is independent of the institution/investigator site. Thus, in case there is indeed only one member of the IRB/IEC which is independent of the institution/investigator site (which means only this one person can vote, see line 357/358), is it then sufficient to have a vote by only one IRB/IEC member to make a decision on clinical trials (favourable/negative opinion)? If one vote is not enough, consider adapting the required number of independent IRB/IEC members according to the number of votes necessary for a decision?	The required minial number of IRB/IEC members for a vaild decision hould be clarified.
EAHP	356		III 1.2.1	Add a new point (d) to ensure that a hospital pharmacy expert is also included in the IRB/IEC.	(d) at least one hospital pharmacy expert in investigational medicinal product management and compounding
DGPharMed e. V. (Deutsche Gesellschaft für Pharmazeutische Medizin)	357	358	III.1.2.1	How could independence be assured if the IEC members are employees of the sponsor institution as it might happen for academic IEC in Germany, e.g. being employee of another clinic within the same clinic association, i.e. of the same legal entity. A slightly softened wording considering independence of the specific investigator and a specific trial conducting entity / department might consider that aspect.	Clarify if independence of the specific investigator and a specific trial conducting entity / department is sufficient
Ollie Östlund	357	359	III.1.2.1	While Sweden, where I work, has a national ethics authority, I know that other countries use university-affiliated committees. In that case this sentence may be a problem for trials where the university is also the sponsor. I guess you have thought about this, but usually regulators just forget about academic trials.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	358	359	III 1.2.1	"A List of IRB/IEC members and their qualifications should be maintained." This is a problem in the EU (in Germany), as ECs do not provide this information with reference to data protection. This also applies to the following lines/sections of this draft guideline: Lines 2765-276; Section C.3.1 Lines 2830-2830, Section C.3 Table 1 - 1.4	
EFPIA Consolidated Comments	365	366	1.2.3	This sections seems to not allow decisions by chairpersons action - all decisions to be taken at a quorate meeting. This might make REC decisions slower, if the final decision can't be given until a certain document has been submitted in follow up or an answer to a specific question is awaited. Athough this is what was in R2, it would be helpful to refer to chairs decisions as part of the procedures. Moved present to after quorum for ease of reading to add proposed text addition.	An IRB/IEC should make its decisions at announced meetings at which at least a quorum is present, as stipulated in its documented operating procedures, see 1.3.5 regarding circumstances for expedited review.
SHIONOGI	375	375	1.2.6	Missing is the requirement to have appropriate (ad hoc) IRB/IEC individuals reviewing the trial protocol and associated documentation, such as informed consents in case the trial involves vulnerable participants, such as, but not limited to: minors, incapitated participants, etc. to comply with other regulatory requirements such as the Clinical Trials Regulation	suggest to add additional information on what the special areas are, such as 'An IRB/IEC may invite non-members with expertise in special areas, such as trials with minors or incapacitated participants, for assistance.
Fergus Sweeney	377	377	1.3	It is not necessary to include "..in writing or electronically.." at sporadic points when the word document is used. Delete these words and if needed replace "..document.." by "…record.." although document is better here. Nowhere in GCP excludes the use of electronic media only, paper records per se are not needed in any instance.	delete "…in wirting or electronically…"
Quotient Sciences	377	378	1.3	Procedures will be in writing, whether in hard copy or electronic. So why is it necessary to say 'in writing or electronically'?	Please delete 'or electronically': The IRB/IEC should establish, document in writing or electronically, and follow its procedures, which should include:
AFI	388	388	1.3.5	Providing, according to the applicable regulatory requirements, expedited review	Please, clarify what is meant by "regulatory requirements" or remove according to the applicable regulatory requirements
EFPIA Consolidated Comments	388	390	1.3.5	suggest incorporating expedited approval for emergency situations	Providing, according to the applicable regulatory requirements, expedited review and approval/favorable opinion of minor change(s) in ongoing trials that have the approval/favorable opinion of the IRB/IEC, or in cases of emergency situations;
EUCROF	388	390	III. 1.3.5	"Providing, according to the applicable regulatory requirements, expedited review and approval/favourable opinion of minor change(s) in ongoing trials that have the approval/favourable opinion of the IRB/IEC;" What is meant by "minor change"? "Non-substantial change"? In some regions, non-substantial modifications are not even to be submitted. Text should provide more clarity.	Providing, if applicable regulatory requirements request submission of non-substantial changes, expedited review and approval/favourable opinion of such non-substantial change(s) in ongoing trials that have the approval/favourable opinion of the IRB/IEC;

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Ludger Wienbrede	388			The sentence "Providing, according to the applicable regulatory requirements, expedited review and approval/favourable opinion of minor change(s) in ongoing trials that have the approval/favourable opinion of the IRB/IEC" should be rephrased to "Providing, according to the applicable regulatory requirements, expedited review and, if applicable, approval/favourable opinion of minor change(s) in ongoing trials that have the approval/favourable opinion of the IRB/IEC". Not in every case review AND approval/favorable opinion are the standard mode of IRB/IEC procedures for minor changes. Rather, in many cases just review would be the applicable procedure.	
EUCROF	392	392	III. 1.3.6	"Specifying that no participant should be admitted to a trial before the IRB/IEC issues its documented approval/favourable opinion of the trial;" "should be admitted to" --> "should be enrolled into" or "should be included in" would represent more common wording	
Ludger Wienbrede	392	393		"Specifying that no participant should be admitted to a trial before the IRB/IEC issues its documented approval/favourable opinion of the trial". This should be re-worded to: "Specifying that the IRB/IEC does not issue its first documented approval/favourable opinion of any trial that was started before its own documented approval/favourable opinion was issued or before the documented approval/favourable opinion of another IRB/IEC with appropriate responsibility was issued". Rationale: The IRB/IEC cannot control the admission of participants. Therefore, the original statement is useless. Problem: It is tricky to find a wording that works for multicenter trials, multinational trials, situations in which the responsibility is transferred from one IRB/IEC to another during the trial.	
Centre for Human Drug Research	395	397	1.3.7	Suggest adding some wording that (non-substantial) logistical and administrative changes do not need IRB approval. As the wording now inplies that any change in the protocol requires a (substantial) amendment that requires approval from the EC - but that is not practical for administrative changes.	Non-substantial logistical and administrative changes do not require IRB approval.
Dr. C. Wilsher	395	397	1.3.7	ICH E6R2. 3.3.7 also says " or when the changes involve only logistical or administrative aspects of trial" . Does this mean that this exception is no longer operational? We need confirmation that this has not just been left off accidentally.	
EUCROF	395	397	III. 1.3.7	"Specifying that no deviations from the protocol should be initiated without prior documented IRB/IEC approval/favourable opinion, except when necessary to eliminate immediate hazards to the participants;" The term "deviation" from the protocol etc is not defined in the glossary and may be interpretable. In other sections of the guideline "important deviations" is used, which is also not defined. It might be more consistent in terminology to talk of substantial changes (amendments/modifications) to the protocol.	"Specifying that no substantial changes to the protocol should be initiated without prior documented IRB/IEC approval/favourable opinion, except when necessary to eliminate immediate hazards to the participants;"

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German Pharmaceutical Industry Association (BPI)	395	397	1.3.7.	The procedures for IRB / IEC do not distinguish any more between substantial and non-substantial deviations. This would implicate that all small changes to the protocol need an approval / favourable opinion which is neither helpful nor doable and would make study conduct much more complicated.	Amend again a further exception acc ICH E6 (R2); i.e.: "except when the the change(s) involves only logistical or administrative aspects" Or restrict the applicability of the section: "Specifying that no important deviations from the protocol should be initiated without prior documented...." Definition of important deviation could be added, using terminology of section 3.9.3.: "...*classifying deviations as important (i.e., those that impact the rights, safety and well-being of trial participants and the reliability of results)*".
German Pharmaceutical Industry Association (BPI)	395	397	1.3.7.	non-substantial modification of the protocol should be possible	
Ipsen	395	397	1.3.6	In E6(R2) logistical/admin changes were allowed without requiring IRB approval. Current language would cause additional burden "Specifying that no deviations from the protocol should be initiated without prior documented IRB/IEC approval/favourable opinion, except when necessary toeliminate immediate hazards to the participants;"	"Specifying that no deviations from the protocol should be initiated without prior documented IRB/IEC approval/favourable opinion, except when necessary toeliminate immediate hazards to the participants or when change(s) involve only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s));"
Ludger Wienbrede	395	396		"Specifying that no deviations from the protocol should be initiated without prior documented IRB/IEC approval/favourable opinion": This should be deleted. The IRB/IEC cannot control this. Therefore, the statement is useless.	
Medicines for Europe	395	397	1.3.7	Planned change might be more appropriate term than deviation in this context. Administrative changes should be added.	Specifying that no deviations planned change from the protocol should be initiated without prior documented IRB/IEC approval/favourable opinion, except when necessary to eliminate immediate hazards to the participants or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s));
PPD	395	397	III. Annex I 1. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC) 1.3 Procedures	The new guideline (R3) has removed the reference to protocol AMENDMENTS, and the new language insinuates protocol deviations should be IRB approved prior to the deviation, rather than referring to changes to the protocol via a protocol amendment.	Recommend reverting to previous language in section 3.3.7 of ICH E6 (R2), which includes favourable opinion of an appropriate amendment.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Quotient Sciences	395	397	1.3.7	The proposed text is less clear than the existing requirement in GCP R2. At regulatory inspections, GCP and GMP inspectors have been clear that *deviations* must not be pre-planned, so they cannot be prospectively approved by regulatory authorities or RECs. Pre-planned changes are amendments/modifications, which may require approval before implementation. In this section, 'deviations' should be replaced with 'amendments/modifications'. However, only *substantial* changes require approval in the UK and EU. Non-substantial amendments/modifications may be implemented without prior approval. Also, it is strange that regulatory approval is referred to here in relation to amendments but is not referred to in relation to starting a trial. Section 1.3.6 says that no participant should be admitted to a trial before the IRB/IEC issues its documented approval/favourable opinion of the trial, but does not refer to regulatory approval. It would be consistent to omit references to regulatory approval from section 1.3.7.	Change 1.3.7 to: 1.3.7 Specifying that: (a) no amendments or modifications to the protocol should be initiated without prior documented IRB/IEC approval/favourable opinion unless changes are exempt from requiring IRB/IEC approval/favourable opinion according to local regulatory requirements (e.g., the change(s) involves only logistical or administrative aspects of the trial); and (b) no deviations from the protocol should be initiated except when necessary to eliminate immediate hazards to the trial participants.
DGPharMed e. V. (Deutsche Gesellschaft für Pharmazeutische Medizin)	399	412	III.1.3.8	The listed reporting liabilities posed on the investigator are a major change in the way of reporting. Actually, the reporting liabilities to the IEC lie with the sponsor who is informed by the investigator via supplied standard tools and reporting channels. Moreover, actual EU legislation does not stipulate a direct reporting obligation of investigators to the IEC. Furthermore, it is technically not implemented in CTIS. That obligation causes an unnecessary additional workload to investigators with no additional safety for trial participants. E.g. Chapters 2.4.5 / 2.6.2 / 2.6.3 open the possibility that the sponsor might send information to the IEC “according local regulatory requirements” / “in accordance with applicable regulatory requirements”; that is a possible solution to this obligation, too.	The responsibility shall lie with the sponsor and not the investigator/ institution
EFPIA Consolidated Comments	399	400	1.3.8	The option for the sponsor to report to the IRB/IEC should be included in order to align with the text in lines 432-437, III.1.5 ("In addition, applicable regulatory requirements may require that submissions to the IRB/IEC are made in some regions by the investigator/institution and in others by the sponsor").	Specifying that the investigator/institution or the sponsor should promptly report to the IRB/IEC (see 399 section 1.5):
EUCROF	399	400	III. 1.3.8	"Specifying that the investigator/institution should promptly report to the IRB/IEC (see section 1.5):" In section 2.4.1 it is mentioned that the investigator/institution or the sponsor may perform the submission to IRB/IEC. This should also be mentioned for all other communication/notifications to the IRB/IEC. Same applies for section 2.13.1 (lines 913-916).	Specifiying that the investigator/institution or sponsor, as applicable, should promptly report to the IRB/IEC
Ludger Wienbrede	399	400		Specifying that the investigator/institution should promptly report to the IRB/IEC: … This should be deleted. The IRB/IEC cannot control this. Therefore, the statement is useless.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUCROF	408	409	III. 1.3.8	"(c) all suspected unexpected serious adverse reactions (SUSARs) in line with applicable regulatory requirements;" Identification of SUSARs is a sponsor task. If there is a reporting line for investigators to IRBs/IECs, it is usually SAEs that have to be reported.	(c) all serious adverse events or suspected unexpected serious adverse reactions (SUSARs) as applicable by regulatory requirements;
Quotient Sciences	408	409	1.3.8 (c)	Could SUSARs please be referred to as serious unexpected suspected adverse reactions? It would make it clearer that a SUSAR is an event that is *suspected* to be a *reaction* rather than an event that is *suspected* to be *unexpected* , while maintaining the internationally recognised abbreviation 'SUSAR'.	Please edit as follows: (c) all suspected serious unexpected serious suspected adverse reactions (SUSARs) in line with applicable regulatory requirements;
EFPIA Consolidated Comments	414	421	1.3.9	addition of 1.3.9. d to cover the termination of a trial by the IRB/IEC. Moved from 2.6.4	the reason for it terminating or suspending its approval/favourable opinion of the trial (see sections 1.1.3and 1.3.9)
Fergus Sweeney	414	415	1.3.9	It is not necessary to include "..in writing or electronically.." at sporadic points when the word document is used. Delete these words and if needed replace "..document.." by "…record.." although document is better here. Nowhere in GCP excludes the use of electronic media only, paper records per se are not needed in any instance.	delete "…in wirting or electronically…"
Quotient Sciences	414	415	1.3.9	Notifications will be in writing, whether in hard copy or electronic. So why is it necessary to say 'in writing or electronically'?	Please delete 'or electronically'. 1.3.9 Ensuring that the IRB/IEC (see section 1.5) promptly notifies in writing or electronically the investigator/institution or sponsor concerning:
Society for Clinical Research Sites	422	437	1.4	The Society for Clinical Research Sites (SCRS) has several clarification requests regarding this section. First it should be clarified how "diversity" is supposed to be measured. Is diversity measured by race, ethnicity, sex, gender identity, sexual preference, age, geography, nationality, neurocognitive ability, religion, and/or socioeconomic status? This definition may be further complicated in a global setting. For example, must a clinical trial for a global product being conducted at a Japanese research site contain the representative sample of global population percentage of Native Americans? If the FDA determines that there is an additional trial required to assess additional safety in the Hispanic population, does that trial have to also recruit global representation? While we applaud the aspirational intent of the principal, we remain concerned that, as written, there is lack of a pragmatic description that contributes to the negative effects that the politicization of the issue is having. Even if that can be addressed, we still believe this would be difficult to do on a trial basis and should be part of an overall development plan, and thus eliminated as an individual trial requirement.	To the extent there is merit in maintaining such a diversity requirement, the guideline should dictate that it is the sponsor's responsibility to make these accommodations as the investigator/sites have little to no control over how the sponsor's design and conduct a multicenter/global trial. With that said, we recognize and support any statement that the investigator's role is to be non-discriminatory in their recruitment and retention efforts.
Fergus Sweeney	423	427	1.4.1	In the absence of ICH setting a minimum retention time, none may exist in some jurisdictions. Consider reinstating a minimum even if many jurisdictions have a longer one	word as needed

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA Consolidated Comments	429	430	1.4.2	The wording should be more binding/authoritative. ("The IRB/IEC may be asked"). The term 'may' is not appropriate in this case. This would be in line with the wording provided in section 1.4.1	The IRB/IEC may be asked Upon request from investigators, sponsor or regulatory authorities, the IRB/IEC should make available their documented procedures and membership lists
GQMA	429	430	III.1.4.2	It should be an obligation for the IECs to provide investigators, sponsors or regulatory authorities the documented procedures and membership lists upon request.	Change to: "The IRB/IEC shall provide investigators, sponsors or regulatory authorities with its documented procedures and membership lists upon request."
IFCT	429	430	1.4.2	not applicable in France	Add "in line with regulatory requirements"
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	429	430	III 1.4.2	In 1.4.2 it says that the IRB/IEC may be asked to provide documented procedures and membership lists implying that this is optional. Appendix C (table 1) on essential records however indicates IRB/IEC composition as essential for all trials, which would mean that provision of membership lists is not optional but rather mandatory.	Suggestion: "The IRB/IEC should provide ist documented procedures and membership lists to investigators, sponsors or regualtory authorities."
Ludger Wienbrede	429	430		"The IRB/IEC may be asked by investigators, sponsors or regulatory authorities to provide its documented procedures and membership lists." This has to be changed to: "The IRB/IEC has to provide to investigators, sponsors or regulatory authorities upon their request its documented procedures and membership lists within 30 days free of charge." The original statement is useless. If the investigators have only the right to ask but not the right to get a response, the requirement could as well be deleted.	
Medicines for Europe	429	430	1.4.2	Too vague, please consider revising.	The IRB/IEC should provide its documented procedures and membership lists to investigators/institutions, sponsors or regulatory authorities.
Society for Clinical Research Sites	429	430	1.4.2	We believe this should be strengthened to be a requirement to provide, rather than simply stating that the IRB/IEC can only be asked. We also believe this item should expand to any essential document or regulatory requirement held by the IRB/IEC that should be required by an investigator.	We suggest the following wording be considered: "The IRB/IEC must timely provide to the requesting sponsors and/or investigators all documentation they generate or maintain that is required of sponsors and/or investigators respectively under applicable regulation or other Essential Records defined in Appendix C."
CARVALHO Carla	432	437	1.5	In some countries, if some specific data are collected and not specific to the disease under investigation (e.g., race), an additional authorization is seek (e.g., authorization from the Data Privacy Authorithy). The objective of the propose change is to clarify this point.	For the submission to or communication with the IRB/IEC, it is recognised that in most regions, there is also a requirement to make a submission to the relevant regulatory authority and/or the data privacy authorithy, and these may be combined, in line with applicable regulatory requirements, in a single submission in some regions.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA Consolidated Comments	432	437	1.5	there are often significant delays in the implementation of amendments when HA and IRB/IEC reviews do not occur in parallel which can impact the scientific integrity of the study, participant safety, and/or participant's willingness to continue in the study. Recommend including a statement that HA and IRB submission and reviews should occur in parallel, but that the trial or amendment may not be implemented until both HA and IRB/IEC approval or acknowledgement is received. To provide clarity in subsequent texts on who is responsible for updates or submissions based on urgent safety measures e.g. deviations to eliminate an immediate hazard.	For the submission to or communication with the IRB/IEC, it is recognized that in most regions, there is also a requirement to make a submission to the relevant regulatory authority, and these may be combined, in line with applicable regulatory requirements, in a single submission in some regions. If not combined, submissions to both the regulatory authority and the IRB/IEC should be reviewed in parallel by both the regulatory authority and the IRB/IEC to minimize delay in implementation of the study or changes to the study. In addition, applicable regulatory requirements may require that submissions to the IRB/IEC are made in some regions by the investigator/institution and in others by the sponsor. It is assumed that the party making the initial submission will be responsible for any subsequent notifications required by this guideline.
SHIONOGI	432	435	1.5	Unclear what 'in most regions' mean	Suggest to be more specific in explaining what most regions mean
AFI	435	437	1.5	submissions to the IRB/IEC are made in some regions by the investigator/institution and in others by the sponsor	Avoiding submission by the investigator/institution since the final responsibility is in charge of the Sponsor
Ludger Wienbrede	438			The E6 guideline has to feature requirements and procedures for regulatory authorities. Otherwise, the concept of GCP has a significant and dangerous gap. It is inconsistent to claim that requirements and procedures for ethics committees belong to GCP and therefore to E6 while requirements and procedures for regulatory authorities do not belong to GCP and therefore not to E6. If no section about regulatory authorities is added, lines 6-8 should be worded like this: The term “trial conduct” in this document includes processes from planning to reporting, including planning, initiating, performing, recording, oversight, evaluation, analysis and reporting activities with the exclusion of activities of regulatory authorities concerning the authorisation of clinical trials.	
Ollie Östlund	439	439	III.2.	Just to note: The “investigator”/“sponsor” roles are mostly confusing in academic trials. In Sweden “sponsor” collides in an unfortunate fashion with the legal term “research principal” (forskningshuvudman), who may have responsibilities more like “investigator”. Similar problems are probably present in other countries. If E6 should never be applied to academic trials, please state so explicitly as guidance to regulatory authorities.	
Ludger Wienbrede	441			"The investigator(s) should be qualified by education, training and experience to assume responsibility for the proper conduct of the trial and should provide evidence of such qualifications." This should be supplemented with: "Experience with clinical trials should only be required for trials with high risks and/or high complexity."	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
PPD	441	443	III. Annex I 2. INVESTIGATOR 2.1 Qualifications and Training	The reference to up-to-date Curriculum Vitae or other documentation requested by sponsor, IRB/IEC and/or regulatory authorities have been removed. This might indicate that the investigator should follow local regulations OR to rely on the Sponsor / CRO for adequate documentation. The Essential document section has also undergone changes with criteria as to what constitutes an Essential document. The curriculum vitae and/or other relevant documents evidencing qualifications of investigator(s) and Sub-investigator(s) are now in Table 2 of Essential documentation: Potential Essential Records	The investigator(s) should be qualified by education, training and experience to assume responsibility for the proper conduct of the trial and should provide evidence of such qualifications as defined per local regulation, regulatory authorities or ethics committee.
Quotient Sciences	441	442	2.1.1	First-in-human trials are unlike other trials and require specialist expertise. Investigators of first-in-human clinical trials should have relevant clinical experience in running Phase 1 trials in addition to any qualifications required by local regulations or guidance.	Please add to 2.1.1 the text in bold: 2.1.1 The investigator(s) should be qualified by education, training and experience to assume responsibility for the proper conduct of the trial and should provide evidence of such qualifications. The investigator of a first-in-human trial should have relevant experience in clinical pharmacology and any additional qualifications required by local regulations or guidance, or delegate to an appropriately experienced sub-investigator aspects of the trial that require clinical pharmacology expertise.
Richmond Pharmacology Dr Ulrike Lorch Dr Jörg Täubel Dr Thomas Ashdown Dr Edward Jackson Dr Thomas York	441	443	2.1.1	As discussed in the general comment in Row 18. It is difficult to ascertain how this section number is upheld given that the majority of investigators fulfil the "one-and-done" criteria. Furthermore, just 6% of annual clinical trial spending is directed towards professional investigators, with the majority awarded to part-time investigators [6].	
Unicancer	445		2.1.2	Propose familiar or trained (important for exemple for new products)	familiar with or trained with the appropriate use
AFI	449	451	2.2.1	The investigator should be able to demonstrate (e.g., based on retrospective or currently available data) a potential for recruiting the proposed number of eligible participants within the recruitment period as agreed with the sponsor	This requirement should be move in another section. Not very pertinent in the one regarding resources.
Beate Kern, Department of Health Brandenburg, Germany	453	455	2.2.2	I miss a clear assignment of which tasks are reserved for qualified investigators staff and which are reserved for medical professionals (important due to the shortage of skilled workers, increased lateral entrants and multiprofessionality). As national regulations set different qualification requirements for persons performing procedures on patients, this should be set out in writing.	Patient procedures should only be performed by personnel, which is adequately qualified and authorised to perform these tasks according to national regulations.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Jazz Pharmaceuticals	453	455	III.2.2.2	Investigator resources should include any required technologies such as telehealth or scheduling capabilities.	
Society for Clinical Research Sites	453	464	2.2.2	Adequate and timely funding from the sponsor is critical and a growing challenge for investigators/institutions to conduct the trials. While the glossary definition of sponsor indicates that arranging for financing is part of the sponsor's obligation, we believe it is imperative that investigators/institutions understand the projected costs and share in the responsibility of the financial sustainability of the trial.	This section should be changed to read, "The investigator should have sufficient time, an adequate number of available and qualified staff, adequate facilities for the foreseen duration of the trial and arranged for any necessary, sufficient and timely financing from the sponsor to conduct the trial properly and safely."
Fergus Sweeney	456	456	2.3	it is strange that Investigator chapter has a "responsibiliites" section but not the sponsor one. It is also misleading as all the subsections of chapter 2 are responsibilities of Investigators and not only 2.3. The equivalent section in the Sponsor chapter is called agreements. That would be preferable also here.	change subsection title to "Agreements" and delete "Responsibiliites"
DGPharMed e. V. (Deutsche Gesellschaft für Pharmazeutische Medizin)	457	464	III.2.3.1	It is essential that distribution of responsibilities between Investigator and Institution is clearly defined. Either in a trial contract or in a contract between the Institution and an Investigator.	The responsibility to delegate trial-specific activities to other persons or parties shall lie with the sponsor
EUCROF	457	457	III. 2.3.1	Maybe a definition of the term "party" would be beneficial. We understand, that it is not the same as "service provider" but could be a service provider. Party could be a satellite site, for example, or an independent entity in a hospital usually not under the supervision of the investigator (e.g., pharmacy). As "service provider" is defined, "party" should be defined as well.	
Good Clinical Trials Collaborative, on behalf of supporting organisations	457	464	Investigator (2.3.1)	The current draft text is inappropriate. It restricts the ability for the investigator (of whom there may be many across multiple sites) to take advantage of central services (e.g. central laboratories, central pharmacy) organised by the Sponsor. Any such activities organised by the Sponsor should be the Sponsor's responsibility for oversight. The assertion (lines 463-464) that by insisting that the Investigator retain ultimate responsibility for such services ensures the rights, safety and well-being of the trial participants and data reliability is unjustified – in many cases the Investigators may lack the resources or skills to provide supervision of third party services organised by the Sponsor and may not have the right to assess an entity with which it does not have a contractual relationship. (In some instances, the organisation that provides a service such as a central pharmacy may be located in a different nation or state from the Investigator.)	The principle of ensuring accountability is a good one but the document as currently drafted would restrict the flexibility to provide the activities in the best way for the context.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Quotient Sciences	457	472	2.3.1-2.3.2	Further thought needs to be given to situations where the sponsor contracts service providers such as expert clinicians, X-ray clinics, MRI/PET scan units, and fertility clinics. This section states that the investigator may be supported by the sponsor to identify a suitable service provider(s), but the investigator makes the final decision on whether the service provider is appropriate based on information provided by the sponsor. The investigator retains ultimate responsibility and maintains appropriate supervision of the persons or parties undertaking the activities delegated to ensure the rights, safety and well-being of the trial participants and data reliability. It's not clear how this will work when service providers (e.g. expert clinicians, such as psychiatrists or ophthalomologists, or PET scan units) are contracted by the sponsor rather than the investigator. It is helpful that the investigator will have a say in which service providers are used in the study, but how much information would the sponsor be required to provide? Would the investigator be asked to review a full audit report covering all aspects of the service, including data security, confidentiality, training, validation and qualification, and evidence of trial-specific training etc? The service provider may have expertise that the investigator does not - could an investigator assess the credentials of an specialist clinician? Oversight would be difficult to maintain if the investigator does not have a contractual relationship with the service provider and if trial activities are done at the service provider's site instead of the investigator site (e.g., MRI scans, X-rays). It would seem more proportionate to give the investigator the final say on the potential suitability of service providers contracted by the sponsor and to oblige sponsors to provide oversight, particularly as the sponsor will monitor the trial. The sponsor should promptly report to the investigator any concerns about the service provider and act promptly upon any concerns raised by the investigator during the conduct of the trial. Please clarify what/how much information the investigator would be required to review to support a decision on service providers. Consider situations where the sponsor, not the investigator, contracts the service provider and is better placed to provide oversight.	
Richmond Pharmacology Dr Ulrike Lorch Dr Jörg Täubel Dr Thomas Ashdown Dr Edward Jackson Dr Thomas York	457	483	2.3	We believe this section should explicitly state the fundamental responsibilities of the investigator. In line with the general comments listed above, this is an excellent opportunity to recognise the experienced investigator. Since the last ICH E6 Revision, the role of the experienced investigator has significantly evolved with the emergence of new advanced therapies, in an increasingly digital and collaborative research environment. Experienced investigators have medical oversight across the regulatory, operational, data management, statistical analysis and quality aspects of a trial. They continuously assess a trials feasibility and risk manage all stages of the trial. This requires excellent oversight and leadership capabilities to successfully navigate this. The ICH revision should not only reflect the advances in data acquisition tools and digital records etc., but it should also reflect the entirely different role that the experienced investigator may now adopt.	"2.3.1 The investigator is fundamentally responsible for ensuring the rights, safety and well-being or the trial participants and data reliability. More experienced investigators may, in collaboration with the sponsor, undertake additional responsibilities for which they are sufficiently experienced and qualified to do so." We would be happy to provide a detailed explanation of the core capabilities of an experienced early-phase investigator to help establish the role in the ICH E6 guideline. Please contact us if this would be beneficial.
Society for Clinical Research Sites	457	462	2.3.1		The wording in lines 462 should be changed from “ultimate responsibility” to “ultimate accountability”. Common definitions differentiate the meaning of “responsible” (as germane to the obligation to perform the task and/or comply with the rule) and “accountable” (as ownership of the results). In the case of the principle, the delegated individuals would be responsible for completing the tasks and/or complying with the rules, but the investigator would remain accountable for their delegate’s performance.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Society for Clinical Research Sites	457	472	2.3.1 – 2.3.2	We appreciate the intent to have the investigator retain the final decision on the choice of sponsor-contracted service providers that are "intended to support the investigator". However, this concept remains ambiguous and contentious. In the example of a sponsor-contracted mobile health professional that performs ECGs that will be sent to the sponsor's central reader first, who will then send the report to the sponsor and investigator, it is heavily debated if this service provider is working on behalf of the sponsor or the investigator. In another example, a sponsor-contracted software service provider providing the investigator's electronic documentation platform is arguably supporting the sponsor as, even if it brings efficiencies to the investigator's workflow, the investigator is essentially a user of that sponsor's system. The debate over these issues remains anxiety-provoking in the investigator community and contributes to the feeling of ultimate responsibility, yet erosion of control. We strongly support giving more control to the individual site investigators. However, it's important to acknowledge that for large clinical trials involving multiple centers globally, the sponsor's involvement in contracting and overseeing service providers is necessary. In this context, the sponsors would also take on the responsibilities of the coordinating investigator as described in the glossary, and they would be held accountable for the work. When this occurs we respect that the sponsor's service provider and the investigator must collaborate with each other, however, the sponsor ultimately must bear the accountability of their contracted service providers.	We encourage the final guidance to clarify what it means to "support the investigator" as there is debate on who these service providers actually support in the dichotomy between the sponsor and investigator.
Association for Clinical Data Management (ACDM)	458	461	2.3.1	We did not understand what the following sentence meant. 'The investigator may be supported by the sponsor to identify a suitable service provider(s); however, the investigator retains the final decision on whether the service provider intended to support the investigator is appropriate based on information provided by the sponsor (see section 3.6.6)'.	This could be interpreted that the investigator should approve global service providers. Please re-write to confirm is only for the specific investigator.
EFPIA Consolidated Comments	458	464	2.3.1	There were a large number of comments as to why this could be misunderstood or misinterpreted. Therefore we proposed some additional language to provide clarity and an example. Issue with determining level of supervision. Need to include in training material.	The investigator may be supported by the sponsor to identify a suitable service provider(s) for site-specific activities; however, the investigator retains the final decision on whether the service provider intended to support the investigator is appropriate based on information provided by the sponsor (see section 3.6.6). Where there are significant issues with the service, the investigator should report them to the sponsor. The investigator retains the ultimate responsibility and maintains appropriate supervision of the persons or parties undertaking the activities delegated to ensure the rights, safety and well-being of the trial participants and data reliability at the trial site. The level of supervision should also take into acocount whether the trial-related activity is part of routine clinical care.
Unicancer	458		2.3.1	(…) the investigator retains the final decision on whether the service.	What is the scope of this ? For example the investigator does not have the choice of the central lab.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Association for Clinical Data Management (ACDM)	466	472	2.3.2	If the sponsor selects a home nursing vendor for multiple global sites where would the investigator be responsible for their selection?	Could clarity been provided for this paragraph as it is unclear how this could work. This is confusing to us with respect to implementation.
Fergus Sweeney	468	468	2.3.2	people with a task of detail only need information in that context	"…and are adequately informed, as required for the activities they undertake, about the protocol…"
Good Clinical Trials Collaborative, on behalf of supporting organisations	468	468	Investigator (2.3.2)	A person to whom an Investigator has delegated a specific activity may not need to know the full details of the protocol in order to perform their role. (E.g. the full details of the sample size calculation and statistical analysis plan are not relevant to somebody tasked with performing imaging studies or collecting blood samples.)	Change to "adequately informed about relevant aspects of the protocol…".
AFI	472	472	2.3.2	To make the text more precise, please see the proposed change	include "even though" that go beyond their usual training and experience
Alexander Wolff, LAVG Brandenburg, Germany	473	473	2.3.2	Definition of the Training-Log: Documentation of specific training for clinical trial staff to whom specific tasks have been delegated by the investigator is essential. Therefore, the following text passage has been supplemented at the mentioned position.	These specific trainings must be documented in a training log, signed by the investigator.
Association for Clinical Data Management (ACDM)	474	478	2.3.3	This aligns with training principles for non-site staff and participants in both FDA draft guidance on DHT and Decentralized Clinical Trials	No Action
Alexander Wolff, LAVG Brandenburg, Germany	475	475	2.3.3	Expanded definition of the Delegation-Log: This expanded definition of the delegation log is important to ensure that not only the delegation of significant study-specific activities is documented, as described in the current version, but all study-specific activities.	… the investigator has delegated any trial-related activities. …
Ipsen	475	477	2.3.3	"In situations where the clinical trial activities are performed in accordance with routine clinical care, delegation documentation may not be required." Routine medical care could be extensive and specific to a specialist physician. Or is Routine Clinical Care only applicable to care like vitals signs. May need to define what is meant by routine clinical care.	
Unicancer	477		2.3.3	The investigator should ensure a record is maintained of the persons and parties to whom the investigator has delegated significant trial-related activities. Please precise that investigational site shoud use the forms provided by the sponsors.	Add 'investigational site shoud use the forms provided by the sponsors or the format of this recording should be agreed with the sponsor'
Society for Clinical Research Sites	479	480	2.3.4	This statement seems ambiguous. Does it mean the agreements must be in writing, or that there be other documentation in addition to the written agreement? If the latter, is it the mere existence of the agreement or the details of the agreement?	We recommend that since there will almost always be a written agreement, the documentation should be limited to the maintenance of the written agreement only, and not any subsequent additive documentation requirements.
Association for Clinical Data Management (ACDM)	481	483	2.3.5	Who will be authorized to approve systems access for service providers? Is this the investigator, the sponsor or the CRA acting for the site?	Please provide clarity on permitting access to perform monitoring and auditing of site specific systems.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Beate Kern, Department of Health Brandenburg, Germany	482	483	2.3.5	I would welcome the following addition to the activities of the GCP inspectors: The activities of GCP inspectors are an important element in protecting the rights, safety and welfare of participants and in ensuring the reliability of quality and integrity of the trial data and results.	Addition of a second sentence to the section: The activities of GCP inspectors are an important element in protecting the rights, safety and welfare of participants and in ensuring the reliability of quality and integrity of the trial data and results.
EFPIA Consolidated Comments	482	483	2.3.5	Original text: "The investigator/institution should permit monitoring and auditing by the sponsor and inspection by the appropriate regulatory authority(ies)." EFPIA recommends clarifying that investigator cannot refuse to allow monitors/auditors to conduct these activities onsite where that is commensurate to the trial design. This is currently an issue being seen, particularly in US sites, where they are denying access to the monitors. In some countries (ex: Taiwan) , IRB/IEC is conducting an audit and IRB review is mentioned in 2.8.11 (n) & 3.6.3 (d) &3.16.4.	The investigator/institution should permit monitoring and auditing by the sponsor, review by the IRB/IEC and inspection by the appropriate regulatory authority(ies). This may be onsite, remote or a combination of both, in-line with the sponsors risk-based monitoring/audit strategy and the regulatory authority(ies) requirements.
Society for Clinical Research Sites	485	486	2.4.1		We recommend that this be expanded to: "…made by the investigator/institution, sponsor, or other entity in accordance with applicable regulatory requirements" to reflect emerging efficiencies being built in certain regions (e.g. European Union's Clinical Trials Information System (CTIS)).
AFI	486	486	2.4.1	To avoid misunderstanding, please see the proposed change	Remove "in accordance with relevant regulatory requirements" or clarify what is meant by "regulatory requirements".
CARVALHO Carla	488	491	2.4.2	The same should applies in case of substantial amendment.	Before initiating a trial, the investigator/institution should have a documented and dated approval/favourable opinion from the IRB/IEC for the trial protocol, informed consent material, participant recruitment procedures (e.g., advertisements) and any other information to be provided to participants. Before implementing a sustantial amendment, a trial, the investigator/institution should have a documented and dated approval/favourable opinion from the IRB/IEC for the concerned documents substantially amended unless such amendment is to eliminate an immediate hazard(s) to trial participants.
Ludger Wienbrede	488	491		"Before initiating a trial, the investigator/institution should have a documented and dated approval/favourable opinion from the IRB/IEC for the trial protocol, informed consent material, participant recruitment procedures (e.g., advertisements) and any other information to be provided to participants." Section 1.1. lists more documents and information that are reviewed and approved by the ethics committee. Why does section 2.4.2 limit the list to the protocol and patient facing material?	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Quotient Sciences	488	491	2.4.2	The requirement for ethical approval of 'informed consent material, participant recruitment procedures (e.g., advertisements) and any other information to be provided to participants' should be clarified - it should apply to written information or information delivered via audio/visual systems (e.g. videos) that is participant-facing (e.g. instructions for urine collections, house rules, diary card, health questionnaires).	Please edit as follows: 2.4.2 Before initiating a trial, the investigator/institution should have a documented and dated approval/favourable opinion from the IRB/IEC for the trial protocol, informed consent material, participant recruitment procedures (e.g., advertisements) and any other participant-facing written information or information to be delivered to participants via audio/visual systems to be provided to participants.
Society for Clinical Research Sites	488	491	2.4.2		As referenced in Annex Item 1.1.2(d), we believe instead of "any other information" should be limited to "informed consent materials" as there are many routine forms and information sheets that are necessary that are independent of the study. The term "informed consent materials" is used in other sections of this draft guidance (e.g. Annex I Items 2.8.2, 2.8.11, 2.8.12, 3.13.1 and Appendix C's Table 2) for similar purposes
AFI	495	495	2.4.3	To be more precise and avoid misunderstanding, please see the proposed change	remove "brochure" from this sentence: "...or basic product information brochure should be provided".
EFPIA Consolidated Comments	495	495	2.4.3	The Draft Guideline states: "As part of the investigator's/institution's or sponsor's …submission to the IRB/IEC, a current copy of the Investigator's Brochure or basic product information brochure…" *Brochure* is not typical language in this context, document may be more suitable. Changed in line with rest of document.	Proposed change: "As part of the investigator's/institution's or sponsor's …submission to the IRB/IEC, a current copy of the Investigator's Brochure or basic product information brochure....
GQMA	496	498	III.2.4.3	If an updated Investigator brochure is to be submitted to the IEC, also any updates of basic product information brochure should be submitted.	Change to: "If the Investigator's Brochure or basic product information brochure is updated during the trial, the IRB/IEC should receive the current version in accordance with applicable regulatory requirements."
AFI	500	502	2.4.4	As the trial progresses, the investigator/institution or sponsor should provide any updates to the participant information according to applicable regulatory requirements.	Please clarify this requirements and remove the sentence "according to applicable regulatory requirements"
Quotient Sciences	500	502	2.4.4	The wording could be improved.	Please edit as follows: 2.4.4 As the trial progresses, the investigator/institution or sponsor should provide to the IRB/IEC any updates to the participant information according to applicable regulatory requirements.
Quotient Sciences	504	506	2.4.5	Requirements for periodic reporting to the REC are sometimes contained in local guidance rather than law.	Please add text in bold: The investigator or the sponsor should submit documented summaries of the trial status to the IRB/IEC in accordance with local regulatory requirements or local guidance or upon request.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Quotient Sciences	508	510	2.4.6	The word 'about' should be deleted.	Delete 'about' from line 509. The investigator or the sponsor should promptly communicate to the IRB/IEC (see section 1.3.8) and, where applicable, the institution about any changes significantly affecting the conduct of the trial and/or increasing the risk to participants.
Beate Kern, Department of Health Brandenburg, Germany	510		2.4	Appending a section: Documents and materials approved by the Ethics Committee must be forwarded without delay to the investigators/trial sites, participants and other parties involved.	Appending a section: Documents and materials approved by the Ethics Committee must be forwarded without delay to the investigators/trial sites, participants and other parties involved.
CARVALHO Carla	512	514	2.5.1	In some countries, it's mandatory that the investigator's coordinator/principal Investigator signs the protocol before the submission to the IRB/IEC. In order tp ensure that the protocol signed by the Investigator is the IRB/IEC Approved protocol, a proposed changed is suggested.	The investigator should comply with the IRB/IEC's approved protocol and GCP and applicable regulatory requirements. The investigator/institution should sign the protocol or an alternative contract to confirm agreement with the sponsor.
EFPIA Consolidated Comments	512	514	2.5.1	too many ands. Per GCP R3 section "2.5.1 PI should sign protocol or alternate agreement". - Sites may end up considering signed protocol signature page as not mandatory, since they signed agreement. Also required by E3. Glossary also indicates that the protocol may form the basis of an agreement.	The investigator should comply with the protocol, and GCP and applicable regulatory requirements. The investigator/institution should sign the protocol , or an alternative contract to confirm agreement with the sponsor.
AFI	513	514	2.5.1	"...or an alternative contract to confirm agreement with the sponsor".	please clarify "an alternative contract"
Association for Clinical Data Management (ACDM)	515	518	2.5.2	Should investigator REVIEW deviations communicated to them by sponsor? That means any deviation across the study? For important deviations, the investigator may not be able to address all issues, if the deviation is for example system related. Section 3.9.3 = sponsor should determine the criteria for classifying protocol deviations (particularly those that impact rights, safety and well being of participants and reliability of results). This paragraph is confusing.	Please clarify investigator role for deviations at other sites. Is this to inform the investigator - particularly is protocol was not followed correctly?
Beate Kern, Department of Health Brandenburg, Germany	515	518	2.5.2	The investigators/trial sites shall have a list of all deviations (categorized) to show it to GCP-inspectors	The investigators/trial sites shall have a list of all deviations (categorized) to show it to GCP-inspectors
Dr. C. Wilsher	515	518	2.5.2	ICH E6 R2 4.5.3 says the investigator or person designated by the investigator". So it looks like it is only the "investigator" and not a "sub-investigator". Also says "Review" therefore needs documenting this review Why only from sponsor?? Deviations could arise at site as well.	The investigator should document all protocol deviations and review deviations communicated to them by the site staff and/or the sponsor. For important deviations, the investigator should explain the deviation and implement appropriate measures to prevent a recurrence, where applicable, see section 3.9.3.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA Consolidated Comments	515	518	2.5.2	Guideline notes for important deviations, the investigator should explain the deviation and implement appropriate measures to prevent a recurrence but does not take into account the need to assess the impact of the devation. Suggest to align with sponsor section regarding how 'important' is defined regarding protocol deviations. The written expectations around documentation of review of protocol deviations is unclear, so it would be useful to have training on this aspect. Training to ensure the investigators are made aware of important deviations in good time. What happens when the deviation is only recently been indicated as important.	The investigator should document all protocol deviations which they become aware of. In addition, the investigator should and review deviations communicated to them by the sponsor. For important deviations, as defined by the Sponsor according to Section 3.9.3, the investigator should explain the deviation and implement appropriate measures to prevent a recurrence, where applicable, see section 3.9.3.
Fergus Sweeney	515	515	2.5.2	absolutes drive a disproportionate recording of detail. "All" is unecessary and disproportionate.	"..document protocol deviations…"
Mandy Jackson National Clinical Trials Office Quality Working Group Ireland	515	518	2.5 Compliance with protocol	Is determination of Important deviations by Investigator based on criteria supplied by Sponsor per 3.9.3	
Medicines for Europe	515	518	2.5.2	We suggest the text to be supplemented with more precise information regarding investigator/institution's obligation when deviations occur.	The investigator should document all protocol deviations, inform sponsor about any significant deviation and review deviations communicated to them by the sponsor. For important deviations, the investigator should explain the deviation, investigate the root cause and implement appropriate measures to prevent a recurrence, where applicable, see section 3.9.3.
Society for Clinical Research Sites	515	518	2.5.2	This section, being prior to Section 3.9.3 where this is better described, leads to an initial uncertainty on what is an "important deviation" as opposed to a deviation that is not an "important deviation".	We encourage clearly defining this term in the Glossary. More importantly, this item and other items that reference this term (i.e. Annex I Items 3.9.3, 3.10.1.6 and 3.11.4.5.1(b)) do not delineate who is responsible for making the determination of whether a deviation is an "important deviation".
Unicancer	515		2.5.2	The investigator should document all protocol deviations and review deviations communicated to them by the sponsor. Do you mean that sponsor should provide a specific form to document the review by the investigator?	Add : 'on terms agreed with the sponsor'
EUCROF	516	516	III. 2.5.2	"For important deviations, the investigator should explain the deviation" A definition for "important deviations" would be helpful. Those which have an impact on participants' safety and/or data robustness? Major deviations?	
Quotient Sciences	516	516	2.5.2	For clarity, please clarify that this section refers to important *protocol* deviations, as *important deviations* from acceptable ranges are referred to elsewhere.	Please add bold text: 2.5.2 The investigator should document all protocol deviations and review protocol deviations communicated to them by the sponsor. For important protocol deviations, the investigator should explain the deviation and implement appropriate measures to prevent a recurrence, where applicable, see section 3.9.3.
Good Clinical Trials Collaborative, on behalf of supporting organisations	517	518	Investigator (2.5.2)	As per Principle 6 (6.3), include purpose and goals of such strategies.	insertion "implement appropriate measures to *address the impact (e.g. on participant safety) and* prevent a recurrence…"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Dr. C. Wilsher	520	523	2.5.3	"In case of deviations undertaken 521 to eliminate immediate hazard to trial participants, the investigator should inform the 522 sponsor, IRB/IEC and/or regulatory authorities promptly". R3 says "promptly" but R2 .4.5.4 says "as soon as possible" . What is the definition of promptly (nothing in Glossary)?	
Society for Clinical Research Sites	520	523	2.5.3		We request that the investigator's obligations herein be limited to the deviations that they, their institution or their subcontractors initiated. When third parties contracted by the sponsor initiate these deviations, it should be their responsibility to report them to both the sponsor and the investigator.
EFPIA Consolidated Comments	521	523	2.5.3	Repetition with 2.5.4, so made it clearer that this was the investigator reporting to the sponsor and then 2.5.4 is the reporting to IRB/IEC and Regulatory Authorities.	In case of deviations undertaken to eliminate immediate hazard to trial participants, the investigator should inform the sponsor, IRB/IEC and/or regulatory authorities promptly.
DGPharMed e. V. (Deutsche Gesellschaft für Pharmazeutische Medizin)	522	523	III.2.5.3	The listed reporting liabilities posed on the investigator are a major change in the way of reporting. Actually, the reporting liabilities to the IEC lie with the sponsor who is informed by the investigator via supplied standard tools and reporting channels. Moreover, actual EU legislation does not stipulate a direct reporting obligation of investigators to the IEC. Furthermore, it is technically not implemented in CTIS. That obligation causes an unnecessary additional workload to investigators with no additional safety for trial participants. E.g. Chapters 2.4.5 / 2.6.2 / 2.6.3 open the possibility that the sponsor might send information to the IEC "according local regulatory requirements" / "in accordance with applicable regulatory requirements"; that is a possible solution to this obligation, too.	The investigator shall inform the sponsor. The responsibility to inform the IEC and/or regulatory authority shall lie with the sponsor.
EUCROF	522	523	III. 2.5.3	The phrase "as applicable per local regulatory requirements" should be added at the end of the sentence, as in some countries the investigator may not be the person to submit to authorities but the sponsor	"… the investigator should inform the sponsor, IRB/IEC and/or regulatory authorities promplty, as applicable per local regulatory requirements".
Ollie Östlund	523	523	III.2.5.2	Unclear what the and/or refers to. Sponsor and (IEC or regulator), sponsor and/or IEC and/or regulator?	
DGPharMed e. V. (Deutsche Gesellschaft für Pharmazeutische Medizin)	525	526	III.2.5.4	The listed reporting liabilities posed on the investigator are a major change in the way of reporting. Actually, the reporting liabilities to the IEC lie with the sponsor who is informed by the investigator via supplied standard tools and reporting channels. Moreover, actual EU legislation does not stipulate a direct reporting obligation of investigators to the IEC. Furthermore, it is technically not implemented in CTIS. That obligation causes an unnecessary additional workload to investigators with no additional safety for trial participants. E.g. Chapters 2.4.5 / 2.6.2 / 2.6.3 open the possibility that the sponsor might send information to the IEC "according local regulatory requirements" / "in accordance with applicable regulatory requirements"; that is a possible solution to this obligation, too.	The investigator shall inform the sponsor. The responsibility to inform the IEC and/or regulatory authority shall lie with the sponsor.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA Consolidated Comments	525	527	2.5.4	States that the investigator should report on a protocol amendment to the IRB/IEC and/or regulatory authorities. Propose to add something in training to also clarify that the reporting to the IRB/IEC could also be done by the sponsor.	The investigator/institution or sponsor (in accordance with applicable regulatory requriements) should report information on the immediate hazard, the implemented change and the subsequent proposed protocol amendment to the IRB/IEC and/or regulatory authorities.
EUCROF	525	527	III. 2.5.4	"The investigator should report information on the immediate hazard, the implemented change and the subsequent proposed protocol amendment to the IRB/IEC and/or regulatory authorities." "or sponsor, as applicable," should be added	The investigator or sponsor, as applicable, should report information on the immediate hazard, the implemented change and the subsequent proposed protocol amendment to the IRB/IEC and/or regulatory authorities.
Fergus Sweeney	525	525	2.5.4	it may not be the investigator who is reporting to the IRB/IEC in a given jurisdiction and sponsor may be acting for multiple sites in addressing an immediate hazard	"The investigator or sponsor…"
Ludger Wienbrede	525	527		"The investigator should report information on the immediate hazard, the implemented change and the subsequent proposed protocol amendment to the IRB/IEC and/or regulatory authorities." This should read, like elsewhere: "The investigator or sponsor should report ..."	
Medicines for Europe	525	527	2.5.4	The paragraph seems to refer to immediate hazard situations described in chapter 2.5.3, therefore 2.5.3 and 2.5.4 should be combined into one paragraph.	
Society for Clinical Research Sites	525	527	2.5.4		We do not believe that any and every immediate hazard will require implementing changes or a change to the whole protocol. We thus request that this section be rewritten as "*The investigator should report information on any immediate hazards, the implemented change (if any) and any proposed protocol amendment to the IRB/IEC (as required by applicable regulations and IRB/IEC policy) and/or regulatory authorities as required by applicable regulations .*"
The GCP Unit at Odense University Hospital, OPEN	525	525	2.5.4	Some countries allow sponsor to communicate with IRB/IEC	The investigator or sponsor should report... (as 2.4.4., 2.4.5., 2.4.6)
AFI	527	527	2.5.3	Add ”and to the Sponsor”	
EUCROF	529	531	III. 2.6.1	"… should assure appropriate therapy and follow-up for the participants" reference to the protocol should be included, also to remind the sponsor to specify the follow-up in the protocol.	… should assure appropriate therapy and follow-up for the participants in accordance with the protocol.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Mithra Pharmaceuticlas SA PV	529	531	2.6	add responsibilities regarding aggregate reporting for trials where sponsor has terminated the trial but where there are still patients in long-term safety follow-up	
Society for Clinical Research Sites	529	531	2.6.1		The word “assure” is an unattainable expectation and that “refer to” is more realistic. We do not believe it is the intent to make the investigator a guarantor of the health payments.
EFPIA Consolidated Comments	531	531	III 2.6.1	Consider replacing therapy with treatment options as there could be a possibility for no therapy for the participant. Suggest reordering, so this becomes 2.6.4 as this is a more sequential scenario.	If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial participants and should assure appropriate treatment options and follow-up for the participants
EFPIA Consolidated Comments	533	536	2.6.2	States that the investigator should inform the IRB/IEC and the regulatory authorities if they terminate or suspend their involvement in a trial.	Where the investigator terminates or suspends their involvement in a trial without prior agreement by the sponsor, the investigator should promptly inform the sponsor. should then inform The IRB/IEC and the regulatory authorities should be informed by the responsible party in accordance with applicable regulatory requirements and should provide a detailed explanation of the reasons.
Medicines for Europe	538	540	2.6.3	If the sponsor terminates or suspends a trial, the first step should be notification of the investigator/institution which is currently not described.	If the sponsor terminates or suspends a trial, the sponsor should promptly inform the investigator, …
DGPharMed e. V. (Deutsche Gesellschaft für Pharmazeutische Medizin)	542	544	III.2.6.4	EC communication is usually transferred to sponsor; add forwarding of notifications also to sponsor responsibilities	EC shall communicate directly with the sponsor
EFPIA Consolidated Comments	542	544	2.6.4	This is more for the IRB, so should be included there under 1.3.9 d	If the IRB/IEC terminates or suspends its approval/favourable opinion of a trial (see 542 sections 1.1.3 and 1.3.9), the investigator should inform the institution, where applicable, and the investigator/institution should promptly notify the sponsor.
EUCROF	542	542	III. 2.6.4	The wording "IRB/IEC terminates or suspends its approval/favourable opinion of a trial" should be supplemented. In some ICH regions only the regulatory authorities can suspend a trial (e.g. FDA hold or MSC revocation of the authorization). Update the wording to clearly specify that clinical trials can (also) be terminated/suspended by regulatory authorities	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
IFCT	542	544	2.6.4	in France : IEC are in link with sponsor, not directly with investigtors	the sponsor should inform the investigator
Quotient Sciences	542	544	2.6.4	This section assumes that the ethics committee will inform only the investigator of suspension of a favourable opinion, and that the investigator/institution will be responsible for informing the sponsor. However, sponsors can submit applications to RECs in the EU and UK. Also, in the UK, RECs cannot suspend or terminate a CTA: only the regulatory authority has the authority to do that.	Please edit as follows: If the IRB/IEC wishes to terminates or suspends its approval/favourable opinion of a trial (see sections 1.1.3 and 1.3.9), the IRB/IEC should notify the regulatory authority, sponsor and/or investigator in accordance with local regulatory requirements. should inform the institution, where applicable, and the investigator/institution should promptly notify the sponsor Upon notification that approval/favourable opinion of a trial has been suspended, sponsors and investigators should promptly ensure that all relevant parties are informed (all sponsors, all investigators/institutions and all service providers).
The GCP Unit at Odense University Hospital, OPEN	542	544	2.6.4	Relevant when only investigator communicate with IRB/IEC. But in EU sponsor is often the only part communication to IEC trough CTIS. Is rephrasing possible?	Is rephrasing possible?
EFPIA Consolidated Comments	547	550	2.7.1(a)	Revert to the original wording with the exception of adding the other HCPs, which is welcomed. How can the sub investigator have overall responsibility.	A qualified physician or, where appropriate, a qualified dentist (or other qualified healthcare professionals in accordance with local regulatory requirements) who is an investigator or a sub-investigator for the trial should be responsible have the overall responsibility for trial-related medical care and decisions.
GQMA	547	550	III.2.7.1 a	The wording used in this section would allow for a sub-investigator to assume overall responsibility (even if the principal investigator is a qualified physician). It is unclear how this corresponds to section III.2.3.1 stating that the (principal) investigator retains ultimate responsibility. The difference between 'ultimate' and 'overall' is not clear and not defined.	Clarify the difference between 'overall' responsibility in section III.2.7.1 and 'ultimate' responsibility in section III.2.3.1.
Society for Clinical Research Sites	547	550	2.7.1		As written, this section is unclear as it seems to confuse the roles and authority of principal investigator and sub-investigator. Because this concept is seemingly adequately addressed in Principle 1.5, this section should either (i) be eliminated, (ii) incorporate Principle 1.5 by reference or (iii) be rewritten using the same verbiage as Principle 1.5.
The GCP Unit at Odense University Hospital, OPEN	549	549	2.7.1.a	Why is "or a sub-investigator" mentioned? Only one person (PI) can have the overall responsibility	…who is an investigator for the trial…
Quotient Sciences	552	554	2.7.1 (b)	This section says that appropriately qualified healthcare professionals may be involved in the medical care of trial participants. In a phase 1 setting, clinical trials technicians/associates may be involved in the medical care of trials participants. They are typically life science graduates who have been trained in clinical procedures. Technicians/Associates are not registered healthcare professionals, but are appropriately qualified and experienced to do clinical procedures, such as monitoring blood pressure and recording ECGs. Please clarify that phase 1 clinical trial staff such as Technicians/Associates who are not registered healthcare professionals may be involved in the medical care of trials participants.	Please edit as follows: (b) Other appropriately qualified healthcare professionals, or other appropriately trained staff (e.g., clinical technicians), may be involved in the medical care of trial participants, in line with their normal activities and in accordance with local regulatory requirements.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUCROF	553	553	III. 2.7.1	"Other appropriately qualified healthcare professionals may be involved in the medical care of trial participants, in line with their normal activities and in accordance with local regulatory requirements." Clinical trial activities might not be in line with "normal activities" - there is room for misunderstanding.	Other appropriately qualified healthcare professionals may be involved in the medical care of trial participants, in line with their qualification and in accordance with local regulatory requirements.
Quotient Sciences	556	556	2.7.1 (c)	Clarity of sentence needs to be improved.	Please add text in bold: (c) During and following a participant's participation in a trial, the investigator/institution should ensure that adequate medical care….
Society for Clinical Research Sites	556	560	2.7.1		As in Annex I Item 2.6.1 We believe the word "ensure" is an unattainable expectation and that "refer to" or "assist in the coordination of" is more realistic. We do not believe it is the intent to make the investigator a guarantor of the health payments.
Fergus Sweeney	557	557	2.7.1.c	Not every adverse event will need care or treatment. Absolutes are not needed, any should be deleted	". To a participant for adverse events…"
Good Clinical Trials Collaborative, on behalf of supporting organisations	562	564	Investigator (2.7.1.d)	The term 'primary physician' is both not well defined and not applicable or relevant in many settings.	Amend to: "The investigator should inform those responsible for the participant's routine clinical care about the participant's involvement in the trial, where relevant, if the participant agrees to this information being shared."
Matthias Lenk	562	564	2.7.1 (d)	Many trial participant do not have a primary physician and the need to formally inform the primary physician seems disproportionate to the risks a trial participant is taking when participating in a study with complete medical monitoring. It is also unclear how the information shall be be documented, whether a confirmation of receipt is required, what the consequences are if a participant does not have a primary physician or does not agree for their physician to be informed. Keeping this requirement in will have a dramatic effect on the effort for study sites in recruiting trial subjects.	Remove complete section (d). If the section is left in, be clear that a participant may still take part in a study even if they do not have a primary physician or do not agree to them being informed. Alternatively, make it mandatory for the investigator to instruct prospective trial participants that they should inform their primary or any other physician they visit about their participation in a study as part of the Informed Consent process
Medicines for Europe	562	564	2.7.1 d)	This may not be relevant for trials performed in healthy subjects (for example, PK studies). Further elaboration in the repsonsibility of the investigators communication with the participant primary physician is needed. For example, should the investigator collects the contact information (e.g. name, email address, phone number, etc.) of participant's primary physician via participant, and should the contact information should be documented in the source records?	(d) For trials performed in patients, the investigator should is recommended to inform the participant's primary physician about the participant's involvement in the trial if the participant has a primary physician and agrees to the primary physician being informed. Patient's agreement and mode of communication with primary physician (e.g. archived e-mail) should be recorded.
The GCP Unit at Odense University Hospital, OPEN	562	564	2.7.1.d	Should only be in place if it is relevant for the primay physician to know abot the participation.	The investigator should - if relevant for the patients treatment at primary physician - inform the….

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Fergus Sweeney	565	565	2.7.2	Safety reporting is not a subsection of Participant Care and should be a section in its own right	"2.8 Safety reporting"
Good Clinical Trials Collaborative, on behalf of supporting organisations	565	585	Investigator (2.72)	It may be helpful, in the relevant sections, to present the glossary definition within the main text to support consistent and proportionate interpretation i.e. Adverse Event (AE) and Serious Adverse Event (SAE) within section 2.7.2, and Adverse Drug Reaction (ADR) and the specific definitions of i) suspected, ii) unexpected, and iii) serious, as derived from the entry for Suspected Unexpected Serious Adverse Reaction (SUSAR) within 3.13.2.	Incorporate glossary definition of AEs and SAEs into section 2.7.2.
Mithra Pharmaceuticlas SA PV	565	568	2.7.2	more emphasis on significance of AE/SAE since many sonsors require reporting as from ICF signature but events occurring prior to study drug administration are not AEs/ SAEs as per definition.	
EFPIA Consolidated Comments	566	568	2.7.2 a Safety Reporting	"Adverse events and/or laboratory abnormalities.." What about measurements collected via digital health and innovation? For example, a patient responds to a structured set of questions in an electronic application	"Adverse events, including those from digital health tools, and/or laboratory abnormalities required for safety evaluations (as outlined in the protocol) should be reported to…"
EUCROF	566	568	III. 2.7.2	Adverse events and /or laboratory abnormalities required for safety evaluations (as outlined in the protocol) should be reported to the sposnor according to the reporting requirements….	Adverse events and abnormalities in laboratoy assessments which are required for safety evaluations (as outlined in the protocol) should be reported to the sposnor according to the reporting requirement….
Mattia Calissano	566	585	2.7.2	Although likely defined in the protocols, it would be usefull for the investigator to be reminded of the importance to provide causality assessment with the IMP when reporting an SAE	Although likely defined in the protoocls, it would be usefull for the investigator to be reminded of the importance to provide causality assessment with the IMP when reporting an SAE.
Mattia Calissano	566	585	2.7.3	As per updated clinical trial regulation, it would be useful to have a sentence related to the use of auxilliary medicines and the need to capture related-safety events. It can be a short statement with a link to the new regulation.	As per updated clinical trial regulation, it would be useful to have a sentence related to the use of auxilliary medicines and the need to capture related-safety events. It can be a short statement with a link to the new regulation.
EFPIA Consolidated Comments	570	575	2.7.2 (b)	The wording in brackets is unclear and confusing as only the investigator is mentioned but not the site staff involved in the study. What should we understand by "after the investigator reasonably becomes aware of the event"? This can be confusing since reasonably can have multiple interpretations/understanding. Better to remove "Reasonably. Using deaths as an example here seems unnecessary.	All serious adverse events (SAEs) should be reported immediately (after the investigator, or delegated staff reasonably becomes aware of the event) to the sponsor. .....SAEs not requiring immediate reporting, for example, deaths or other events that are endpoints
Ipsen	570	571	2.7.2b	All serious adverse events (SAEs) should be reported immediately (after the investigator reasonably becomes aware of the event) to the sponsor : remove the term "reasonably" to avoid possible misinterpretation due to different language meaning	All serious adverse events (SAEs) should be reported immediately (after the investigator becomes aware of the event) to the sponsor

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
PPD	570	571	2.7 Participant Medical Care and Safety Reporting	Responsibility of reporting of SAEs should fall under all staff with such delegated responsibility. Is "immediately" a feasible request? Would alternative language be more appropriate (i.e., within 24 hours or as soon as possible)?	All serious adverse events (SAEs) should be reported immediately (after the investigator and/or delegated site staff reasonably becomes aware of the event) to the sponsor.
SHIONOGI	570	576	2.7.2(b)	There is currently only mentioned that all SAEs should be reported immediately to the sponsor, but there is no-where any requirement for immediate SUSAR reporting. Suggest to add.	Please add the requirement for immediate SUSAR reporting by the investigator to the sponsor
Society for Clinical Research Sites	570	575	2.7.2		We recommend "immediately" be changed to "promptly" as the immediate concern of the investigator is the well-being of the participant, not the reporting which can be done promptly after the immediate concern is addressed.
Unicancer	570		2.7.2	All serious adverse events (SAEs) should be reported immediately	immedialety and no later than 24h
EUCROF	571	571	III. 2.7.2 (b)	"All serious adverse events (SAEs) should be reported immediately (after the investigator reasonably becomes aware of the event) to the sponsor." What does "reasonably becomes aware" mean? The investigator either becomes aware or not.	"All serious adverse events (SAEs) should be reported immediately (after the investigator reasonably becomes aware of the event) to the sponsor according to the reporting requirements specified in the protocol."
Ollie Östlund	571	575	III.2.7.2	More explicit guidance on proportionate SAE reporting would be welcome: In comparative effectiveness trials in the very elderly, for example, there will be lots of "routine" hospitalisations and deaths. Regulators have a history of being maximalist in reporting requirements in such situations, which can make important research unfeasible.	
PPD	571	574	2.7 Participant Medical Care and Safety Reporting	We generally consider death to be an outcome, so it wouldn't be recorded as an event term on the AE form.	In accordance with applicable regulatory requirements, the protocol may identify SAEs not requiring immediate reporting, for example, events leading to deaths or other events
EUCROF	574	574	III. 2.7.2 (b)	"… that are endpoints." There might be a process to identify whether an event qualifies as endpoint or not. The word "qualify" expresses this process better than "that are endpoints".	… that qualify as endpoints.
CARVALHO Carla	577	580	2.7.2.c	Submission of the copy of an autopsy report or a death report (ie., copy of the source documents) to the sponsor should be authorized by the patient and this should be clearly indicated in the informed document provided to the patient during the initial informed consent process.	For reported deaths, the investigator should supply the sponsor, the IRB/IEC and, where applicable and authorized by the trial participant, the regulatory authority with any additional requested information (e.g., autopsy reports and terminal medical reports) when they become available.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
GQMA	577	580	III.2.7.2 c	Sending of medical records to external parties other than monitoring, even if pseudonymised, is source of data breaches and potentially not described in the informed consent form.	Change to: "For reported deaths, the investigator should supply the sponsor, the IRB/IEC and, where applicable, the regulatory authority with any additional requested information (e.g., autopsy reports and terminal medical reports) when they become available and if this proceeding is covered by the informed consent and applicable regulations."
Quotient Sciences	577	580	2.7.2 (c)	In line 577, 'reported' could refer to events reported by the investigator to the sponsor or events reported to the IRB/IEC and regulatory authority.	Please edit as follows: For reported deaths deaths reported to the IRB/IEC and, where applicable, the regulatory authority, the investigator should supply the sponsor, the IRB/IEC and, where applicable, the regulatory authority with any additional requested information (e.g., autopsy reports and terminal medical reports) when they become available.
Society for Clinical Research Sites	577	580	2.7.2		We recommend that in addition to "…when they become available" to also include "…and as permissible by law and the consent of the participant or their next of kin" to reflect the possibilities that there may be restrictions on such disclosures, especially if there is pending litigation resulting from the death.
CARVALHO Carla	582	285	2.7.2.d	The information related to the safety event and reported to the sponsor should have been reviewed firstly by a qualified medical staff. As an example, the relationship between the event and the product reported should have been assessed by a qualified medical staff.	The investigator may delegate activities for safety reporting to qualified investigator site staff but retains the overall responsibility for safety of participants under their responsibility and compliance with the reporting requirements (ie., relationship between the event and the investigational product should have been assessed by an investigator before reporting to the sponsor).
EUCROF	582	585	III. 2.7.2 (d)	The investigator may delegate activities for safety reporting to qualified investigator site staff but retains the overall responsibility for safety of participants under their responsibility and compliance with the reporting requirements. This sentence is difficult to understand.	The investigator may delegate activities for safety reporting to qualified investigator site staff but retains the overall responsibility for safety of participants under their responsibility and compliance with the and respective reporting requirements.
Jazz Pharmaceuticals	586	774	III.2.8	As patient centricity is rightly elevated in the revision, in the ICF, perhaps there should be language around "patient assistance" such as transportation etc during the trial. Its not clear whether this would be a new section or an addition to an existing section, but perhaps around other sections addressing patient needs such as sections 2.7 or 2.8.	
Ollie Östlund	586	774	III.2.8	The ICH demands concerning informed consent documentation are both unnecessarily inflexible in a way that is not in line with a fit for purpose quality approach, and simplistic. Issues include:	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Ollie Östlund	586	774	III.2.8	· Conflating different informed consents as one concept. In a clinical trial, consent may be given for interventions, measurements/assessments, access to data, and data processing. Conflating these is a root cause of a persistent problem in clinical trial conduct, the "withdrawal" concept, which confounds non-adherence with discontinuation of data collection. In the EU, data processing is usually not based on informed consent, but in some cases access to data may be. When data is collected from public sources or sources where consent to access for research already has been given in a different setting, consent does not cover data collection. For trials using routinely collected data for primary or enhanced follow-up, the lack of differentiation of different consents in the ICH framework does and will cause problems.	Differentiate and exemplify the informed consents appropriate in specific trials.
Ollie Östlund	586	774	III.2.8	· Conflating informed consent and informed consent *documentation* . Documentation issues - archiving a signature - are currently included in the glossary term "informed consent". As a different example, in Sweden *all* medical or health care procedures require informed consent by law, with information and consent specified in chapters 4 and 5 of the patient law, respectively. However, there is no requirement to obtain a "signed and dated informed consent form" for informed consent to have been given: That is not a consent issue, but a documentation issue. Separating these will clarify the E6 demands and their motivation.	Clearly separate the concept of informed consent from documentation of informed consent.
Ollie Östlund	586	774	III.2.8	· Unproportional demands for consent documentation not necessarily fit for purpose. This point is about the need for physical or electronic documentation of informed consent by signatures. As noted above, routine clinical care uses informed consent, and the level of documentation which is considered fit for purpose in the clinic does not include signed forms. Unproportional consent documentation demands are known to be an important hindrance for research aiming to optimise standard-of-care, such as comparative effectiveness trials. Clinical trials not involving drugs, such as trials of surgical procedures, do not necessarily demand documentation of written consent, creating double standards for similar trials only depending on whether a drug is involved. Two examples of trials stopped by such unproportional demands is the Danish DANNOAC-AF trial, which aimed to randomise which of the four marketed standard-of-care direct-acting oral anticoagulants was prescribed for patients with atrial fibrillation, and the Swedish SE-CURE trial, which aimed to provide a head-to-head comparison of the available covid-19 vaccines during the roll-out in 2021, by including randomisation in an algorithm to create efficient shipping schedules of vaccine batches to vaccination centres. Also note that the EU clinicla trials regulation allows drug trials without written consent ("article 30 trials"), which causes a mismatch between ICH and the more flexible EU law. Informed consent is an area of very active research and innovation, with "studies-within-trials" investigating the effectiveness of new approaches, such as "staged and tailored" consent, and Zelen designs may be gaining interest for pragmatic trials. Large simple trials in routine care are increasing in number, with increased availability of routinely collected data for follow-up and initiatives for learning healthcare systems. It is possible that this kind of trial-specific documentation of informed consent is motivated mainly to protect the investigator and/or sponsor, or even the regulator, from liability. This should not be the purpose of the informed consent process, as by paragraph 2.8.4, line 626-630, and does not add to quality as defined in this document. Consequently, signatures should not be a demand, but if it is, E6 must explicitly state that this only concerns trials within the official scope of the guideline, as clear guidance to regulatory authorities.	Remove the absolute demand for documentation of informed consent by signature (written or electronic). Clarify that consent procedures should be proportionate and add to quality.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Ollie Östlund	586	774	III.2.8	· Assumption that "legally acceptable representatives" can be used. In Sweden, the situation has been that only court appointed representatives are legally acceptable, which may be present for a patient with intellectual disabilities, but not for a "standard" patient in an emergency situation. On the other hand, the Swedish research ethics law allows for retroactive consent in emergency situations. It might be possible to make allowance for that legal construction, which may provide an alternative to consent by representative. Hopefully more research will be done on these consent modes.	
Association for Clinical Data Management (ACDM)	587	591	2.8.1	According to local laws applying, electronic consent is not allowed. So electronic consent is not in accordance with GDPR. - So recommendation to include "according to local laws" as it may be contradictions between this requirement and local laws.	We are not certain what the aim of the paragraph is. We are aware that some countries do not allow eConsent. If the purpose is to encourage eConsent then please write the paragraph with that emphasis. If the purpose is just to accept eConsent that add where local laws allow.
The GCP Unit at Odense University Hospital, OPEN	587	587	2.8.1	Not nessecary to write (paper or electronic format) - see line 57	Delete (paper or electronic format)
Ludger Wienbrede	590			Delete "See the glossary term "informed consent."" This is redundant. Otherwise you should add everywhere in this text where glossary terms are used "see the glossary term X".	
Ludger Wienbrede	593			Which act of trial conduct does the term "enrolling" refer to? As consenting is the ultimate prerequisite of a subect's participation in a clinical trial, one needs to assume that, here, reference is intended to be made to situations where a subject who is incapable of providing consent is exposed to trial-specific measures. Therefore, if such assumption was correct, the sentence should be rephrased to "Prior to consenting and/or enrolling participants, (...)" and a definition should be included in the ICH GCP guideline for the term "enrollment": "first act or procedure in a subject which is undertaken in the context of the clinical trial and which goes beyond or deviates from the subject's standard medical care"	
Ludger Wienbrede	593	595		"Prior to consenting and enrolling participants, the investigator should have the IRB/IEC's documented approval/favourable opinion of the informed consent materials and process": This statement should be modified to reflect that in some countries also the regulatory authority and other institutions approve the informed consent materials and process and that approval is not in all countries be obtained by the investigator. This applies also to some parts of the subsequent text.	
Association for Clinical Data Management (ACDM)	597	602	2.8.1 (b)	For future reference FDA guidance on DHT and DCT both contain recommendations for detailing clinical and privacy risks associated with using DHT and/or decentralized vendors in the consent	No Action
Beate Kern, Department of Health Brandenburg, Germany	597	602	2.8.1	One conceivable way to promote patient-friendliness is to make it mandatory to test the readability of patient information for informed consent, similar to the process of testing the readability of the package leaflet in the drug approval procedure.	It is mandatory to test the readability of patient information for informed consent

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA Consolidated Comments	597	638	2.8.1 (b)	Can item 2.8.6 be merged with 2.8.1 (b)	Identical text in 2.8.1 (b) and 2.8.6 "The information provided during the informed consent process and translations should be relevant, clear, simple, concise and understandable to the participant or the participant's legally acceptable representative and the impartial witness, where applicable".
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	599	600	III 2.8.1	Understanding is also important for the impartial witness (refer to section 2.8.6)	Suggestion: "… the trial participants or their legally acceptable representatives, or impartial witness, where applicable, have an adequate understanding of the objectives of the trial, …"
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	600	600	III 2.8.1	Trial participants should be also informed about trial procedures/treatment.	Suggestion: "...adequate understanding of the objectives of the trial, trial procedures and treatment, alternative treatments, ...". Alternatively, refer to 2.8.11 which lists all topics an informed consent should address.
Fergus Sweeney	601	601	2.8.1.b	The term "obligation" must not be used here and is unethical in concept. Participants cannot be presented as having obligations. Consent is not a contractual process. The term "responsibilities" has worked well for paritcipants in E6 to date and should continue to be used. This is a very important issue and must be corrected.	"…burdens and their rights and responsibilities…"
Medicines for Europe	603	604	2.8.1c	including' to be removed.	may be used in the informed consent process including for providing...'
IFCT	605	606	2.8.1.c	"where appropriate" : to be detailled	add "electronic signature is mandatory"
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	605	606	III 2.8.1	The conditions and requirements for obtaining informed consent remotely are not clear, more guidance is requested.	
PPD	605	606	2.8 Informed Consent of Trial Participants	There is insufficient clarity regarding how this should be undertaken. Could there be more guidance about what should be documented (e.g., proof of identity, follow up with signatures later on-site, etc.)?	Obtaining consent remotely may be considered where appropriate. All other requirements such as using concise language and helping with adequate understanding even during remote consent are expected. Where regulations allow, proof of identity should be provided either remotely or during next in person visit.
Society for Clinical Research Sites	608	621	2.8.2	Unfortunately, many people believe the only way to do this is to have consent forms fully revised and signed, but there are many other options for accomplishing this goal, especially for minor or inconsequential changes.	We agree in concept; however, we hope that the guidance can encourage less burdensome approaches to the documentation needs other than having to provide updated/revised informed consent forms for signature to participants in every instance. Unfortunately, many people believe the only way to do this is to have consent forms fully revised and signed, but there are many other options for accomplishing this goal, especially for minor or inconsequential changes. Examples may include simple written updates provided to the participants that do not require signatures.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Society of Quality Assurance (SQA)	619	619	2.8.2	From a data integrity perspective, it is important that all informed consent documents from a participant are clearly linked with each other so that there is traceability around what the participant was aware of at what period during the trial.	"....., identified in the revised informed consent materials and appropriately linked with prior informed consent materials."
Fergus Sweeney	621	621	2.8.2	The current approach to the process of reconsenting participants when new information arises, whereby the entire information sheet used at the start is re-presented with the new information or change made, but often not clear is a constant source of complaint, over work etc.. There is a need to be clear that in such case only the essentail new items need to be presented to the participant, so often a simple paragraph is all that is required. Please add text to make this clear.	Suggest as new tekst: " For a participant who has already consented teh revised informatio to support re-consent may be restricted to the new information arising and any essentail context."
Ludger Wienbrede	626	628		"None of the information provided to the participant during the informed consent process should contain any language that causes the participant or the participant's legally acceptable representative to waive or to appear to waive any legal rights, …": This is in contradiction to EU data protections laws, which deprives study participant from their right to have persoal data deleted. There are very good reasons for this provision (the scientific value of the trial is protected and the impairment of the rights of patients is minimal and acceptable). Perhaps the text should be amended with something like "except local laws permit such waivers".	
DGPharMed e. V. (Deutsche Gesellschaft für Pharmazeutische Medizin)	628	628	III.2.8.4	Not waiving any legal right will lead to conflict with GDPR's right to be forgotten. This has to be waived in ICF.	The current wording is in conflict with III.2.9.1 (line 779-781). Right to be forgotten according to GDPR has to be waived in ICF
AFI	632	634	2.8.5	The informed consent process should be conducted by the investigator or other investigator site staff delegated by the investigator, in accordance with applicable regulatory requirements	Please remove "in accordance with relevant regulatory requirements" or clarify what it is meant for regulatory requirements
EFPIA Consolidated Comments	632	636	2.8.5	recommend this state qualified since there are different rules per country and site regarding who can consent aside from the Investigator	...process should be conducted by the investigator or other qualified investigator site staff delegated..
EUCROF	638	641	III. 2.8.6	The information in this section is very similar to that in section 2.8.1 b consider to avoid duplication of content	
GQMA	638	641	III.2.8.6	Translations during the Informed Consent Process are mentioned without any further clarification, e.g., when a translation is required, what about the qualification of the translator for oral information, and whether relatives could be used.	Clarify the circumstances under which translations may be used and which quality requirements would apply.
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	638	641	III 2.8.6	Duplication with 2.8.1 b)	Can be deleted, if "impartial witness" is included in 2.8.1.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Ludger Wienbrede	638	641		"The information provided during the informed consent process and translations should be relevant, clear, simple, concise and understandable to the participant …". The ICH GCP text should reflect legal realities in a honest way. Therefore, the following should be added: "This does not apply for parts of the information that concern data pretection rights and parts or the text that is required or recommended by IRB/IECs or authorities." Information that concern data pretection rights and parts or the text that is required or recommended by IRB/IECs or authorities often tend to be not relevant, not clear, not simple, not concise and not understandable to the participant. This is the reality of the last 20 years. Sponsors and investigators cannot change this. Therefore, they should not be made responsible for it.	
Medicines for Europe	638	641	2.8.6	The information provided during the informed consent process should also be complete and accurate. 'Relevant' may cover but does not convey the importance of completeness. Accuracy is a critical step in the QC process to ensure that no important relevant information is missing	The information provided during the informed consent process and translations should be complete, relevant, clear, simple, concise, accurate and understandable
Society for Clinical Research Sites	638	641	2.8.6		It is unclear as to who is given the authority of determining the "where appropriate" standard for requiring the impartial witness. We believe the standard should instead be "where required by the protocol, the IRB/IEC, applicable regulations or, absent these requirements, at the discretion of the investigator".
Unicancer	638		2.8.6	translation	translation (if nedeed)
Unicancer	646		2.8.7	ample time is inaccurate (because it's depending of the pathology and the trial : ie : oncology).	subject can accept the participation without reflection time "ample time unless justified (e.g., in an emergency situation)". This time should be adapted to the progression of the pathology
Dr. C. Wilsher	652	656	2.8.8	To be consistent with E6 R3 Step 2 section 2.8.10 (line 674) and with ICH E6 R2 4.4.8; the word "personally" should be inserted. Otherwise, not only will it be inconsistent, but it may lead to some people saying that investigators can pre-date (or post date) the forms for the participant.	Prior to trial participation, the informed consent form should be signed and personally dated by the participant or by the participant's legally acceptable representative and, where appropriate, impartial witness and by the investigator or delegated investigator site staff who conducted the informed consent discussion. The informed consent process may involve a physical signature or an electronic signature.
EFPIA Consolidated Comments	652	656	2.8.8	The esignature date can be system generated. Local regulatory requirements proposed due to differences in territories.	The informed consent process may involve a physical signature and date, or an electronic signature and system generated date in accordance with applicable regulatory requirements.
German Pharmaceutical Industry Association (BPI)	652	656	2.8.8.	CTR and MDR requieres only physical signature for ICF	We expressly welcome the progressive nature of the R3 version in this regard and encourage these discrepancies to be resolved

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Society for Clinical Research Sites	652	656	2.8.8		It is unclear as to who is given the authority of determining the "where appropriate" standard for requiring the impartial witness. The standard should instead be "where required by the protocol, the IRB/IEC, applicable regulations or, absent these requirements, at the discretion of the investigator".
PPD	653	656	2.8 Informed Consent of Trial Participants	"…electronic signature." Are there any requirements related to this (e.g., validation, visibility of true name, etc.)?	Prior to trial participation, the informed consent form should be signed and dated by the participant or by the participant's legally acceptable representative and, where appropriate, impartial witness and by the investigator or delegated investigator site staff who conducted the informed consent discussion. The informed consent process may involve a physical signature, an electronic signature or a digital representation of signature. Also recommend defining Electronic Signature (or similar terms) in Glossary
The GCP Unit at Odense University Hospital, OPEN	654	655	2.8.8	The informed consent process consist of more than one discussion. First the oral information and handing out the written information and secondly - after the subjects consideration - answering questions and recieving the signed informed consent form. This should be described. Often two different persons (investigator or delgated) are performing the two discussions. Mus both sign the informed consent?	
Medicines for Europe	655	656	2.8.8	In certain regions the term "electronic signature" has specific legal requirements. The possibility of usiging digitised signatures should not be excluded.	The informed consent process may involve a physical signature, a digitised signature, or an electronic signature.
DGPharMed e. V. (Deutsche Gesellschaft für Pharmazeutische Medizin)	656	656	III.2.8.8	Shouldn´t it be a qualified electronic signature?	Clarify that only qualified electronic signatures are acceptable
Fergus Sweeney	666	666	2.8.9	"as appropriate" seems odd to state here, consent should be requested	reword "..as soon as possible, and consent should be requested (see section 2.8.9)
Beate Kern, Department of Health Brandenburg, Germany	669	679	2.8.10	I propose an addition to the informed consent form for participants who do not speak the local language and need a translator, analogous to participants who cannot read and have a witness with them	If participants do not speak the local language and the patient information is only available in foreign languages they do not speak, a translator should be consulted whose name and signature are documented on the consent form.
DARQA	669	679	2.8.10	Informed consent form should be signed by independent witness contemporanously (line 674-675), but this has not been mentioned as a requirement for the investigator.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
FVR-Finnish Vaccine Research	669	679	2.8.10	This section is conflicting with the section 2.8.1 c, which states that e.g., videos may be used in the informed consent process including providing information to the participant. If the video information is relevant (e.g., the information letter is read on the video), the use of impartial witness is not feasible and proportional to the risks, if the person to be recruited cannot read, but is able to date and sign him/herself. Instead, guidance to use impartial witness would be needed for the case where the person to be recruited can read and understand the information but they is not able to write (e.g., both hands put in plaster), and can thus only give an oral consent.	
GQMA	669	679	III.2.8.10	The guideline considers only subjects who cannot read but not subjects who cannot write.	A process for obtainig written informed consent by means of an impartial witness should also be defined for subjects who cannot write (i.e. who cannot provide their informed consent in writing).
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	669	671	III 2.8.10	"...an impartial witness should be present (remotely or in-person) …" Please specify, that in this case only a video call is acceptable.	
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	669	679	III 2.8.10	Participants who can read but not write should be included in this section.	
Society for Clinical Research Sites	669	679	2.8.10		We request this section include clarifications germane to situations where the impartial witness may not be local and that alternate methods of obtaining a witness attestation may be available to the institution such as documenting their concurrence on the telephone or obtaining written communications from them (i.e. email) that accomplish the same goal without the burden and risk of having to ship consent forms to varying geographies.
EUCROF	675	675	III. 2.8.10	"contemporaneously" - not sure to which extent this can work and be done in case of remote/electronic signatures when all signatures by participant, LAR, witness and investigator have to be collected literatly at the same time.	
Jazz Pharmaceuticals	681	748	III.2.8.11	Investigators should be required to provide prospective participants with a standard, one-page, plain language, trial synopsis that is easy for participants to understand. The one-page summary should include objectives of the trial, alternative treatments, potential benefits and risks, participant burdens (time, travel, lodging, meals, dollars, childcare, caregiver involvement, missed work, etc.…), participant rights, obligations, and the ensure potential participants are offered audio recordings or braille versions of the one-page document if needed	
AFI	689	690	2.8.11 (C)	the trial's investigational product(s) and the probability for random assignment to the investigational product, if applicable;	It is advisable to add "including placebo"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Fergus Sweeney	694	694	2.8.11.e	The term "obligation" must not be used here and is unethical in concept. Participants cannot be presented as having obligations. Consent is not a contractual process. The term "responsibilities" has worked well for paritcipants in E6 to date and should continue to be used. This is a very important issue and must be corrected.	reword to "the participant's responsibilities;"
EAHP	695	696	III 2.8.11	Besides risks also adverse drug reactions need to be included in point (f).	(f) the reasonably foreseeable risks, adverse drug reactions or inconveniences to the participant and, when applicable, the participant's partner, to an embryo, foetus or nursing infant;
Society for Clinical Research Sites	701	702	2.8.11	We are concerned with the use of the words "important" and "may be available". It gets responses such as "important to who?", "important when?", "routinely available or possibly available?", "actually available to this patient and their geography/socioeconomic status or theoretically available?" reflecting that each healthcare setting and each patient is unique. We do not want to simply remove the word "important" as the potential benefits and risks to alternative procedure(s) or course(s) of treatment can be voluminous.	As the disclosure of benefits and risks of routine care procedure(s) and course(s) of treatment is outside of the scope of GCPs, we recommend that this this section either be deleted or, recognizing the need to assure participants understand their totality of choices, altered to "the alternative procedure(s) or course(s) of treatment described to the participant in a manner consistent with routine care at the investigator's institution".
DGPharMed e. V. (Deutsche Gesellschaft für Pharmazeutische Medizin)	704	704	III.2.8.11	Not appropriate: Not all treatments available for any (unforeseeable) possible trial-related injury may be foreseen or to be listed completely.	Change wording to "examples of treatment available", as complete listing is impossible
Ludger Wienbrede	711	713		"that the participant's trial participation is voluntary, and the participant may refuse to participate or may withdraw, at any time, without penalty or loss of benefits to which the participant is otherwise entitled" should be supplemented as: "... and the participant may refuse to participate or may withdraw, at any time, without giving reasons, without penalty or loss of benefits ..."	
eClinical Forum	715	717	III 2.8.11(m)	This states that the informed consent should explain; (m) the process by which the participant's data will be handled, including in the event of the withdrawal of participation in accordance with regulatory requirements. This should include both the process and the location.	Revise paragraphs to state "the process by which the participant's data will be handled, including the location of the participant's data, and (if applicable) withdrawal of participation, in accordance with regulatory requirements;
Quotient Sciences	715	717	2.8.11	From a GDPR perspective, the lawful basis is important to communicate as well as the process, and directly affects the data subjects' rights should they wish to withdraw.	Add the text in bold: (m) the process by which the participant's data will be handled, and the legal basis for data processing, including in the event of the withdrawal of participation in accordance with regulatory requirements; Training material should be provided on this point to help clarify lawfulness and establish the corresponding subject rights.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Quotient Sciences	719	725	2.8.11 (n)	Many RECs ask us to remove from the ICF statements that the REC could have access to source records, because they do not see that as part of their remit. Reference to access by RECs should be in line with local rules and guidance. Also, clarification is needed - the participant or their legal representative doesn't safeguard the confidentiality of the participant.	Please edit as follows: (n) that by agreeing to participate in the trial, the participant or their legally acceptable representative allows direct access to original medical records, per applicable regulatory requirements, on the understanding that the confidentiality of the participant will be safeguarded while safeguarding the confidentiality of the participant. This access is limited for the purpose of reviewing trial activities and/or reviewing or verifying data and records by the IRB/IEC(s), regulatory authority(ies) and the sponsor's representatives, for example, monitor(s) or auditor(s), and, in accordance with local regulatory requirements and guidance, the IRB/IEC.
Society for Clinical Research Sites	719	725	2.8.11	We have concerns over the use of the term "direct access" (both here as well as in Annex I Items 2.12.12, 3.6.3(d), 3.11.4.1(c), 3.16.4(a), 3.16.4(b), the Glossary and Appendix B.11). The phrase "direct access" (as opposed to "access") is interpretable as supporting an activity that is generally prohibited with established healthcare privacy/security practices and regulations across the globe (i.e. providing login IDs directly into to electronic health records).	We request the deletion of the word "direct" (or change the phrase to "access to view") here and in the other sections referenced to avoid this confusion and that the guidance can recognize the variety of ways source document verification has been accomplished over the past decade without "direct" access (but with "access to view"). This would also bring these sections to be consistent with Annex I Item 3.11.4's requirement that monitors "adhere to data protection and confidentiality requirements in accordance with applicable regulatory requirements, institution policy and established data security standards."
EUCROF	722	723	III. 2.8.11 (n)	"This access is limited for the purpose of reviewing trial activities…" The above sentence is not fully correct as SDV must be possible to verify inclusion /exclusion criteria. For example, if an inclusion criterion requires that a computer tomography (CT) was performed within 3 months before the start of the trial, this has to be verified, however the CT was not a trial activity.	This access is limited for the purpose of reviewing trial activities and/or data pertaining to inclusion/exclusion criteria ..
GQMA	722	725	III.2.8.11 n	In the EU the IEC is not allowed for going on site and doing any source data review. The wording in this respect should allow more flexibility. Applies to several sections.	Change to: "This access is limited for the purpose of reviewing trial activities and/or reviewing or verifying data and records by the IRB/IEC(s), in accordance with regulatory requirements, regulatory authority(ies) and the sponsor's representatives, for example, monitor(s) or auditor(s);" A similar adjustment should be made to lines 909 to 911, section III.2.12.12, lines 982 to 984, section III.3.6.3d, and lines 1777 to 1785 in section III.3.16.4.
Fergus Sweeney	724	724	2.8.11.n	ensure foreign inspections are not hindered	"regulatory authority(ies) (domestic and foreign)"
Association for Clinical Data Management (ACDM)	727	726	2.8.11 (o)		Add 'align with local data privacy laws'

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
CARVALHO Carla	727	731	2.8.11.O	In order to avoid copy of medical dossiers taken by the sponsor even if pseudo-anominyzed while not clearly specified in the informed document.	that records identifying the participant will be kept confidential and, to the extent permitted by the applicable regulatory requirements, will not be made publicly available and no copy will be taken unless accurately indicated for the concerned visits. If the trial results are published, the participant's identity will remain confidential. The trial may be registered on publicly accessible and recognised databases, per applicable regulatory requirements;
EUCROF	727	731	III. 2.8.11 (o)	… to the extent permitted by the applicable regulatory requirements, will not be made publicly available. Not clear what is meant by the above. Is there an example for which applicable regulatory requirements would NOT allow for confidentiality? Court case? Does not become clear.	
EUCROF	730	731	III. 2.8.11 (o)	"The trial may be registered on publicly accessible and recognised databases, …" See Principle 9.7. There is no "may be" plus it is a requirement of the Declaration of Helsinki	The trial should be registered on publicly accessible and recognised databases, …
Fergus Sweeney	730	730	2.8.11.o	Registration of trials is now a global expectation not just an aspiration	"The trial will be registered…"
EUCROF	747	748	III. 2.8.11 (u)	"that trial results and information on the participant's actual treatment, if appropriate, will be made available to them should they desire it." The timepoint of making such information available is crucial and might not be the timepoint when the information is desired by the participant.	that trial results and information on the participant's actual treatment, if appropriate, will be made available to them at an appropriate time point, should they desire it.
Medicines for Europe	747	748	2.8.11 (u)	In blinded studies, trial results and information on the participants actual treatment can be only made available after the study completion where unblinding of the data takes place and finalisation of the reports. Paragraph should be revised to reflect this, and also encourage sponsors on the establishment of appropriate procedures towards this direction.	That trial results and information on the participant's actual treatment, if appropriate, will be made available to them should they desire it, after the study finalisation. The sponsor may establish an appropriate procedure and notify the subject if requested.
PPD	747	748	2.8 Informed Consent of Trial Participants	Any blinded information will be controlled by the sponsor and thus dependent on that entity to empower the site to fulfill. Later language in section 2.9.3 elaborates on notifying participants of trial results once information is received from the sponsor after unblinding.	Where relevant, the investigator should inform the participant about the trial results and treatment received when this information is available from the sponsor after unblinding, with due respect to the participant's preference to be informed.
Quotient Sciences	747	748	2.8.11 (u)	Unlike patients, the vast majority of healthy volunteers show no interest in seeing the results of the phase 1 trials in which they have participated – in our experience, having offered volunteers the opportunity to see the results, very, very few take up the offer. In phase 1 healthy volunteer trials, it is proportionate to give volunteers a summary of the results *on request* ; it should not be mandatory to make results available to all healthy volunteers.	Please add bold text: (u) that trial results and information on the participant's actual treatment, if appropriate, will be made available to them should they desire it (or on request for phase 1 trials in healthy volunteers)

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EAHP	749		III 2.8.11	Add a new point (v) to ensure that the information provided to the patient is shared in a manner understandable for the patient.	(v) all the information provided to the patient needs to be understandable according to the patient's health literacy.
EFPIA Consolidated Comments	749	749	2.8.11v	Suggesting a new bullet point. To anticipate the need for follow-up of the baby after the end of a pregnancy of a trial participant or trial participant's partner, should the appropriate language be included in the informed consent?	that any pregnancies either of the participant or the participant's partner, if applicable, will be followed up after the end of a pregnancy where necessary.
GQMA	750	753	III.2.8.12	Analoguos to the requirement of having certified copies for source documents, the copy of the signed informed consent form handed out to the subject should also fulfill this requirement, if it is not provided as original hardcopy.	Change to: "Prior to participation, the participant or the participant's legally acceptable representative should receive a copy (certified paper or electronic) of the signed informed consent form and ...."
EUCROF	753	753	III. 2.8.12	"… or in accordance with applicable regulatory requirements." Not clear what is meant	
Fergus Sweeney	753	753	2.8.12	delete "or"	delete "or"
Fergus Sweeney	756	756	2.8.12	add reference to procedure when trials are performed	"See 2.8.9 re urgent treatment in emergency situations"
Society for Clinical Research Sites	758	762	2.8.13		We request that this section not refer to "age-appropriate" but ask that it recognize and accommodate for the more important "appropriate to the intellectual capacity of the minor" to accommodate for the physical and neurological diversity of minors. This brings this section more in line with the wording in Annex I Item 2.8.14. Similarly, there are many legal exceptions to solely one's age that allows a minor to be able to provide legal consent, as thus the turning point should not be "reaches the age of legal consent" but changed to "reaches the legal status to be able to consent for themselves".
Quotient Sciences	765	766	2.8.14	Please add patients with learning difficulties to the list of patients who may need a legal representative.	Please add bold text: ...(e.g., minors, patients with severe impaired decision-making capacity, patients with learning difficulties)…

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Ludger Wienbrede	771	774		"In exceptional circumstances (e.g., public health emergencies), when the usual methods to obtain and document informed consent are not possible, the use of alternative measures and technologies in accordance with local IRBs/IECs and applicable regulatory requirements should be considered." should be replaced by "In accordance with local IRBs/IECs and applicable regulatory requirements, methods to obtain and document informed consent may include measures and technologies that do not neccessitate visits of participants at the investigator site." Rationale: Approaches that simplipy the participation at clinical trials should not be limited to exceptional circumstances. There is a need to unburden participation also in "normal times".	
Mithra Pharmaceuticlas SA PV	776	781	2.9	make clear what information can still be collected in CRF after subject's withdrawal	
Richmond Pharmacology Dr Ulrike Lorch Dr Jörg Täubel Dr Thomas Ashdown Dr Edward Jackson Dr Thomas York	776	790	2.9.1/2.9.2	We are concerned about the tone of the language used in this section. Withdrawal of consent is a crucial pillar of ethical clinical trial conduct, and the investigator is the ultimate advocate of the participant. The use of the term "instructions" is dictatorial and the investigator must utilise their discretion to protect participant autonomy. We advocate a collaborative approach to the end of trial participation, please see suggested wording. In addition, we are also concerned that Line number 788-790 may sound coercive and should therefore be removed.	778- "…follow the protocol and, in collaboration with the sponsor, determine appropriate follow up measures"
Unicancer	776		2.9	the investigator should follow the protocol and othe sponsor instructions to determine appropriate follow-up measures	the investigator should follow the protocol and othe sponsor instructions to determine appropriate follow-up measures, especially patient's safety
DGPharMed e. V. (Deutsche Gesellschaft für Pharmazeutische Medizin)	779	781	III.2.9.1	Reads like a contradiction to 2.8.4	
Fergus Sweeney	780	780	2.9.1	this applies to data already collected and not only critical data. This is important to avoid censoring of data due to participants discontinuing trial participation	reword "…unecessary loss of data laready collected…"
EFPIA Consolidated Comments	783	790	2.9.2	The latter sentence appears somewhat coercive and could promote a legal challenge. It would be better to remove this and then the previous sentence does try to support remaining in the trial.	Although a participant is not obliged to provide a reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the participant's rights. The investigator should consider discussing with the participant or the participant's legally acceptable representative the reasons for withdrawal to determine if there are ways to address the concerns. The investigator site staff should make an effort to explain to the participant the value and importance of continuing their participation to minimise trial participants withdrawal.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	783	790	2.9	The paragraph should be revised to exclude any suspicion of encouragement for manipulation of the participants by the Investigator.	Although a A participant is not obliged to provide a reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the participant's rights. The investigator should consider discussing with the participant or the participant's legally acceptable representative the reasons for withdrawal to determine if there are ways to address the concerns. The investigator site staff should make an effort to explain to the participant the value and importance of continuing their participation to minimise trial participants withdrawal.
Society for Clinical Research Sites	783	790	2.9.2		To assure proper ethics and make technical corrections, we request that this be rewritten as: "To ethically minimise trial participants withdrawal, the investigator and their site staff should make an effort to explain to the participant, in manners that are not coercive or present undue influence, the value and importance of continuing their participation".
EUCROF	788	790	III. 2.9.2	"The investigator site staff should make an effort to explain to the participant the value and importance of continuing their participation to minimise trial participants withdrawal." The above sentence can be interpreted as coercion and influencing. A more neutral approach should be taken.	The investigator site staff should make an effort to explain to the participant any aspects associated with discontinuation of the trial to enable the participant to make an informed decision regarding trial withdrawal.
PPD	792	794	2.9 End of Participation in a Clinical Trial	All trial results can be considered "relevant" and thus subject to different interpretations. There are concerns about the feasibility of this process, particularly for Early Phase studies where ultimate trial results may not be known for years and PI may not always be informed (for example, of drugs that fail in later phase trials), difficulty in contacting participants after years, relevance of trial results to normal healthy volunteers not receiving any therapeutic benefit from study, etc.	Where relevant to the participant and their medical care, and where this information will not jeopardize the study integrity or any other trial in the drug development program, the investigator should inform the participant about the trial results and treatment received when this information is available from the sponsor after unblinding, with due respect to the participant's preference to be informed
Quotient Sciences	792	794	2.9.3	Unlike patients, the vast majority of healthy volunteers are not interested in seeing the results of the phase 1 trials in which they have participated – in our experience, having offered volunteers the opportunity to ask about the results, very, very few volunteers show any interest in them. In phase 1 trials, it is proportionate to offer to give volunteers a summary of the results on request; it should not be mandatory to provide results to healthy volunteers.	Please edit as follows: 2.9.3 Where relevant, the investigator should inform the patient participants about the trial results and treatment received when this information is available from the sponsor after unblinding, with due respect to the participant's preference to be informed. A simple summary of trial results, and treament allocation, should be made available to healthy volunteers in phase 1 trials if requested by the participant.
Society for Clinical Research Sites	792	794	2.9.3		The term "where relevant" should clarify as to who determines when this is relevant. In this case, we recommend "Where the investigator determines it to be relevant".

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Association for Clinical Data Management (ACDM)	795	795	2.1	General comment: For future refenced FDA draft guidance on DCT Section 1 indicates that the safety profile of the IP must be taken into consideration when determining if non-site personnel can administer IP remotely	No Action
Society for Clinical Research Sites	795	822	2.10	As we have in other areas in this response, we point out that the more that the sponsor removes tasks from the investigator (for reasons such as building efficiencies, cost containment or for decentralization of the trials), the less control the investigator has over the processes of the sponsor and/or the service provider working for the sponsor. We maintain that the investigator should be accountable only for the investigational product that they themselves inventory and dispense and that the sponsor should be accountable for the investigational product that they inventory and dispense. We do support that the sponsor or their service provider should not be able to ship the investigational product to participants without the orders of the investigator to do so with the acknowledgement that controls need to be in place to control for the emerging prevalence of AI driven and auto-refill systems.	This section should be rewritten in its entirety as "Responsibility for investigational product accountability rests with the facilitator of the process, specifically the investigator is accountable for the investigational products that they, or their service providers, inventory and dispense while, accordingly, the sponsor is accountable for the investigational products that they (or their service providers) inventory and dispense."
Good Clinical Trials Collaborative, on behalf of supporting organisations	796	797	Investigator (2.10.1)	This states that "Responsibility for investigational product(s) accountability rests with the investigator/institution. The sponsor may facilitate this process." In some trials, a more convenient (for the participant) and high quality way to manage supply of treatment to participants may be via a third party central pharmacy. In such circumstances, the third party central pharmacy should be responsible for investigational product(s) accountability and the organisation (which is more likely to be the sponsor than the investigator) should be responsible for oversight of that central pharmacy.	Reword to account for and enable practices that improve quality, feasibility, and convenience.
Medicines for Europe	796	797	2.10.1	The statement is too general, the investigator/institution cannot be considered responsible for drug accountability while it is under control of the sponsor (e.g. prior to shipment)	Responsibility for investigational product(s) accountability rests with the investigator/institution from the time it is received by the investigator/institution until return or destruction. The sponsor may facilitate this process.
EUCROF	797	797	III. 2.10.1	"The sponsor may facilitate this process." The above sentence represents an invitation to the monitor to perform drug accountability on behalf of the investigator. This means crossing the lines of responsibilities. The monitor should QC but not perform investigator tasks.	Delete the sentence.
CARVALHO Carla	799	801	2.10.2	In France as per law, the activities made by the pharmacy cannot be delegated by the Investigator where there is a pharmacy in the institution (e.g., reception of the investigational product).	When the investigator/institution assigns some or all of their activities for investigational product(s) accountability to a pharmacist or another individual, they should be under the supervision of the investigator/institution and as per the local regulations.
EAHP	799	801	III 2.10.2	Add an additional sentence on the training by the investigator in relation to the protocol.	When the investigator/institution assigns some or all of their activities for investigational product(s) accountability to a pharmacist or another individual, they should be under the supervision of the investigator/institution. The investigator needs to ensure that the pharmacist or another individual is well trained on the protocol and the training needs to be documented.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA Consolidated Comments	799	801	2.10.2	Can use of supervision in the sentance "...they should be under the supervision of the investigator/institution" be clarified. For example this doesn't mean the Investigator needs to be physically present to supervise the delegated individual, more that the investigator maintains the oversight/overall accountability for the activity.	Include in the glossary or introduction what we mean by investigator supervision and sponsor oversight to incidcate that supervision isn't necessarily over the should oversight.
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	799	801	III 2.10.2	The investigator is not authorized to issue instructions to the pharmacist but may oversee or monitor the execution of the assigned tasks. Thus, the wording should rather be "oversight" instead of "supervision". Also, what would be proof of effective supervision/oversight in this context?	Suggestion: "When the investigator/institution assigns some or all of their activities for investigational product(s) accountability to a pharmacist or another individual, they should be under the oversight of the investigator/institution."
Quotient Sciences	799	801	2.10.2	Please provide clarification of the nature of supervision by the investigator/institution of a pharmacist or another individual delegated activities for accountability of investigational product(s).	Please provide clarification.
DGPharMed e. V. (Deutsche Gesellschaft für Pharmazeutische Medizin)	801	801	III.2.10.2	Investigator's oversight over pharmacy is often not possible as the work is independently organized or is a task of unblinded site personnel.	Pharmacy oversight shall not be an investigator responsibility
EFPIA Consolidated Comments	803	811	2.10.3	For authorised medicinal products a proportionate and risk-based approaches can be implemented.	For authorised medicinal products, alternative and proportionate risk-based approaches to the aforementioned may be considered, in accordance with local regulatory requirements.
Medicines for Europe	807	809	2.10	The necessity for unique code numbers are necessary for multiple centre trials to avoid confusion and multiple assignment of the number. For single centre trials the allocation of participant numbers are done once and confusion with partipants allocation in other trial sites are not the case.	These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable) and the unique code numbers assigned to the investigational product(s) and trial participants (only for multicenter trials).
AFI	813	814	2.10.4	The investigational product(s) should be stored as specified by the sponsor and in accordance with applicable regulatory requirement(s).	remove "in accordance with relevant regulatory requirements"
Beate Kern, Department of Health Brandenburg, Germany	813	814	2.10.4	Where applicable, an obligation for the sponsor to provide patient-friendly information on the storage of the IMP in the patient's home environment should be defined	Where applicable, an obligation for the sponsor to provide patient-friendly information on the storage of the IMP in the patient's home environment should be defined
CARVALHO Carla	813	814	2.10.4	For some products, a reconstitution step is necessary.	The investigational product(s) should be stored and prepared as specified by the sponsor and in Accordance with applicable regulatory requirement(s).
EAHP	813	814	III 2.10.4	Add an additional sentence to include the safeguard that the sponsor guarantees to carry out the delivery in a manner that safeguards the stability and traceability of the investigational medicinal product.	The investigational product(s) should be stored as specified by the sponsor and in accordance with applicable regulatory requirement(s). The sponsor needs to ensure that the investigational medicinal product is delivered in the way that the investigational medicinal product stability and the traceability of the delivery temperature through an electronic system is guaranteed.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Society for Clinical Research Sites	819	822	2.10.6		We acknowledge the relationship between the participant and the investigator/site is critical. However, we hope that the guidance can acknowledge the need for the sponsor to provide a common written set of instructions for the participants.
DGPharMed e. V. (Deutsche Gesellschaft für Pharmazeutische Medizin)	824	824	III.2.11	Replace should with must	Replace should with must
Good Clinical Trials Collaborative, on behalf of supporting organisations	826	826	Investigator (2.11)	Add after "in accordance with the protocol *since inappropriate unblinding can damage the reliability of the trial results*."	
Medicines for Europe	826	827	2.11	Some trials where the risk to participants is not negligible (for example, first in man or SAD/MAD studies) are performed in healthy subjects. Therefore the text should not cover patients only.	In the case of an emergency, to protect subject patient safety, the investigator should be prepared and capable from the start of the trial to perform unblinding without undue delay and hinderance
Fergus Sweeney	828	828	2.11	spelling	"…hindrance."
EFPIA Consolidated Comments	835	843	2.12.2	to facilitate the understanding of the requirements for records to be accessible in years to come, include enduring as per EMA guidelines.	...enduring...
GQMA	835	843	III.2.12.12	In some countries, many sites maintain study specific source documentation, which is separate from the routine medical records system. Only study specific source is shown to monitors, auditors and inspectors. As a consequence, CRAs, auditors and inspectors might not receive all trial relevant information about the subject, and future physicans might not be properly informed about the previous treatments of the participants.	Clarify that all available medical documentation with trial-relevant contents shall be made available for monitoring, auditing and inspection.
Medicines for Europe	838	839	2.12.2	It's not clear why changes to source records must be explained (if necessary) via an audit trail. No audit trail is required in section 2.12.6	Delete "(via an audit trail)"
Fergus Sweeney	839	839	2.12.2	the explanation may be in a document, description or report and not alway in an audit trail	reword "..explained if necessary."
German Pharmaceutical Industry Association (BPI)	842	843	2.12.2.	Sentence "Unnecessary transcription steps in between the source record and the data acquisition tool should be avoided". The consequence of this sentence could be that authorities or inspectors ask for a digital connection between source record and DAT (if both are electronic systems) to avoid manual transcription as an "unnecessary" step. However, such a digital transfer of data is challenging and requires extensive validation in each and every study site with electronic source data system.	Delete respective sentence
Ipsen	842	843	2.12	"Unnecessary transcription steps in between the source record and the data acquisition tool should be avoided" need to clarify the meaning of unnecessary transcription as it is very subjective.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Association for Clinical Data Management (ACDM)	845	850	2.12.3	What do you consider as timely review? Should be enough at agreed timelines (e.g. interim analysis) as mentioned below (2.15.2)... as per the EMA guidance on Computerised System asking for more frequent review by PI apart from end of study and interim analysis. The timing of the Investigator review will need to align with the safety monitoring plan as I suspect the intent is to ensure Investigators are aware of and managing potential safety risks. The FDA draft guidance on DCT section H contains the following statement : if authorized in the protocol, routine safety monitoring involving laboratory testing and imaging may be performed using local clinical laboratory facilities close to trial participants (see section III.D.2). Investigators should ensure they promptly receive reports of these services and review them in a timely manner.	Please add examples of what timely review means for different role, so we can implement appropriately.
EFPIA Consolidated Comments	845	850	2.12.3	This section defines data from external sources quite narrowly and just includes ePROs as a source of data that may be captured electronically. Need to include some training on this section.	...and if appropriate, measures captured through digital health technologies.
Good Clinical Trials Collaborative, on behalf of supporting organisations	845	850	Investigator (2.12.3)	"The investigator should have timely access to and be responsible for the timely review of data, including relevant data from external sources…" This requirement includes no consideration of whether the data is fit for clinical decision making (many central laboratories, imaging providers or core interpretation facilities are accredited only for research use, not clinical use) or of the timing with which information becomes available (for example, many central laboratory assays may be batched and analysed weeks, months or years later (meaning that their results cannot be available for clinical decisions). Reviewing data does not necessarily improve data quality – the Investigator has no way of knowing whether data generated by a third party is valid; likewise, if data is entered by an appropriately qualified/trained member of their team (with appropriate delegation of duties recorded), review by an Investigator will have little or no value.	
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	845	850	III 2.12.3	Review and endorsement of reported data at previously agreed milestones (line 856-860, 2.12.5) implies that signing off single visits or single CRF-pages is not required/recommended, which is a much appreciated clarification. However, it appears to be in contradiction to section 2.12.3 (timely review of data).	Suggestion: Change "timely review of data" to "timely review of original data" or "source data" to avoid confusion with CRF data.
GCP-unit, Copenhagen	848	848	2.12.3	Migth an idea to put ePRO in Glossary?	
Association for Clinical Data Management (ACDM)	852	854	2.12.4	Systems are fit for purpose, they collect what it is needed by protocol (no more data). Sentence is ambiguous more clarify	Please clarify what this means by expanding this sentence - so it is clear what the limitations of the investigator responsibilities are - I don't expect them to be involved in UAT or what data the systems collect - rather that they ensure their site staff are trained to use the system correctly. If this is the case then please elaborate to make clear.
Medicines for Europe	852	853	2.12.4	there should be no limitation to systems deployed by the sponsor	The investigator should ensure that data acquisition tools and other systems deployed by the sponsor for clinical trial purposes are used as specified in the protocol or trial-related instructions.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Richmond Pharmacology Dr Ulrike Lorch Dr Jörg Täubel Dr Thomas Ashdown Dr Edward Jackson Dr Thomas York	852	854	2.12.4	We appreciate that this section is applicable when investigators are using systems deployed by the sponsor. In line with other changes made with the revision, we suggest taking the opportunity to reiterate that the investigator may use their own systems, if agreed with the sponsor.	
Society for Clinical Research Sites	852	854	2.12.4	The reality is that the investigator has little to no control over the programming or the settings of these digital health technologies. The service providers of these products, along with the individuals contracting for their service who are not the investigator, are in complete control of the functionality of these products. If they do not code the products correctly or change the settings (neither of which are under the investigator's control), the investigator cannot compensate for that. Additionally, to make it easier on participants, studies are starting to embrace a "bring your own device" stance and thus the investigator cannot control what a participant does with their own device. Finally, many participants, especially those of lower socioeconomic status, get medical benefit from using the devices in the trial, so much that they desire to keep them after the study is over.	While we appreciate the intent to have the investigator in control, we encourage the guidance to put accountability on the entity that has actual control over the data acquisition technology. Again, we appreciate the intent to reinforce investigator control, but this seems to be an area where investigators can only "encourage" and not "ensure"." We appreciate the intent to reinforce investigator control, but this seems to be an area where investigators can only "encourage" and not "ensure".
Association for Clinical Data Management (ACDM)	856	860	2.12.5	Does it mean that external data systems are subject to Inv. Approval? Does it means that PI signature is required on Data Collection Tools as evidence of PI data review	Please clarify in the document so intention is understood.. Does this mean the investigator is responsible for assuring the data is entered accurately and quickly after data is available.
Good Clinical Trials Collaborative, on behalf of supporting organisations	856	860	Investigator (2.12.5)	"The investigator should review and endorse the reported data at milestones agreed upon with the sponsor (e.g. interim analysis)." This is rarely of any true value. If the data were originally reported by a member of the investigator team (appropriately trained, appropriately delegated), then the Investigator review achieves nothing – they cannot possibly know whether answers the patient gave to the team member were faithfully recorded (that's what the training is for). There are also other ways to assess for the presence of erroneous data (e.g. from simple field validation checks through to use of central statistical monitoring and machine learning/AI). It is not that such review is never useful (in some particular circumstances it might be) but it should not be a rigid requirement. This requirement lacks flexibility for the context, proportionality for the relevance, and careful consideration about whether such review and endorsement will improve the reliability of the results or the safety of participants. Imposing work on Investigators if it does not add value to the quality of the trial is counter-productive.	For similar reasons, Sponsor section. Point 3.16.1.n should be deleted.
EFPIA Consolidated Comments	858	860	2.12.5	The requirement for the investigator to review and the reported data at agreed milestones could imply that PI signatures are only required at milestones. However, experience from regulatory authority inspections (especially EMEA and PMDA) indicates that PI signatures are expected to be completed on an ongoing basis with a risk based approach to be taken (see reference below). As such frequencies for endorsing data records should also be determined by the sponsor, based on study requirements. In addition, guidance would be welcome regarding which criteria the sponsor should consider when establishing frequency for endorsement.	The investigator should review and endorse the reported data at frequencies and milestones (e.g., interim analysis) agreed upon with stipulated by the sponsor .

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
PPD	866	870	2.12 Records	Guidance should make clear that access to subject identifying information is appropriate and acceptable in specific circumstances (e.g. monitoring, auditing, regulatory authority inspection, etc.).	The investigator/institution should implement appropriate measures to protect the privacy and confidentiality of personal information of trial participants…Data reported to the sponsor should be identified by an unambiguous participant code... Suggest adding (following the end of sentence in original text): Access to participant identifying information is limited for the purpose of reviewing trial activities and/or reviewing or verifying data and records by the IRB/IEC(s), regulatory authority(ies) and the sponsor's representatives, for example, monitor(s) or auditor(s).
Society for Clinical Research Sites	866	870	2.12.7	While we appreciate the need for anonymity of the trial participants, we request that this section recognize that there may be times where the sponsor will need to know the identity of the participants. This may be for payment/reimbursement related issues or in the event that the institution is requested to report litigation-related matters.	We request that the additional sentence be added: "In the event, for a bona-fide reason, it is required for a sponsor to receive data elements that are personal identifiers of the participant(s), only the minimal necessary amount of information will be provided for the sponsor to accomplish their task."
Ollie Östlund	868	870	III.2.12.7	While the new E6 definitely does not say that the sponsor only should have access to pseudonymised data, I stongly recommend including an *explicit* statement that there is no prohibition for the sponsor to have access to participant identities, as guidance to regulators. The reason is that the absence of a tick mark in the "sponsor" column in the old E6 caused decades of regulatory auditing in Sweden to ensure that the sponsor *never* had access to identifiers, which hardly contributed to quality. Trials using routinely collected data use central data acquisition, which can be provided by the sponsor. The same holds for electronic informed consent systems. In both cases, the participant list must reside also in sponsor systems. Swedish registry-integrated large simple trials have had to use contorted legal arguments to allow central data acquisition, such as naming one university department "sponsor" and another "provider". Problems caused by the old interpretation have included regulatory authorities not allowing personal identifiers being handled in the secure and access-controlled eCRF system, causing them to instead being e-mailed between investigators as unencrypted Excel documents.	Add "The sponsor may also need access to the participant identities, for example for acquisition of external data".
eClinical Forum	869	869	III 2.12.7	This clause states that a participant code must be unambiguous which is not a standard term. GDPR uses the term "pseudo-anonymous". We think both terms apply.	Revise to state that a participant code must be unambiguous and pseudo-anonymous.
EUCROF	870	870	III. 2.12.7	"...by the investigator/institution."	"...by the investigator/institution only."
SHIONOGI	877	894	2.12.9	Missing instructions that the investigator/institution should ensure that when using computerized systems, that the software and harware/equipment used for the computerized systems are maintained to ensure the data reamins accesibles/readible (e.g. if the CRFs are saved on a CD-rom, then there should be computers/accesories available that can read the CD-rom, as well as the software required to read the CD-rom.	Please add instructions on requirement to ensure that data generated cia computerized systems remain accessable and readible (see column H32)
EFPIA Consolidated Comments	880	881	2.12.9 (a)	This point should specify that systems access for "appropriate" individuals includes Sponsor Monitors, Sponsor Auditors, and Regulatory Inspectors.	"For systems deployed by the investigator/institution, ensure that appropriate individuals, including Sponsor Monitors, Auditors, and Regulatory Authorities, have secure and attributable access;

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eClinical Forum	883	885	III 2.12.9(b)	This states that the investigator (b) for systems deployed by the investigator/institution specifically for the purposes of clinical trials, ensure that the requirements for computerised systems in section 4 are addressed; It is unusual for an investigator to bring in a system specifically for sponsored clinical trials; more typical is that the sponsor provides any systems the investigator will need to use for that sponsor's trial. This item only applies to systems deployed by the site, and this should be clearly stated.	Please supply clarity, such that it is clear that it is not referring to any system used by the investigator but supplied by the sponsor.
Society for Clinical Research Sites	887	889	2.12.9		The criteria of "provided to trial participants by the investigator" needs to be clarified. Consistent with the previous two subsections, it should be delineated that the investigator is only be responsible for the equipment they deploy. It should be clarified that the sponsor is responsible for sponsor-issued equipment that the investigator is simply passing along to the participants.
eClinical Forum	891	893	III 2.12.9(d)	This states (d) ensure that incidents in the use and operation of computerised systems, which in their judgement may have a significant and/or persistent impact on the trial data, are reported to the sponsor and, where applicable, to the IRB/IEC. The investigator cannot be aware of all incidents. It should be clarified to say only those incidents they are aware of.	Revise the statement to insert "encountered" after "incidents" such that it reads: (d) ensure that incidents encountered in the use and operation of computerised systems ...
GQMA	891	893	III.2.12.9 d	Reporting of significant data breaches should not only occur to the IEC, but also to (data protection) authorities.	Change to: "ensure that incidents in the use and operation of computerised systems, which in their judgement may have a significant and/or persistent impact on the trial data, are reported to the sponsor and, where applicable, to the IRB/IEC and/or authorities, as per regulatory requirements."
GQMA	891	893	III.2.12.9 d	As per EU GDPR personal data breaches with high risk to the rights and freedoms of natural persons should be notified.	Change to: "ensure that incidents in the use and operation of computerised systems, which in their judgement may have a significant and/or persistent impact on the trial data or result in a high risk to the rights and freedoms of the trial participants, are reported to the sponsor and, where applicable, to the IRB/IEC." A similar adjustment should be made to lines 1001 to 1004, section III.3.6.7.
Society for Clinical Research Sites	891	893	2.12.9	We respect the need for investigator's need to do this reporting. However, as technology is increasingly supplied to the sites by the sponsors and such data are stored at and/or controlled by the sponsors or their service providers, the reciprocation is as important to the integrity of the study data and human subject protection.	An added paragraph in the sponsor section should state the mutual responsibility to each other of "sponsor shall ensure that incidents in the use and operation of computerised systems, which in their judgement may have a significant and/or persistent impact on the trial data or protection of the subjects, are reported to the investigator."
Association for Clinical Data Management (ACDM)	895	902	2.12.10	Positive comment - as it is reminder to investigator to ensure traceability on training	No Action

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Society for Clinical Research Sites	895	902	2.12.10	Unlike R2, the draft in Appendix C no longer delineates who, between the sponsor and the investigator, is responsible for which information. As much of that information is not generated by or even in the hands of the investigator, we believe that this section should rearrange the first two sentences and include additional context.	We believe that this section should rearrange the first two sentences with an accompanying clarification to read "The investigator/institution should have control of all essential records generated by the investigator/institution before, during and after the trial. The investigator/institution should maintain these trial records as specified in Appendix C. Essential Records for the Conduct of a Clinical Trial and as required by the applicable regulatory requirement(s)." This way it better aligns the investigator/institution's duties and obligations.
EFPIA Consolidated Comments	899	902	2.12.10	it would be good to add unauthorized access, even in the light of cyberattacks, etc. may be an institution rather than an individual Is there a possiblity to bullet point this.	The investigator/institution should take measures to prevent accidental or premature destruction of and unauthorized access to these records. .....appropriate individual/institution responsible....
eClinical Forum	900	902	III 2.12.10	This section states that the sponsor should be notified of who is responsible for a closed site's essential records. This works if the site is an institution but does not discuss the process when a site goes out of business with no forwarding info or responsible person.	This scenario should be addressed in this section.
EUCROF	901	901	III. 2.12.10	"...the sponsor should be notified of the appropriate individual responsible for retention of the site's essential records." It could take forever before the sponsor is notified, if at all.	"...the sponsor should be notified promptly of the appropriate individual responsible for retention of the site's essential records."
AFI	902	902	2.12.10	"...appropriate individual responsible for retention of the site's essential records".	It is advisable to add to responsible "and arrangements identified"
GQMA	904	907	III.2.12.11	The current wording might lead to problems if the sponsor fails to inform the investigator. In that case the investigator could never stop the retention, because the site could not be sure, whether the sponsor needs the records to be retained longer than the regulatory requirements stipulate. Furthermore, there should be a written agreement between sponsor and investigator/institution for the required retention time.	Change to: "The investigator/institution should retain the essential records for the required retention period in accordance with applicable regulatory requirements or for a longer period as defined in a written agreement with the sponsor. The sponsor shall inform the investigator/ institution once the end of the required retention time is reached." A similar adjustment should be made to lines 977 to 980 in section 3.6.3 c.
Karolinska University Hospital, Stockholm, Sweden	904	907	2.12.11	It is difficult for the Investigator or Institution to know the needs of the sponsor. Extended retainment of personal data may require renewed consent from the data subjects or/and from the ethics committee. Therefore, it is suggested that the wording is changed as to make the sponsor responsible for reaching out to the site should extended archiving be needed, instead of site having to retain until sponsor informs the site that records are no longer needed. Sponsors often require sites to get sponsor approval before destruction of any trial-related documentation. This imposes an disproportionate burden to the site many years after the conduct of the trial as investigational products tend to change owners as sponsors merge or sell their products. Finding out who is the owner of the IMP 25 years after the end of the trial is almost impossible as getting approval for destruction of source data that may not be GDPR compliant to keep eternally.	The investigator/institution should retain the essential records for the required retention period in accordance with applicable regulatory requirements *or longer if the sponsor has requested extended retention and obtained applicable approvals for extended data processing* (Appendix C)

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Society for Clinical Research Sites	904	907	2.12.11	The clinical research site community appreciates that the guideline is moving away from its previous unpredictable record retention requirements and aligning with that of the investigator's local regulatory requirements. However, we fundamentally and emphatically disagree with the notion that it is the investigator/site's responsibility to retain the records after their local regulatory obligations have expired should the sponsor have their own business needs for them. We note that the revision in Annex I Item 1.2.2 rightfully changed from a previous three-year retention period to one of "applicable regulatory requirements" and request that investigator records obligations delineated in this section also fall in line with the caveat that the sponsor may maintain the right to have those records shipped to them in lieu of destruction. The way the draft guideline is currently written forces the site to be available for indefinite storage, which is not only untenable but also not in the interest of record-keeping. Unlike sponsors and CROs, investigators/sites are generally not equipped with the expertise or resources to archive records for extended periods. To be clear, a sponsor simply offering additional funds to the investigator/institution does not in-and-of-itself create this competency at the investigator/institution, nor eliminate the risk. Additionally, emerging financial and operational concerns such as technology degradation, technology obsolescence, cybersecurity, password management and similar obstacles germane to the record archiving industry are outside of a site's core competency and not scalable unless controlled by the sponsor or CRO. We understand the desire for the need for the site/investigator's records being independent of the study sponsor/CRO. However, most technologies are provided by the sponsor/CRO. Therefore, it is all-too-often the sponsor/CRO sends the investigator/site their records at the end of the study for storage to meet these kinds of requirements.	We very strongly recommend this section to be rewritten as "The investigator/site should retain the essential records for the required retention period in accordance with their local applicable regulatory requirements. After the retention period for investigators/institutions under applicable regulatory requirements have expired the investigator/institution may either destroy the records or transfer the records to the sponsor's custody. In the event the investigator/institution becomes unable to maintain the records during their regulated time period, they may ship the records to the sponsor's custody in accordance with applicable regulatory requirements."
Society for Clinical Research Sites	904	907	2.12.11	We do call to your attention that the growing incapability of the site/investigator's ability to adequately keep the records will directly contribute to the inability to adhere to the guidance. We firmly and wholeheartedly attest that such changes to this section (as well as Annex I Item 3.16.3(b) and Appendix C.1.3) this is in the best interest of the ability for the sponsor and regulators to reproduce those records when needed for their respective needs as opposed to furthering the fragmentation of the trial records around the globe and imposing indefinite and in-perpetuity storage obligations upon entities (i.e. investigators/sites) that are ill-prepared in record-archiving practices.	We very strongly recommend this section to be rewritten as "The investigator/site should retain the essential records for the required retention period in accordance with their local applicable regulatory requirements. After the retention period for investigators/institutions under applicable regulatory requirements have expired the investigator/institution may either destroy the records or transfer the records to the sponsor's custody. In the event the investigator/institution becomes unable to maintain the records during their regulated time period, they may ship the records to the sponsor's custody in accordance with applicable regulatory requirements."
EFPIA Consolidated Comments	909	911	2.12.12	Please rephrase per 2.8.11 (n) as there could be other sponsor representatives that may need access to trial-related records. On-site or in-person access for monitoring needs to be called out specifically in relation to direct access as we are seeing a trend in sites refusing onsite access to permit monitoring. Direct access can be remote if all the source records are accessible remotely. We find majority of sites do still have paper source in addition to electronic records. If there is no remote system e.g. eISF, that provides the monitor access to the paper source the monitor cannot access all records. This needs to be called out in the guidance so that sites that prefer remote access only understand their responsiblity to provide remote access to all source including paper source in order to permit direct access and monitoring. If sites cannot provide remote access then they have a responsibility to allow direct access onsite	Proposed change: "Upon request of the sponsor representatives, for example the monitor and auditor, IRB/IEC or regulatory authority, the investigator/institution should make available for direct access (onsite/in-person access, as appropriate) all requested trial related records.

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Society for Clinical Research Sites	909	911	2.12.12	We have concerns over the use of the term "direct access" (both here as well as in Annex I Items 2.8.11(n), 3.6.3(d), 3.11.4.1(c), 3.16.4(a), 3.16.4(b), the Glossary and Appendix B.11). The phrase "direct access" (as opposed to "access") is interpretable as supporting an activity that is generally prohibited with established healthcare privacy/security practices and regulations across the globe (i.e. providing login IDs directly into to electronic health records).	We request the deletion of the word "direct" (or change the phrase to "access to view") here and in the other sections referenced to avoid this confusion and that the guidance can recognize the variety of ways source document verification has been accomplished over the past decade without "direct" access (but with "access to view"). This would also bring these sections to be consistent with Annex I Item 3.11.4's requirement that monitors "adhere to data protection and confidentiality requirements in accordance with applicable regulatory requirements, institution policy and established data security standards."
EFPIA Consolidated Comments	912	917	2.13.1	Clarify if this can be delegated to Sponsor in alignment with rest of the guideline	The investigator/institution should provide the IRB/IEC with a summary of the trial's outcome and, if applicable, the regulatory authority(ies) with any required reports. Submission to the IRB/IEC may also be completed by the sponsor where applicable (see 1.5).
Mithra Pharmaceuticlas SA PV	913	916	2.13	PI to provide IRB/EC (and RA) with a summary of trial's outcome??? Does sponsor review this kind of CSR?	
Quotient Sciences	913	916	2.13.1	UK RECs no longer require a copy of the synopsis of the clinical trial report, and provision of a lay summary of results to the REC is not compulsory for phase 1 trials. Therefore, provision of results to RECs should be in line with national regulations or guidance. This section assumes that only the investigator/institution will be responsible for informing the IRB/IEC. However, sponsors can submit applications to RECs/IECs in the EU and UK.	Please edit as follows: 2.13.1 Upon completion of the trial, the investigator, where applicable, should inform the institution. In accordance with local regulations and guidance, tThe sponsor or investigator/institution should provide the IRB/IEC with a summary of the trial's outcome and, if applicable, the regulatory authority(ies) with any required reports.
The GCP Unit at Odense University Hospital, OPEN	913	916	2.13.1	it should be added that this can also be done by sponsor. In CTR this is done by sponsor in CTIS Is rephrasing possible?	
DGPharMed e. V. (Deutsche Gesellschaft für Pharmazeutische Medizin)	914	916	III.2.13.1	a) To comply with EU legislation (CTR / CTIS) the wording should be adapted: "… should provide, if applicable / according local regulatory requirements … the IRB/IEC and/or the regulatory authority…" In the EU it is an obligation of the sponsor. Please specify: b) Should the investigator report the results of the participant treated at his site, only? c) Additionally, what is meant by "Trial´s outcome"? Is "Clinical Trial/ Study Report" meant? Or, please, provide a list/template of required content.	a) To comply with EU legislation (CTR / CTIS) the wording should be adapted: "… should provide, if applicable / according local regulatory requirements … the IRB/IEC and/or the regulatory authority…" In the EU it is an obligation of the sponsor. Please specify: b) Should the investigator report the results of the participant treated at his site, only? c) Additionally, what is meant by "Trial´s outcome"? Is "Clinical Trial/ Study Report" meant? Or, please, provide a list/template of required content.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUCROF	914	916	III. '2.13.1	"The investigator/institution should provide the IRB/IEC with a summary of the trial's outcome and, if applicable, the regulatory authority(ies) with any required reports." Due to the nature of the Clinical Study Report (i.e. cover the outcome of the trial over all participating countries) it can only be compiled and provided by the sponsor. At least the interface to the regulatory autrhority should remain with the sponsor, the interface to the IRB/IEC should be flexible: investigator/institution or sponsor.	"The investigator/institution or the sponsor should provide the IRB/IEC with a summary of the trial's outcome and, if applicable, the sponsor should provide the regulatory authority(ies) with any required reports."
GQMA	914	916	III.2.13.1	In the EU the obligation to provide study reports to IECs and regulatory authorities is the responsibility of the sponsor. This might result in redundant reporting.	Change to: "The investigator/institution or sponsor as per applicable regulations should provide the IRB/IEC with a summary of the trial's outcome..." A similar adjustment should to be made to line 2830 in section C.3 1.12.
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	914	914	III 2.13.1	For trials under CTR the report has to be provided by the sponsor	Suggestion: "The investigator/institution or sponsor should provide…"
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	914	916	III 2.13.1	Please add: "…in accordance with applicable regulatory requirements."	Suggestion: "The investigator/institution should provide the IRB/IEC with a summary of the trial's outcome and, if applicable, the regulatory authority(ies) with any required reports in accordance with applicable regulatory requirements."
The GCP Unit at Aalborg and Aarhus University Hospital	914	916	2.13.1	The investigator/institution should provide the IRB/IEC with a summary of the trial's outcome and, if applicable, the regulatory authority(ies) with any required reports. According to the EU regulation this is the responsability of sponor	The investigator/institution or the sponsor should provide…..
EFPIA Consolidated Comments	923	923	III.3	While the focus of the statement is on participant safety and trial reliability, it is essential to include a reference to the ethical considerations involved.	The responsibility of the sponsor entails the implementation of risk-proportionate processes to ensure the rights, safety and well-being of the trial participants and the reliability of the trial results throughout the clinical trial life cycle.
Fergus Sweeney	928	928	3.1.1	the concept of "real world data" is very loose. It is real world experience that is key, and better expressed perhaps as "prior clinical experience" in the context of this sentence	replace "..and/or real world data.." with "..and/or data on clinical experience…"
EFPIA Consolidated Comments	932	932	III.3.1.2	To provide better clarity, the statement could include examples or specific guidance on factors that are critical to the quality of a trial. This may include aspects such as study design, data integrity, participant selection criteria, investigational product handling, monitoring and data analysis.	Sponsors should incorporate quality into the design of the clinical trial by identifying factors that are critical to the quality of the trial and by managing risks to those factors. See ICH E8, General Considerations for Clinical Studies.

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Fergus Sweeney	933	933	3.1.2	Not every minor risk identified that may be linked to a critical to quality factor will need managing. Suggest to state "significant risks"	reword to "..managing significant risks.."
ACRO	935	936	3.1.3	ACRO welcomes the acknowledgment that the use of innovative clinical trial designed and technologies may help include diverse patient populations. However, ACRO would welcome further emphasis in the draft of the importance of ensuring diversity of patients in order to ensure that trial outcomes are relevant to a wider set of communities.	To add "from diverse communities" to line 936: "Sponsors should consider inputs from a wide variety of stakeholders , for example, healthcare professionals and patients from diverse communities, to support the development plan …"
ACRO	935	943	3.1.3 & 3.1.4	We welcome the focus on operational feasibility and consideration for the compatibility & consistency in data acquisition tools as a method of quality control and reduction of site & patient burden. We would welcome the inclusion of a recommendation for various stakeholder engagement during this planning and selection process.	To add ", to ensure operational feasibility" to line 937: "... to support the development plan and clinical trial protocols as described in ICH E8(R1), to ensure operational feasibility and when developing the informed consent material and any other participant-facing information."
Quotient Sciences	935	938	3.1.3	Patient involvement in development of protocols and participant-facing information can benefit patients and sponsors. However, it is inappropriate to involve *healthy volunteers* in the design and management of phase 1 trials, for the reasons given above (row 18). Phase 1 healthy volunteer trials are developed in line with: international guidance; industry, regulatory and ethical standards; the safety profile, pharmacokinetics and pharmacodynamics of the IMP; and phase 1 units' many years' experience of volunteer trials. We aim to minimise inconvenience to volunteers wherever possible, but we must ensure the safety of the volunteers and the quality of the data. So we ensure that we inform volunteers of all the burdens and inconvenience of taking part in the trial. While we do not consider it appropriate to seek input from volunteers on trial design and management, we value their views on our facilities, processes and documents. Thus, we seek feedback from our Volunteer Advocacy Panel and ask all volunteers to provide feedback at the end of their study. In particular, we ask volunteers about the content and clarity of our informed consent material, our processes, our documents and the study experience. Wherever possible, we implement changes based on volunteer feedback, such as improving our document templates and upgrading our volunteer facilities.	Please add bold text: 3.1.3 Sponsors should consider inputs from a wide variety of stakeholders, for example, healthcare professionals and patients, to support the development plan and clinical trial protocols as described in ICH E8(R1) and when developing the informed consent material and any other participant-facing information. <u>While involvement of healthy volunteers in the design of phase 1 trials is not usually necessary, phase 1 investigators are encouraged to seek regular feedback from their healthy volunteers on participant-facing documents and other aspects of the volunteer's clinical trial experience.</u>
Richmond Pharmacology Dr Ulrike Lorch Dr Jörg Täubel Dr Thomas Ashdown Dr Edward Jackson Dr Thomas York	935	938	3.1.3	As discussed in our general comments, we believe that collaboration during the protocol development phase should be actively encouraged. A recent survey showed that many investigators do not feel like their sites are taken into consideration when protocols are designed by sponsors [3]. The current wording misses an opportunity to promote the investigator as a key stakeholder in protocol development. Please see suggested wording.	935 - "…a wide variety of stakeholders, for example, investigators, healthcare professionals and patients,…"
Society for Clinical Research Sites	935	938	3.1.3		We strongly encourage that the sponsor also includes investigators and their institution in the list of those that should have input into the protocol.

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Association for Clinical Data Management (ACDM)	940	944	3.1.4	Could we reference the quality be design and link the dots with ICH Q8? Or point to 3.10 below.	Refer to ICH E8 R1
EFPIA Consolidated Comments	940	940	3.1.4	Suggest to add a new section (3.1.5): With the changing clinical trial landscape and the use of data from trials in other trials or meta analysis.	The sponsor should ensure the confidentiality and rights of the trial participants both for the primary and any secondary use of their data".
EFPIA Consolidated Comments	940	943	3.1.4	"The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures and data collection. Protocols, data acquisition tools and other operational documents should be fit for purpose, clear, concise and consistent, when applicable". for consistency with previous statements (e.g."Careful evaluation of the priorities involved in each trial and the risks associated with the priorities will help ensure efficiency by focusing on activities critical to achieving the trial objectives.") this paragraph should mention that protocols, data acquisition tools and other operational docuemnts should be fit for purpose, focused on study prororities and mitigation of risks , clear, concise, and consistent, when applicabe.". Protocols, data acquisition tools and other operational documents always should be fit for purpose, clear, concise and consistent. It is recommended that reference to "when applicable" is in the wrong place.	We propose to add to the folwing sentence to ensure consistency across the document: "The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures and data collection. Protocols, data acquisition tools and other operational documents, when applicable, should be fit for purpose, focused on trial priorities and mitigation of risks, clear, concise, and consistent.
Fergus Sweeney	940	940	3.1.4	There is no need for absolutes "all" does not add.	reword to "ensure that trials are operationally feasible…"
Jazz Pharmaceuticals	940	943	III.3.1.4	We support the intent of the new Revision 3 to describe guidance for more flexible study conduct, and this paragraph as it is drafted aligns to the spirit of that intention. However, we believe there may be an opportunity to give greater emphasis to the new flexibility in this paragraph. Could it include language around decentralized clinical trials, eCOA, or mobile health (at least refer to the specific guidance around those topics)?	
Quotient Sciences	940	943	3.1.4	Sponsors should be encouraged to take investigators' feedback into account when assessing operational feasibility of protocols	Please edit as follows: 3.1.4 The sponsor should ensure that all aspects of the trial are operationally feasible, taking into account feedback from investigators, and should avoid unnecessary complexity, procedures and data collection. Protocols, data acquisition tools and other operational documents should be fit for purpose, clear, concise and consistent, when applicable.
Society of Quality Assurance (SQA)	941	943	3.1.4	The paragraph ends in 'when applicable'. Recommend to remove the qualifier and end the sentence with consistent.	Remove 'when applicable'.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Society for Clinical Research Sites	945	946	3.2		We applaud this statement but it must be clarified by revising it to read "The sponsor should ensure that sufficient resources are available for themselves and provided to the investigators/institutions in sufficient amounts and timeframes to appropriately conduct the trial."
AFI	948	948	3.3	Prior to initiating clinical trial activities, the sponsor should determine the roles	It is advisable to add 'and responsibilities of the resources'
EFPIA Consolidated Comments	951	953	3.4	Terminology different from Principle 5.1, so aligned.	The sponsor should utilise appropriately qualified individuals for the activities to which they are assigned (e.g., biostatisticians, clinical pharmacologists, physicians, data scientists/data managers, auditors and monitors physicians, scientists, ethicists, technology experts, trial coordinators, monitors, auditors and statisticians) throughout the trial process.
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	951	953	III 3.4	When changes occur regarding the clinical trial during the conduct of such trial, the sponsor should provide training for the concerned staff.	Suggestion: "In case of changes to the protocol or trial processes, sponsor should provide adequate training during trial conduct."
IPFA, International Plasma and Fractionation Association	954	956	3. SPONSOR; 3.4 Qualification and Training; 3.4.1 Medical Expertise	Comment: in the current version of ICH E6, an outside consultant may be appointed as medical expert. This information was removed in the proposed text, should we consider that it is no more possible?	please add back: "the appointment of an outside consultant should be kept."
Medicines for Europe	954	956	3.4.1	Further clarification is needed on the use of outside consultant(s) as the mention of outside consultant(s) was removed from the medical expertise section (ICH E6. R2. Section 5.3).	The sponsor should have medical personnel readily available who will be able to advise on specific trial-related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose.
EFPIA Consolidated Comments	955	956	III.3.4.1	Suggest changing "problems" to "issues", consistent with the rest of the text.	The sponsor should have medical personnel readily available who will be able to advise on specific trial-related medical questions or issues problems.
Unicancer	955		3.4.1	The sponsor should have medical personnel readily available who will be able to advise on specific trial-related medical questions or problems. Depending on the organisation: for academic structures, this role is assumed by the coordinating investigator.	The sponsor should have access to medical personnel readily available who will be able to advise on specific trial-related medical questions or problems
Quotient Sciences	961	964	3.6.1	It should be possible for service providers to start preparatory activities that do not carry any risk to participants, such as review of the protocol or drafting documents, before the agreement is signed.	Please add bold text: 3.6.1 Agreements made by the sponsor with the investigator/institution, service providers and any other parties (e.g., independent data monitoring committee (IDMC), adjudication committee) involved with the clinical trial should be documented prior to initiating the activities (with the exception of preparatory administrative activities, such as protocol review or drafting documents).

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Good Clinical Trials Collaborative, on behalf of supporting organisations	966	967	Sponsor (3.6.2)	Change from "Agreements should be updated when necessary to reflect changes *in the activities delegated"* to "*…in the activities and responsibilities* ."	
Society for Clinical Research Sites	966	967	3.6.2	We support the need for this statement knowing that activities can, and often do change. However, it is also not uncommon for costs to change as well, even if delegated activities stay the same, which can also have a deleterious effect on study conduct if not promptly addressed.	This section should state "Agreements should be updated when necessary to reflect significant changes in the activities delegated or costs incurred."
PPD	969	973	III. Annex I 3. SPONSOR 3.6 Agreements	Request clarification of "approved protocol". Approved by whom?	3.6.3 The sponsor should obtain the investigator's/institution's and, where applicable, service provider's agreement: (a) to conduct the trial in accordance with the sponsor, IRB/IEC and regulatory authority approved protocol, and in compliance with GCP and applicable regulatory requirement(s);
EFPIA Consolidated Comments	975	975	3.6.3(b)	Whose data recording/reporting procedures are listed? Although understanding the intent, we would welcome additional clarifications.	to comply with agreed procedures for data recording/reporting, including timelines;
EFPIA Consolidated Comments	977	980	3.6.3 (c)	The Draft Guideline states: "to retain the trial-related essential records…that these documents are no longer needed…" The term records should be utilized consistently.	Proposed change: "to retain the trial-related essential records…that these documents records are no longer needed…"
Karolinska University Hospital, Stockholm, Sweden	977	980	3.6.3 c	See comment and rationale regarding 2.12.11	to retain the trial-related essential records for the required retention period in accordance with applicable regulatory requirements *or longer should the sponsor request extended retention and obtain applicable approvals for extended data processing and record retention* .
Society for Clinical Research Sites	977	980	3.6.3		Similar to our comment on Annex I Item 2.12.11, this section should be rewritten as "The investigator/site should retain their essential records for the required retention period in accordance with their local applicable regulatory requirements. After this period is expired, or if the investigator becomes unable to maintain the records during their regulated time period, the sponsor may retain the option to have the records transferred to their custody." This revision would be in the best interest of the sponsor to reproduce those records when needed for their business, instead of imposing indefinite storage upon investigators/sites that are often ill-prepared in record-archiving practices.
EFPIA Consolidated Comments	982	984	3.6.3 (d)	Suggest adding "on site/remote" to ensure that the sponsor has the opportunity to undertake these activities in person, where required. Rewording to confirm sponsor doesn't inspect.	to permit on-site/remote monitoring, auditing by the sponsor, review by IRB/IECs and inspections by regulatory authorities (domestic and foreign) including providing direct access to source records and facilities, including to those of service providers.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Society for Clinical Research Sites	982	984	3.6.3	We have concerns over the use of the term "direct access" (both here as well as in Annex I Items 2.8.11(n), 2.12.12, 3.11.4.1(c), 3.16.4(a), 3.16.4(b), the Glossary and Appendix B.11). The phrase "direct access" (as opposed to "access") is interpretable as supporting an activity that is generally prohibited with established healthcare privacy/security practices and regulations across the globe (i.e. providing login IDs directly into to electronic health records).	We request the deletion of the word "direct" (or change the phrase to "access to view") here and in the other sections referenced to avoid this confusion and that the guidance can recognize the variety of ways source document verification has been accomplished over the past decade without "direct" access (but with "access to view"). This would also bring these sections to be consistent with Annex I Item 3.11.4's requirement that monitors "adhere to data protection and confidentiality requirements in accordance with applicable regulatory requirements, institution policy and established data security standards."
Good Clinical Trials Collaborative, on behalf of supporting organisations	984	984	Sponsor (3.6.2)	Change from "… including to those of service providers" to "including to those of key service providers." To add an element of proportionality – not every mailing house, printing firm, cleaning service, etc is relevant for audits and inspections by sponsors, IRB/IECs, regulatory authorities, etc. and this is not generally part of the standard terms and contracting conditions of such suppliers.	
Ipsen	986	987	3.6.4	Suggest clarifying the sentence and what is meant by other participating investigators. Are these other investigators at different site or sub-investigator?	
Association for Clinical Data Management (ACDM)	994	996	3.6.6	More clarity is needed here. The sponsor is who will choose global service providers, so which are the expectations for the investigator? Both FDA draft guidance on DHT and DCT include additional details on sponsor versus investigator responsibilities. In those documents the investigator appears to be responsible for training and oversight of staff who use or provide the services for participants in their trial (ex: ensuring the site staff are trained to use a system), while the sponsor responsibilities are focused more on study wide activities such as selection, contract, validation, change control).	Please re-write so it is clear this is investigator being responsible for activities, not for the selection of global service provide. This could be misconstrued as currently written
CARVALHO Carla	994	996	3.6.6	In order to confirm that the investigator agrees with the identified service provider by the sponsor, it's adviced to reflect this authorization through an agreement.	The sponsor should provide information to the investigator on any service provider identified by the sponsor to undertake any activities under the responsibility of the investigator. The responsibility for such activities remains with the investigator and is reflected in a signed agreement with the investigator.
eClinical Forum	994	996	III 3.6.6	This states that the investigator remains responsible for sponsor appointed service provider activities. III 3.6.7 further states that a service provider is supposed to report any incidents only to the sponsor. This seems in conflict as there is no requirement to also notify the investigator who is the responsible party. There is no mechanism for the investigator to be responsible for service providers with which they have little or no interface. How is this supposed to work in practice?	Revise III 3.6.6 to state how each investigator in a trial are supposed to be responsible for sponsor service providers.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA Consolidated Comments	994	996	3.6.6	Ensure there is a clear limit of the investigator responsibilities, therefore trying to bring it back to the medical care and assessment of efficacy and safety as per the protocol.	The sponsor should provide information to the investigator on any service provider identified by the sponsor to undertake any activities under the responsibility of the investigator. The responsibility for such activities remains with the investigator when these activities involve trial-related medical decisions (e.g. participant eligibility and enrolment, protocol specified medical procedures, assessment of efficacy/safety, evaluation of test results, decision to dispense or make changes to the trial medication).
German Pharmaceutical Industry Association (BPI)	994	996	3.6.6.	Sentence is difficult to understand. What situation is described with the wording "service provider *identified* by the sponsor"? What kind of sponsor activity is described here by the wording "identified" (is it e.g., contracted, or is it qualified?)? Without clear description of the situation, sponsor will not know when and how to fulfill this requirement.	rewording recommended
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	994	996	III 3.6.6	The wording should be adapted to the wording in section 2.3.1 to avoid misunderstanding.	Suggestion: "The sponsor may support the investigator to identify a suitable service provider to undertake any activities under the responsibility of the investigator (for "activities under the responsibility of the investigator" see chapter 2). The sponsor should provide adequate information concerning the service provider to the investigator. The final decision and the responsibility for the activities done by the service provider remains with the investigator." See section 2.3.1
Kotagiri Srinivasa Rao	994	996	3.6.6	The sponsor should provide information to the investigator on any service provider identified by the sponsor to undertake any activities under the responsibility of the investigator. The responsibility for such activities remains with the investigator	In some cases investigator may not directly interacting with sponsor. In this case institute also can be in contact with sponsor for such information.
PPD	994	996	3.6 Agreements	"...under the responsibility of investigator." Would this include any medical assessments and therefore also "central reviewer service provider for images", and what is the consequence of this? (similar situation for central labs, home health care, etc.)	The sponsor should provide information to the investigator on any service provider identified by the sponsor to undertake any activities under the responsibility of the investigator. The ultimate responsibility for and oversight of such activities remains with the investigator.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Society for Clinical Research Sites	994	996	3.6.6		As referenced previously, the draft guideline is reinforcing the misalignment between the sponsor controlling the contracted entity with the statements that the investigator remains responsible. Suggesting that the local site investigators are accountable for service providers they have little to no control over (i.e. controlled by the sponsor or a CRO acting as a coordinating investigator) is a well-documented barrier to investigators/institutions adopting the more modern and scalable infrastructure that sponsors are capable of setting up. Without alignment on this issue, such guidance will continue to create anxiety in the investigator community and continue to prevent the benefit of those trial expansion efforts that can be advantageous. We maintain that while it is necessary for the investigator and the sponsor's selected service provider to work in conjunction with each other, if the sponsor is selecting and contracting with that service provider, the sponsor bears the responsibility and accountability for oversight of that service provider, especially if the sponsor is acting as a coordinating investigator as defined in the glossary.
The GCP Unit at Odense University Hospital, OPEN	994	996	3.6.6	Make a reference to 2.3.1 (as done to 3.6.6 in 2.3.1)	(se section 2.3.1.)
Good Clinical Trials Collaborative, on behalf of supporting organisations	996	996	Sponsor (3.6.6)	Delete "The responsibility for such activities remains with the investigator." If it is agreed that the Sponsor rather than the Investigator will arrange a particular service provider, responsibility for oversight of the activities performed must remain with the Sponsor (who organised it and has a contract with it) rather than the Investigator (who had no role in the selection and does not have a contractual relationship with the service provider).	Delete "The responsibility for such activities remains with the investigator."
EFPIA Consolidated Comments	998	1004	3.6.7	We would suggest moving the Section 3.6.7 directly after section 3.6.5 for better consistency.	We suggest moving section 3.6.7 directly after section 3.6.5.
Society for Clinical Research Sites	998	1004	3.6.7		For reasons mentioned above, we believe that the word "responsibility" (Line 999) should be changed to "accountability".
ACRO	1001	1004	3.6.7	ACRO members have world-wide experience of translating sponsor oversight into practical actions. With this perspective, ACRO feels that the terminology regarding sponsor oversight of providers is ambiguous and may be subject to overinterpretation. A potential unintended consequence is limitation of the influence of service provider to ensure change by the sponsor in case of non-compliance. This could impact safety. ACRO would welcome further clarity on this.	To add "and/or regulatory or ethics committed as required, " to line 1002: "Any service provider used for clinical trial activities should implement appropriate quality management and report to the sponsor, and/or regulatory or ethics committed as required, any incidents that might have an impact on the safety of trial participants or/and trial results.".
Fergus Sweeney	1003	1003	3.6.7	there is no need for absolutes . "any incidents" can drive a demand for massive over reporting to sponsors wiithout any sense of proportion	reword to "..and report to the sponsor incidents that might have a significant impact on the safety or participants…"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
eClinical Forum	1006	1008	III 3.6.8	This states the sponsor is responsible for assessing the suitability and selecting service providers. Line 458-461 III 2.3.1 says the investigator retains the final decision on whether the service provider intended to support the investigator is appropriate based on information provided by the sponsor (see section 3.6.6). This could cause confusion to sites.	Revise both III 3.6.8 and III 2.3.1 to be consistent as to who is responsible for service providers at each point of time. Sites can only be responsible when they directly deploy the service provider.
Ipsen	1006	1009	3.6.8	It is not clear if the sponsor responsiblities in 3.6.8 are also the sponsor's responsiblities if services are sub-contracted by a service provider to a third party.	
Association for Clinical Data Management (ACDM)	1011	1012	3.6.9	Most vendors (aside from CRO)s will only provide access to SOPs during an audit or inspection. Many times SOPs are only reviewed during qualification/selection and audit. I think it is clear that SOP access is needed during selection, but what is mean by oversight? Is routine audit schedule sufficient?	If there is a requirement for the sponsors to have continued access to any SOPs/processes etc used by their vendors? If yes please confirm this in the guidance. Also if the sponsor needs to assure vendors have access to any SOPs they require the vendors to follow.
CARVALHO Carla	1011	1012	3.6.9	When selecting a service provider it's important to know the quality events detected by the service provider such as the complaints and category of complaints, system deviations, planned change controls. In order to avoid any brake by the service providers, it's recommended to frame such points.	The sponsor should have access to relevant information (e.g., SOPs, complaints, system deviations, planned change controls and performance metrics) for selection and oversight of service providers.
Ipsen	1011	1012	3.6.9	The sponsor should have access to relevant information (e.g., SOPs and performance metrics) for selection and oversight of service providers. What about sub-contracted service provider (third party)? Is it under the service provider’s responsibility or remain under Sponsor’s responsibilities?	
SGS Health Sciences	1011	1012	3.6.9	adding UPON REQUEST would allow the possibility for sponsor to review SOPs periodically during an audit of a CRO, and for CRO to provide access to sponsor when needed. If not adding this, this could be interpreted by sponsors as a requirement for them to have continuous access to up to date versions of all applicable CRO SOPs. For a CRO, extra resources would be needed to provide/send/upload SOP copies, keep track, send updated versions to all sponsors/clients which would not be feasible + our SOPs are proprietary information, continuously improved based on experience, to meet high quality standards and regulations - we are proud of them so we are not keen on distributing them to third parties, not even to our clients/sponsors - for permanent access. Could this be made more clear in R3, so that this can not be understood as a requirement for sponsors to have up to date copies of SOPs of their service providers at any time?	Sponsor should have access to relevant information UPON REQUEST (e.g., SOPs and performance metrics) for selection and oversight of service providers.
EFPIA Consolidated Comments	1014	1015	3.6.10	Clarify what is meant by important and ensure the appropriate oversight of subcontracted activities	The sponsor should ensure appropriate oversight of the relevant important trial-related activities, especially those critical to quality, that are transferred to service providers and including further activities subcontracted by the service provider.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUCROF	1014	1014	III. 3.6.1	"important trial-related activities" The word "important" is used to describe something that relates to protection of trial participants and reliability of trial results. Examples are: important trial-related activities, important protocol deviations. Definition of important in the context of the guideline should be considered.	
Dr. C. Wilsher	1017	1019	3.6.11	What is the utility of saying that providers might have this already fulfilled this? Suggest remove the text - "which may be fulfilled by a service provider's existing processes". Addition of "protocol and applicable regulatory" in order to be consistent and avoid any misunderstanding that service providers must conduct their activities in compliance with all three.	Trial-related activities performed by service providers should be conducted in accordance with relevant protocol, GCP and applicable regulatory requirements.
EUCROF	1017	1018	III. 3.6.11	"Trial-related activities performed by service providers should be conducted in accordance with relevant GCP requirements…"	"Trial-related activities performed by service providers should be conducted in accordance with relevant GCP and the applicable regulatory requirements…"
Kotagiri Srinivasa Rao	1027	1034	3.7.1	The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by education, training and experience and should demonstrate they have adequate resources and facilities to properly conduct the trial.If organisation of a coordinating committee and/or selection of coordinating investigator(s) are to be utilised in multicentre trials, their organisation and/or selection are the sponsor's responsibility, and their roles should be documented prior to their involvement in the trial.	In some situations investigator selection lies with institutions . During the course of the study / trial duration investigator may change because of some administartive changes. Please provdie the same provision in the clause
Medicines for Europe	1028	1034	3.7.1	The term "coordinating committee" was removed from the glossary. However, if the terms will be used in the revised gudiance we recommend keeping the definition for "coordinating committee" in the revised guideline.	Below to be added to the Glossary: Coordinating Committee: A committee that a sponsor may organize to coordinate the conduct of a multicentre trial.
Society for Clinical Research Sites	1028	1034	3.7.1		We request an alteration of the clause that the investigator "…should demonstrate they have adequate resources and facilities to properly conduct the trial." While we understand that the investigator must demonstrate certain capabilities on their own (e.g. adequate office space, sufficient time), the investigators are almost exclusively dependent on the sponsors to resource the study and to do so in a timely fashion. Regardless if the investigator has the proper space and equipment in place, without the added resources from the sponsor (e.g. financing and/or other in-kind items or services necessary for study conduct), the costs to conduct and maintain the study are beyond the scope for the investigator to provide. Therefore, we ask that the clause be revised to "…should, assuming the added resources from the sponsor are provided in amounts and schedules commensurate for study conduct, demonstrate they have adequate resources and facilities to properly conduct the trial."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	1031	1033	III 3.7.1	Investigator selection: In IITs, the coordinating investigator is usually the one who has the study idea and formulates the scientific-medical question. Then, the investigator's institution usually takes over the sponsor function or an institution is selected to take over the sponsorship (university, university hospital, CRO assuming sponsorship). So it is often the other way around, the sponsor does not choose the coordinating investigator, but the coordinating investigator chooses a sponsor. Please take this into account.	
EAHP	1036	1038	III 3.7.2	Besides the Investigator's Brochure also the Pharmacy binder and the safety data sheet need to be included.	The sponsor should provide the investigator(s)/institution(s) with the protocol and an up-to-date Investigator's Brochure, Pharmacy binder and the investigational medicinal product safety data sheet as well as sufficient time for the review of the protocol and the information provided.
EFPIA Consolidated Comments	1036	1038	3.7.2	language removed about when the protocol and IB should be provided. This was R2 text 5.6.2	Before entering an agreement with an investigator/institution to conduct a trial....
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	1036	1038	III 3.7.2	According to 1.1.2 c "current scientific information" can be used instead of an IB; please add.	Suggestion: "The sponsor should provide the investigator(s)/institution(s) with the protocol and an up-to-date Investigator's Brochure or current scientific information …"
EUCROF	1039	1039	III. 3.8	Would switch the sequence in the heading in order to align with the sequence of 3.8.1 and 3.8.2	Communication with IRB/IEC and Regulatory Authorities
Ipsen	1046	1060	3.8.2	The details from EC (name/ members) are not available under CTIS	
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	1055	1056	III 3.8.2	In some countries such a statement is not necessary as - according to national law - only IRBs/IECs that are organised and operate according to GCP are officially registered and allowed to approve/ to review a clinical trial.	Suggestion: "(aa) a statement that it is organised and operates according to GCP and the applicable regulatory requirements; unless organisation and operation according to GCP is guaranteed/ regulated by national law. "
Association for Clinical Data Management (ACDM)	1062	1064	3.9.1	The records should be attributable, legible, contemporaneous, original, accurate and complete under investigators' responsibility at 2.12.2	Please add that all documentation should meet the ALCOA standards from sponsor, investigator, CRO and any other vendors.
EFPIA Consolidated Comments	1062	1064	3.9.1	To be consistent with the principles we would suggest to change to good decision making and include rghts safety and wellbeing. Principles 6 and 9.	...trial participant's rights safety and well-being and good appropriate decision making.
Quotient Sciences	1064	1064	3.9.3	Typographic error - apostrophe in wrong place.	Please change " participant's " to " participants' ".
AFI	1070	1072	3	As this is required in Appendix C (B.12.3), reccomended a cross reference, to clarify that it should be reported in the protocol	see Appendix C (B.12.3)

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA Consolidated Comments	1070	1072	3.9.3	This section refers to classifying important deviations (ie, major deviations), and states "i.e., those that impact the rights, safety and well-being of trial participants and the reliability of results". This can be interpreted that the deviation must meet all of these criteria in order to classify as "important" due to the use of the word "and".	The sponsor should determine necessary trial-specific criteria for classifying protocol deviations as important (i.e., see ICH E3) with respect to those that impact on the rights, safety, well-being of trial participants and or the reliability of results).
EUCROF	1070	1072	III. 3.9.3	"The sponsor should determine necessary trial-specific criteria for classifying protocol deviations as important (i.e., those that impact the rights, safety and well-being of trial participants and the reliability of results).	A definition for "important" is given here, but would be helpful in the Glossary
GCP-unit, Copenhagen	1070	1072	3.9.3	Sorry, but it seems that the sentence is difficult to read and understand	Perhaps write more clearly, that the sponsor has to classify what aspect of the trial it is important to be aware of in concern to avoid deviations
Mandy Jackson National Clinical Trials Office Quality Working Group Ireland	1070	1072		Is sponsor required to document trial-specific criteria for classifying protocol deviations as 'Important' for every trial	Can a generic SOP with regards to deviations be used
Medicines for Europe	1070	1072	3.9.3	shared responsibility with coordinating investigator and/or institution	The sponsor, together with coordinating investigator/institution, should determine necessary trial-specific criteria for classifying protocol…
Quotient Sciences	1070	1072	3.9.3	For the avoidance of doubt, important deviations should be distinguished from serious breaches, which require regulatory & REC reporting in the UK and have a *significant* impact on the safety or physical or mental integrity of the subjects of the trial or the scientific value of the trial. Please clarify that important deviations may also constitute a serious breach.	Please add bold text: 3.9.3 The sponsor should determine necessary trial-specific criteria for classifying protocol deviations as important (i.e., those that impact the rights, safety and well-being of trial participants and the reliability of results).Where applicable, any important protocol deviations that also meet criteria for a serious breach of GCP or the protocol should be reported in line with local regulatory requirements.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Society for Clinical Research Sites	1070	1072	3.9.3	Annex I Item 3.9.3 delineates that it is the sponsor who determines the criteria for an "important deviation", but nowhere in the draft have we found who the arbitrator is that applies the circumstances for the deviation to the sponsor's criteria and makes the determination. Considering the varying negative impacts and the amount of work that needs to be done for an "important deviation" (as opposed to a deviation that is not an "important deviation"), we suggest that neither the sponsor nor investigator should be able to make that determination without concurrence from the other as well as the item should delineate a process for the parties to follow if there is disagreement.	Considering the varying negative impacts and the amount of work that needs to be done for an "important deviation" , neither the sponsor nor investigator should be able to make that determination without concurrence from the other as well as the item should delineate a process for the parties to follow if there is disagreement. We also challenge the notion that the investigator is solely responsible for explaining the (important) deviation and implementing appropriate measures to prevent recurrence. More protocol deviations are occurring through no fault of the site investigator, and their explanations and corrective/preventative action plans are outside of the control and capabilities of the investigator. An example of such circumstance would be a deviation caused by sponsor-provided technology or a sponsor-contracted service provider. In these cases, the deviation should not be attributable to the investigator and it should be the responsible party's obligation to explain the deviation to both the sponsor and investigator as well as create the corrective and preventative action plan acceptable to both the sponsor and the investigator. Arguably, it would be up to the deviating parties or their contracting entity to provide this explanation and plan to the investigator instead.
Society for Clinical Research Sites	1070	1072	3.9.3		As referenced in our comments for Annex I Item 2.6.2, although this section delineates that it is the sponsor who determines the criteria for an "important deviation", nowhere in the draft have we found who is the arbitrator who applies the circumstances around the deviation to the sponsor's criteria and makes the determination. Considering the varying negative impacts and the amount of work that needs to be done for an "important deviation" (as opposed to a deviation that is not an "important deviation"), we suggest that neither the sponsor nor investigator should be able to make that determination without concurrence from the other and that should there be disagreement, an escalation process to an independent party (perhaps the IRB/IEC) should be the final arbitrary.
eClinical Forum	1076	1077	III 3.9.4	This states; Risks related to such decisions should be suitably managed throughout the planning, conduct and reporting of the trial.	This clause should also require that risks be periodically updated.
Ipsen	1091	1096	3.9.8	The need for an endpoint assessment/adjudicationcommittee to be blinded in an open label trial adds a potentially unnecessary layer of complexity to trial conduct and burden.	
IFCT	1092	1092	3.9.8	"certain trials" : to be detailled	Give details.
Good Clinical Trials Collaborative, on behalf of supporting organisations	1095	1096	Sponsor (3.9.8)	Amend the current text from: "to ensure that the data reviewed by committee are as free of bias as possible" (which is unclear and somewhat inaccurate) to "to minimise bias in the interim analyses reviewed by the IDMC and in the final results."	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUCROF	1098	1101	III. 3.9.9	"Committees established for purposes that could impact participant safety or the reliability of trial results should include members with relevant expertise and with managed conflicts of interest, have written operating procedures (e.g., charters) and document their decisions." We thnk that the requirements pertain to all committees the sponsor establishes. No need to specify impact on participant safety or reliability of trial results.	"Committees established by the sponsor should include members with relevant expertise and with managed conflicts of interest, have written operating procedures (e.g., charters) and document their decisions."
ACRO	1102	1403	3.10	ACRO notes that there is no reference to Quality Tolerance Limits (QTLs) within the R3 draft, a change that has been made since R2.When applied as intended, QTLs are a valuable tool to detect systemic issues earlier than they would otherwise be flagged. QTLs are an important risk management and oversight tool, and regulatory support of the adoption of QTLs should be demonstrated clearly in guidance. ACRO recognizes that after the release of R2, there was confusion in the industry around QTLs and adoption generally lagged behind where we thought it should be. The distinctions between KRIs, KPIs and QTLs were not always defined, therefore companies had difficulties establishing QTLs. However, in recent years, this began to shift as companies became more and more comfortable implementing QTLs. ACRO is concerned that the proposed change in terminology will further add to any hesitancy to adopt these valuable tools. A landscape analysis of over 4,000 clinical trials conducted by ACRO showed a slow but steady increase in the uptake. In 2019, 10% of the studies within our dataset had utilized QTLs and by 2022, that had increased to 29%. This demonstrates that while adoption has been slow, the industry is just starting to utilize QTLs. ACRO is therefore disappointed to see that at this junction, QTLs have been subsequently inexplicably removed from the R3 draft. In addition, QTLs are included in ICH M11 section 11.1 and ACRO believes that consistency between M11 and E6(R3) is essential to avoid any unnecessary confusion in the industry.	ACRO suggests that ICH add QTLs back into the guidance document. The general consensus among ACRO members is that the new verbiage of "acceptable ranges" should be interpreted as a QTL-equivalent. However, further regulatory clarity on this definition would be valuable to ensure that industry is consistently interpreting the terms as intended by the regulators. ACRO also asks for clarity around whether acceptable ranges should go into the CSR, as QTLs did.
Fergus Sweeney	1102	1153	3.10.	Quality assurance and quality control are part of quality managment and should be grouped under the quality management heading, or directly referenced from 3.10 as being part of QM. GCP needs to make very clear that quality assurance does not equal audit and the "quality" is owned by management and operational functions and not by a separate audit group. The approach that is current to call the audit group QA means that management and operational groups have a diminshed sense of responsibility for quality.	either regroup 3.11 under 3.10 simply by adjusting overall numbering of the 3.11 section or add a sentence to 3.10 that states "Quality assurance and quality control are key components of the quality management approach."
German Pharmaceutical Industry Association (BPI)	1102	1403	3.10. 3.11.	The logic of the chapters "Quality Management" and "Quality Assurance / Quality Control" is not clear. QA and QC are part of Quality Management, why are they described in a separate chapter, whereas the chapter Quality Management only describes risk management processes? A more logical structure would facilitate understanding of the important topic of quality.	Restructure quality chapters.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Jaldip Vyas	1102	1152	3.10	I strongly believe that the sponsor should not only implement an appropriate system to manage quality throughout all stages of the trial process, they should also be able to quantify the effectiveness of their current QMS. One way of achieving this is by implementing risk based QMS, embadding performance and compliance mesurement criteria in the QMS. A performance and compliance matrix is a crucial tool in the planning, execution, and monitoring of clinical trials. It serves as a comprehensive framework that outlines the various performance metrics and compliance measures that need to be tracked during the course of the trial. Here are some key reasons why a performance and compliance matrix is important in clinical trials: Ensuring Quality Data Collection: The matrix helps define specific performance indicators and compliance criteria that are essential for collecting high-quality and reliable data. It ensures that the data collected throughout the trial is accurate, complete, and adheres to the predefined standards, minimizing errors and biases. Adherence to Protocols and Regulations: Clinical trials must adhere to strict protocols and regulatory guidelines to ensure patient safety and the validity of the results. The matrix outlines the key compliance requirements and facilitates monitoring to confirm that all procedures and protocols are followed correctly.	The sponsor should implement an appropriate risk based system to manage quality throughout all stages of the trial process. Sponsor should develop thair Quality Management System to measure quality through out the study conduct by implementing compliance metrics and performance measurements.
Jaldip Vyas	1102	1152	3.10	Identifying and Addressing Non-Compliance: Non-compliance can jeopardize the integrity of the trial and the credibility of its results. By having a clear matrix, sponsors, investigators, and monitors can quickly identify areas of non-compliance and take corrective actions promptly to bring the trial back on track. Resource Management: Clinical trials can be complex and resource-intensive endeavors. The performance and compliance matrix help allocate resources efficiently by identifying critical areas that need more attention and resources. Risk Management: By defining performance metrics and compliance criteria, the matrix enables the identification of potential risks early on. This allows stakeholders to proactively develop risk mitigation strategies and contingency plans to address any challenges that may arise during the trial.	The sponsor should implement an appropriate risk based system to manage quality throughout all stages of the trial process. Sponsor should develop thair Quality Management System to measure quality through out the study conduct by implementing compliance metrics and performance measurements.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Jaldip Vyas	1102	1152	3.10	Real-time Monitoring and Reporting: The matrix facilitates ongoing monitoring of trial progress, allowing stakeholders to have real-time insights into the trial's performance and compliance status. This enables timely decision-making and the ability to intervene if necessary. Enhanced Communication and Collaboration: The matrix serves as a common reference point for all stakeholders involved in the clinical trial, fostering better communication, and collaboration. It ensures that everyone is on the same page regarding the objectives, expectations, and compliance requirements of the trial. Regulatory Submission and Inspection Preparation: When it comes to regulatory submissions and inspections, having a well-documented performance and compliance matrix can streamline the process. It provides evidence that the trial was conducted in a rigorous and compliant manner. Continuous Improvement: By analyzing performance data and compliance metrics, clinical trial teams can identify areas for improvement in future trials. Lessons learned from one trial can be applied to optimize the design and conduct of subsequent studies.	The sponsor should implement an appropriate risk based system to manage quality throughout all stages of the trial process. Sponsor should develop thair Quality Management System to measure quality through out the study conduct by implementing compliance metrics and performance measurements.
EAHP	1103	1104	III 3.10	Compounding should be added as an element of the trial process.	The sponsor should implement an appropriate system to manage quality throughout all stages of the trial process, including the potential compounding.
German Pharmaceutical Industry Association (BPI)	1111	1112	3.10.	"*sponsor should describe the quality management approach… in the clinical trial report (see ICH E3)*" ICH E3 currently only foresees a chapter "*Data Quality Assurance*" for the report. Data Quality Assurance is only a part of the overall quality management approach. Is the intention that this chapter should be used for description of the quality management approach?	Update of ICH E3 in this regard seems necessary.
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	1111	1112	III 3.10.	"The sponsor should describe the quality management approach implemented in the trial in the clinical trial report (see ICH E3)." It reads as if there is always an E3 report, but that is not the case, especially not in IITs. Therefore please add: "... for trials supporting marketing authorisation application."	Suggestion: "The sponsor should describe the quality management approach implemented in the trial in the clinical trial report (see ICH E3), for trials supporting marketing authorisation application."
EFPIA Consolidated Comments	1115	1119	3.10.1.1	Some additional examples are proposed to provide additional clarity and focus on some risk areas.	Risks should be considered across the processes used in the clinical trial (e.g., trial design, blinding, participanttient selection, informed consent process, randomisation and investigational product administration, data collection and handling, and service provider activities)
GCP-unit, Copenhagen	1116	1117	3.10.1.1.	The sentence do not make sence "The sponsor should identify risks that may have a meaningful impact on critical to quality factors"	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	1117	1119	3.10.1.1	Some trials where the risk to participants is not negligible (for example, first in man or SAD/MAD studies) are performed in healthy subjects. Therefore the text should not cover patients only.	Risks should be considered across the processes used in the clinical trial (e.g., patient subject selection, informed consent process, randomisation and investigational product administration, data handling, and service provider activities).
SHIONOGI	1118	1118	3.10.1.1	inconsitent use of patient selection, whereas the guideline uses the term participant	replace patient seleciton by participant selecton to ensure consistency throughout the guideline
DGPharMed e. V. (Deutsche Gesellschaft für Pharmazeutische Medizin)	1120	1127	III.3.10.1.2	The guideline bases the risk evaluation procedure on a FMEA concept. That is a limitation and unnecessarily excludes further (appropriate) approaches for risk evaluation. For the guideline claim to be open for different (modern) solutions and approaches, this wording should also be open for further appropriate approaches. E.g.: ICH Q9 is more open at this point and offers the possibility to use different risk management methodologies (Chapter 5).	The wording should also be open for further appropriate approaches
AFI	1122	1127	3.10.1.2	For clarity suggested to add Probability, Detectability and Seriousness	(a) the likelihood of harm/hazard occurring (probability); (b) the extent to which such harm/hazard would be detectable (detectabilty); (c) the impact of such harm/hazard on trial participant protection and the reliability of trial results (seriousness).
EAHP	1122		III 3.10.1.2	In relation to the likelihood of harm/hazard occurring it should be specified that these can occur for patients and compounders.	(a) the likelihood of harm/hazard occurring for patients and compounders;
EFPIA Consolidated Comments	1122	1127	3.10.1.2	Harm/hazard is not intuitive. So we would prefer to revert to the old text, but include issues as well. Currently doesn't cause problems. Removal of 'evaluate…against existing controls' does not give definite parameter of measuring the risk proactively	The sponsor should evaluate the importance of potential risks against risk controls considering:change a) the likelihood of the error or issue occurring b) the extent to which the error or issue would be detectable c) the impact of such error or issue on.....
Fergus Sweeney	1128	1134	3.10.1.3	the concept of risk acceptance is not mentioned at all. It is part of ICH E8(R1) and is a critical part of risk management approaches including in high risk areas, and is an important component of a proportionate approach. The sponsor should determine which risks can be accepted and which need to be mitigated.	include text at the end of 3.10.1.2 or in 3.10.1.3 "Based on the risk evaluation the sponsor shoudl determine which risks need to be mitigated and wihich risks can be accepted."
Association for Clinical Data Management (ACDM)	1129	1134	3.10.1.3	This aligns with ICH Q9 and also with FDA draft guidance on DHT (section H) and DCT (multiple sections). There is increased emphasis across agencies on evaluating risk and designing proportionate processes to mitigate risk (ex: use of direct to patient IP, validation of systems)	Please reference ICH Q9

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA Consolidated Comments	1129	1134	3.10.1.3 (a)	some addittional examples included for clarity as they may be incorporated into other documents and these are examples. There was a worry that this list was prescriptive.	Risk mitigation activities may be incorporated into protocol design and implementation. Other risk mitigation activities may be incorporated in, but not limited to, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to SOPs, and training in processes and procedures, and other types of plans, manuals or specifications for the clinical trial where relevant.
GCP-unit, Copenhagen	1131	1131	3.10.1.3	"Risk mitigation activities may be incorporated (…)", it sounds as if there is a choice not to do it. Mayby change the sentence, so its more an obligation to incoporate were relevant	Perhaps change to "Risk mitigation activities sholud be incorporated where its relevant in the protocol design (…etc.)"
GCP-unit, Copenhagen	1136	1139	3.10.1.3	Its not totaly clear what processes this refers to. Might be relevant with a section in between to explain how identiffied risk could be handled	
Jazz Pharmaceuticals	1136	1139	III.3.10.1.3	The requirement to "set acceptable ranges" requires further discussion on the expectation for this change. What is considered "acceptable ranges" if the concept of QTL is not used? What is considered required vs. nice to have?	
PPD	1136	1139	3.10 Quality Management	Concerns regarding the removal of the language (Quality Tolerance Limits) that allows for clear communication between sponsors, CROs, and regulators related to tolerance limits. Over the past 7 years, the industry seems to have finally achieved a relatively consistent understanding of what QTLs are (though methodology varies). Removing this as a term is a risk to this progress and will again create confusion across the industry in trying to define the expectations. Ideally, instead of removing the term, regulatory bodies would provide insight into expectations to help alleviate the confusion and uncertainty. The removal of language related to what the 'ranges' should apply presents a similar concern.	Suggest not removing the language used in the previous version R2 (sections 5.04 and 5.07), or using similar language to what was used in the previous version R2. (b) The sponsor should set acceptable ranges (e.g., Quality Tolerance Limits) to support this process within which variation can be accepted. Where deviation beyond these ranges is detected, an evaluation should be performed to determine if there is a possible systemic issue and if action is needed.
Quotient Sciences	1136	1139	3.10.1.3 (b)	*Acceptable ranges* is a clearer term than *quality tolerance limits*, but it would be helpful to include some examples (e.g., number of deviations per site, repeated deviations, recruitment rates?)	Please consider adding some examples to aid understanding of acceptable ranges.
Sandoz AG, Switzerland	1136	1139	3.10.1.3	The section is refering to "acceptable ranges to support the risk control process step". In ICH GCP E6(R2) is referring to "Quality Tolerance Limit (QTL)". Suggest to use same wordings in E6(R3) as it is now widely used in the organizational processes.	Suggest to use "Quality Tolerance Limits" instead of "Acceptable ranges" wordings in E6(R3).
EFPIA Consolidated Comments	1141	1144	3.10.1.4	the if applicable was not clear in relation to mitigating activites, as there may not be any, so proposal changed.	The sponsor should communicate the identified risks and any mitigating activities, if applicable, to those who are involved in taking action or are affected by such activities."
EFPIA Consolidated Comments	1146	1148	3.10.1.5	remove quality management as this term was removed in R3 in relation to risk and change this to risk management activities	..... Implemented quality risk management activities....

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KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	1150	1152	III 3.10.1.6	"… and document them in the clinical trial report (ICH E3)" It reads as if there is always an E3 report, but that is not the case, especially not in IITs. Therefore please add: "... for trials supporting marketing authorisation application."	Suggestion: "The sponsor should summarise and report the risks and the remedial actions taken in relation to important deviations from the acceptable ranges as detailed in section 3.10.1.3(b) and document them in the clinical trial report (ICH E3), for trials supporting marketing authorisation application."
Quotient Sciences	1150	1152	3.10.1.6	How is an *important* deviation from acceptable ranges to be defined? For example, is it a deviation from acceptable ranges that results in closure of a site or rejection of data?	Please clarify what consitutes an *important* deviation from acceptable ranges.
EFPIA Consolidated Comments	1153	1205	3.11.4	Audits are more optional and should be applied, when needed, rather than by default	Change title to Quality Control and Quality Assurance to make the order of activities chronologically. Put section 3.11.4 "Monitoring" above 3.11.2 "Audit" to highlight that monitoring is an ongoing quality control activity where as audits are quality assurance. And if there are no quality signals there might be no need of audits at all.
PPD	1167	1169	3.11 Quality Assurance and Quality Control	This appears to exclude the current reason for most audits, which is to assess the conduct of the study and its compliance with the protocol, GCP, and regulation(s). Does this imply that the purpose is to evaluate processes but not conduct? Should the language include and assessment of study conduct?	The purpose of a sponsor's audit, which is independent of and separate from, routine monitoring or quality functions, is to evaluate study conduct and determine whether the processes put into place to manage and conduct the trial are effective and compliant in support of participant's safety and data integrity.
CARVALHO Carla	1171	1172	3.11.2.1.a	The audits conducted can be specific to a clinical trial and can be system audit. The auditors appointed should be independant from the system being audited.	The sponsor should appoint individuals who are independent of the clinical trial or system being audited.
Kotagiri Srinivasa Rao	1171	1175	3.11.2.1	Selection and Qualification of Auditors	In some situations sponsor themselves act as auditors for compliance verification.
EFPIA Consolidated Comments	1182	1185	3.11.2.2 b	Should auditing procedures and audit plans be guided by the risk proprtionate, CTQ-focused approach agreed for an audited study? This would help acclearating adoption of a risk-proportionate approaches to study execution.	The sponsor’s audit plan, program and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of participants in the trial, the type and complexity of the trial, the level of risks to the trial participants and any identified problem(s), and should also take into account critical to quality factors(see Section 3.10).
EFPIA Consolidated Comments	1187	1187	3.11.2.2 c	audits as opposed to auditors and bringing in the concept of CAPA	The observations and findings of the auditor(s) as well as the need for corrective and preventative actions should be documented
GQMA	1195	1196	III.3.11.2.2 e	Providing the auditee with an audit certificate should be good practice regardless of applicable regulatory requirements.	Delete the words "When required by applicable regulatory requirements,..."

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EUCROF	1198	1199	III. 3.11.3	"Quality control should be applied to each stage of the data handling to ensure that data are reliable and have been processed correctly." The heading is "Quality Control" in general, not only pertaining to data handling. There are many QC activities not having to do with data handling (e.g., checking the storage of IP)	"Quality control should be applied to each trial procedure and to each stage of the data handling to ensure that trial precedures are performed in accordance with the protocol and that data are reliable and have been processed correctly."
EFPIA Consolidated Comments	1202	1204	3.11.3	Paragraph was not clear, so have made a proposal	The quality control process may be undertaken using a risk based approach and would include not only investigator sites, but also other facilities used during the conduct of the trial, for example centralised imaging reading facilities. of sites (other than investigator sites, such as centralised imaging reading facilities), including on site and/or centralised activities, including investigator sites, centralised imaging facilities and other sites w may be undertaken
EUCROF	1202	1204	III. 3.11.3	"The quality control of sites (other than investigator sites, such as centralised imaging reading facilities), including on site and/or centralised activities, may be undertaken and reported using a risk-based approach". This paragraph is superfluous here as it is contained under "Monitoring", see lines 1225, 1226, 1266, 1267. This means monitoring should be based on risks and should also include entities other than the investigator sites (e.g., central reading facilities, central laboratories).	
GCP-unit, Copenhagen	1202	1204	3.11.3	It seems a bit confusing that the term site is used. Mayby more appropriate to use another word like parties or survice providers?	
Good Clinical Trials Collaborative, on behalf of supporting organisations	1210	1210	Sponsor (3.11.4)	Monitoring: Change to "~~verification~~ assessment of the investigator and investigator site staff qualifications and site resources…" since the question is not whether the answers reflect the truth but whether the truth is that the staff, resources, etc are suitable for the task.	
EUCROF	1213	1213	III. 3.11.4	"…data anaylitcs.." Not clear what is meant by "data analytics" Rewording would be appreciated. Besides, the sentence is difficult to understand (6 lines)	
Dr. C. Wilsher	1214	1215	3.11.4	"Some of these monitoring activities may be conducted by different methods 1214 and persons with different roles" . "Persons with different roles" does not make sense because when their role is a monitor they are a monitor. I wonder if it means that persons can have a variety of other roles?	Some of these monitoring activities may be conducted by different methods and by persons with a variety of other roles.
Jazz Pharmaceuticals	1214	1215	III.3.11.4	"some of these monitoring activities may be conducted by different methods and persons with different roles" This is vague. Can this be clarified?	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Good Clinical Trials Collaborative, on behalf of supporting organisations	1215	1216	Sponsor (3.11.4)	It is not always necessary for monitoring to be performed by persons "not involved in the clinical conduct of the trial being monitored". Indeed such independence can result in less effective monitoring practice if the monitors are too remote to understand which issues or behaviours matter to trial quality or to have meaningful interactions with other members of the sponsor team who might be able to assess the impact and formulate corrective and preventative actions. In some trials, staff involved at one Investigator site can be deployed by the Sponsor as very effective monitors for other sites. It would be damaging to the ambitions of this guideline to rule out such practice.	Therefore delete, "Monitoring should be performed by persons not involved in the clinical conduct of the trial being monitored."
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	1215	1216	III 3.11.4	"…, monitoring should be performed by persons not involved in the clinical conduct of the trial being monitored." In academic clinical trials dual roles covering Project Management and Monitoring are common. If the intention of the above mentioned description is to prevent these dual roles, this will lead to more required study personnel. If these dual roles are not meant to be prevented, please consider rephrasing to avoid misunderstanding.	Suggestion: "…, monitoring should be performed by persons not otherwise involved in the clinical conduct at the trial sites of the trial being monitored."
Fergus Sweeney	1216	1216	3.11.4	Monitoring structures and the personnel involved will vary greatly. What is important is that people do not monitor their own work per se. Segregation is between the activities and or locations/processes and not entire trials.	"..not involved in the conduct of the trial activities being monitored."
Association for Clinical Data Management (ACDM)	1222	1224	3.11.4	We would like just to mention central and risk based monitoring also emphasized in the FDA draft guidance on DCT	No Action
GCP-unit, Copenhagen	1222	1224	3.11.4	"Monitoring may include site monitoring". Afraid that the sponsor will take this approach that site-monitorig is not nessescary any longer. In R2 its stated that "In general there is a need for on-site monitoring, before, during, and after the trial", we expect that this is also the most commen in the future, and should be written in R3.	
EUCROF	1225	1228	III. 3.11.4	"The sponsor should determine the appropriate extent and nature of monitoring, based on identified risks. Factors such as the objective, purpose, design, complexity, blinding, number of trial participants, investigational product, current knowledge of the safety profile and endpoints of the trial should be considered." Experience of involved individuals or parties should be included as well	"The sponsor should determine the appropriate extent and nature of monitoring, based on identified risks. Factors such as the objective, purpose, design, complexity, blinding, number of trial participants, investigational product, current knowledge of the safety profile, endpoints of the trial as well as experience of involved individuals or parties should be considered."
Association for Clinical Data Management (ACDM)	1239	1240	3.11.4.1©	I assume this includes electronic health records, if so I would imagine this needs to comply with local regulations/laws	Please add "alignment with local laws"
CARVALHO Carla	1239	1240	3.11.4.1	In some countries it is not authorized for the sponsor to have a remote access to medical dossier. The proposal is to reflect such point in the statement.	(c) Monitoring may include secure, remote, direct read-only access to source records, other data acquisition tools and essential record retention systems. Access to medical records remotely should be in compliance with the applicable regulatory requirements and authorized by the trial participant.

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EFPIA Consolidated Comments	1239	1240	3.11.4.1 (c)	The wording 'may include secure' could be confusing, it must be secure, may be remote.	Monitoring may include remote read-only access to source records, other data acquisition tools and essential record retention systems, that is secure and direct.
PPD	1239	1240	3.11.4 Monitoring	Our internal practice also considers country-specific requirements on rSDV and should still be confirmed for each country prior to its implementation.	(c) Monitoring may include secure, remote, direct read-only access to source records, other data acquisition tools and essential record retention systems, and/or as per local regulations.
Quotient Sciences	1239	1240	3.11.4.1 (c)	Remote monitoring carries a higher risk of breach of confidentiality, because of the potential for monitors to make copies of shared documents and for monitors' screens to be viewed by other people. Sponsors must ensure that monitors' written procedures specify that no screenshots, photography or other means of recording are allowed during remote document sharing and that monitors must not view shared documents from locations where their screen could be viewed by other people.	Please add bold text: (c) Monitoring may include secure, remote, direct read-only access to source records, other data acquisition tools and essential record retention systems. Accessing documents remotely carries a higher risk of breach of confidentiality, so monitoring procedures should prohibit copying of shared documents (e.g., photography, screenshots) and specify that monitors must not view shared documents from locations where their screen could be viewed by other people.
Society for Clinical Research Sites	1239	1240	3.11.4.1	): We have concerns over the use of the term “direct access” (both here as well as in Annex I Items 2.8.11(n), 2.12.12, 3.6.3(d), 3.16.4(a), 3.16.4(b), the Glossary and Appendix B.11). The phrase “direct access” (as opposed to “access”) is interpretable as supporting an activity that is generally prohibited with established healthcare privacy/security practices and regulations across the globe (i.e. providing login IDs directly into to electronic health records).	We request the deletion of the word “direct” (or change the phrase to “access to view”) here and in the other sections referenced to avoid this confusion and that the guidance can recognize the variety of ways source document verification has been accomplished over the past decade without “direct” access (but with “access to view”). This would also bring these sections to be consistent with Annex I Item 3.11.4’s requirement that monitors “adhere to data protection and confidentiality requirements in accordance with applicable regulatory requirements, institution policy and established data security standards.”
Swedish Monitors attending NORM meeting 2023	1242	1244	3.11.4.2 a	This is a definition, and should be found in the glossary. Here it should be stated that IF centralised monitoring is available, it can help/assist in the monitoring process or something similar. Not all studies/trials have this kind of support.	Move definition to glossary.
Kotagiri Srinivasa Rao	1254	2363	3.11.4.3	Monitoring Plan	In some situations sponsr directly may not send the monitoring plan /agenda. They may appoint the third paty agency to monitor the study /trial. In such cases monitoring agenda/plan shall be obtained from the sponsor appointed agency. This shaould be claerly mentioned to avoid any misundestadings during the study conduction.
Association for Clinical Data Management (ACDM)	1255	1258	3.11.4.3	Alignment with FDA draft guidance on DCT	No Action
EFPIA Consolidated Comments	1255	1267	3.11.4.3	Monitoring plans can evolve over time, so could we include updates.	The plan and any updates.....

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Society for Clinical Research Sites	1255	1267	3.11.4.3		We request that this section strongly encourage, if not require, the sharing of the risk assessment and monitoring plan with the investigators/institutions. The sponsor's insights into the high-risk areas of risk and quality would be a critically important asset to the investigators/institutions in their own risk and quality assessment. Yet the site community has experienced that these documents seem to be held privately by sponsors for reasons, often touted as "we don't want the sites to know what we are looking for". Such a reason evokes a culture of "quality by inspection" as opposed to the desired "quality by design". We encourage that the sponsors share their risk assessment and monitoring plans as modified so that the efforts at the investigator's institution can be better aligned.
Society of Quality Assurance (SQA)	1255	1256	3.11.4.3	Add timing of when plan should be available to be added (monitoring plan is to be drafted prior to first participant in).	"The sponsor should develop a monitoring plan, prior to first participant in, that is tailored to the identified potential safety risks, the risks to data quality…"
AFI	1262	1262	3.11.4.3	As per 3.11.4.5.4 ii, to specify critical data in monitoring manual	The plan should focus on aspects that are critical to quality and should specify critical data
Ipsen	1264	1267	3.11.4.3	"Monitoring of endpoints performed outside the investigator site (e.g., central reading facilities, central laboratories) should be addressed in the monitoring plan." Recommend that ICH E6 R3 also provide expectations with regards to potential involvement of satellite sites and adequate supervision by sponsor and investigator at multiple sites? (e.g. IP availability / transfer between parent and satellite sites, maintenance of source records, monitoring, etc)	
Medicines for Europe	1264	1267	3.11.4.3	Some trials where the risk to participants is not negligible (for example, first in man or SAD/MAD studies) are performed in healthy subjects. Therefore the text should not cover patients only.	Monitoring of key data and processes (e.g., those related to primary endpoints and key secondary endpoints and processes intended to assure patient subject safety) performed outside the investigator site (e.g., central reading facilities, central laboratories) should be addressed in the monitoring plan
Sunnikan Consulting	1264	1265	III 3.11.4.3	Purpose is to emphasize the importance of inclusion/exclusion criteria as part of key data to be monitored, given the fact that: - in certain trials, the inclusion/exclusion critera would not be directly linked to the endpoints (from a physiopathological point of view), while obviously linked from a data quality and integrity perspective - and that some sponsors may focus on the examples provided only.	It could be relevant to add "inclusion/exclusion criteria" within examples for key data and processes.
Sunnikan Consulting	1264	1265	III 3.11.4.3	Purpose is to emphasize the importance of inclusion/exclusion criteria as part of key data to be monitored, given the fact that: - in certain trials, the inclusion/exclusion critera would not be directly linked to the endpoints (from a physiopathological point of view), while obviously linked from a data quality and integrity perspective - and that some sponsors may focus on the examples provided only.	The monitoring of central facilities (outside the Investigator Site) should consider key data and processes but also identified issues related to these data / processes. Shall a cross reference to section 3.9.6 be considered ?

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Swedish Monitors attending NORM meeting 2023	1273	1273	3.11.4.5	Monitoring should be performed: "across the clinical trial life cycle". This wording is quite unclear, and we miss the "before, during, and after".	Add clarification: "across the clinical trial life cycle, i.e. before, during, and after the start of the study, as applicable."
EFPIA Consolidated Comments	1275	1295	3.11.4.5.1 (b)	As a line of communication between the sponsor and investigator, the Draft Guideline should consider the involvement of the monitor in communicating critical to quality factors and/or risks.	Proposed change: "(b) Informing the investigator or other parties and individuals involved in the trial conduct of significant risks and/or the factors that are critical to quality, identified deviations from the protocol…
Society for Clinical Research Sites	1275	1295	3.11.4.5.1	We are concerned that any ambiguity in the guidance will be interpreted as if the monitor finds "entry errors or omissions in data acquisition tools" from these independent service providers that it will be inappropriately construed as the investigator's responsibility to ensure "that corrections, additions or deletions are made as appropriate, dated, explained (if necessary) and that approval of the change is properly documented" in the source documents or data entered by those independent parties. In essence, the monitor (and or others at the sponsor) should deal directly with those service providers or healthcare practitioners.	With a slight clarification, this section can more adequately address the monitoring of trial activities not conducted by the investigator. With the emerging use of non-investigator health care providers as assistants in routine care items and services required by the protocol, there is a growing amount of data collected by parties either under the control of the sponsor (e.g. a sponsor-contracted network of providers) or not under contractual control by either the investigator or sponsor (e.g. a completely independent healthcare provider).
GCP-unit, Copenhagen	1276	1279	3.11.4.5 (a)	It sounds as if the monitor is the primary communication line between sponsor, investigator site and other parties, and have responsibility for this. This is not the occacion in academic trials.	Suggest that the sentence is changed
GCP-unit, Copenhagen	1281	1283	3.11.4.5 (b)	Is a long sentence and it could sound (line 1283) as if its the monitor who shall take appropriate actions - please change so its clear that its the investigator who shall take actions	Change sentence
GQMA	1281	1284	III.3.11.4.5.1 b	The wording of this section suggests that it is the responsibility of the monitor to take action to prevent recurrence of protocol deviations. The responsibility for such actions should remain with the investigator. The monitor should only be responsible for informing the investigator of the need for such actions and supporting him where reasonably possible.	Change to: "..., GCP and the applicable regulatory requirements and supporting them in taking appropriate action designed to prevent recurrence of the detected deviations."
EFPIA Consolidated Comments	1284	1286	3.11.4.5.1 (b)	The Draft Guideline states: "Important deviations should be highlighted and should be the focus of remediation efforts as appropriate." All identified protocol deviations are to be shared. The sponsor defines the classification and the sponsor designation of classification is not generally shared. Highlighting important deviations is not supported.	Proposed change: "Important deviations should be highlighted and should be the focus of remediation efforts as appropriate."
EUCROF	1284	1285	III. 3.11.4.5.1 (b)	"Important deviations" See previous comments on Definition of "important"	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA Consolidated Comments	1288	1290	3.11.4.5.1 c	We would suggest a slightly clearer amendment on the section c) "Informing the investigator or other parties and individuals involved in the trial conduct of source record(s) or entry errors..."	Informing the investigator or other parties and individuals involved in the trial conduct of source record(s) or data entry errors
Fergus Sweeney	1289	1289	3.11.4.5.1.c	The sentence is missing words and not well constructed	reword to "Informing the investigator….trial conduct of discrepancies with source documents and entry errors or omissions in data acquisition tools.."
Fergus Sweeney	1292	1292	3.11.4.5.1.c	changes in data reported by the investigator should generally be approved by the investigator	add at end of sentence "…that approval by the investigator is properly documented."
Fergus Sweeney	1292	1292	3.11.4.5.1.c	consider adding a process enabling the sponsor monitor or data team to make certain corrections with the agreement of the investigator	
EFPIA Consolidated Comments	1294	1295	3.11.4.5.1 d	We would suggest moving the section d), currently under 'Communication with Parties Conducting the Trial', to under 3.11.4 'Monitoring' for improved consistency. (d) Actions taken in relation to the deviations, errors or omissions should be proportionate to their importance.	This would benefit from being outside of communications in the preamble to monitoring? 3.11.4
Society for Clinical Research Sites	1296	1334	3.11.4.5.2	Similar to our comments in Annex I Item 3.7.1, while we understand that the investigator must demonstrate certain capabilities on their own (e.g. adequate office space, sufficient time), the investigators are almost exclusively dependent on the sponsors to resource the study and to do so in a timely fashion. Regardless if the investigator has the proper space and equipment in place, without the resources from the sponsor (e.g. funding and/or other in-kind items and services necessary for study conduct), the costs to conduct and maintain the study are beyond the scope for the investigator to provide.	The clause should be revised to demonstrate that the investigator should be able to demonstrate capabilities to properly conduct the trial assuming the resources from the sponsor are provided in amounts and schedules commensurate for study conduct.
GCP-unit, Copenhagen	1297	1297	3.11.4.5.2.	"Selecting the site" is written as a monitor activity, monitors do not select sites in academic trial	Perhaps delete or change
Swedish Monitors attending NORM meeting 2023	1297	1297	3.11.4.5.2a	"Selecting the site". This is found under Monitoring activites, and as monitors we find it a bit unclear what a monitor should do. It is stated under 3.7 that it is Sponsor responsibility to select Investigator, and by that indirectly select participating sites. Monitor can support, but seldom or never actually contribute in the selection of sites.	Clarify what in the site selection can be done/performed as "Monitoring activites".
EFPIA Consolidated Comments	1303	1307	3.11.4.5.2 (b)	IB is not included study procedure/instruction, so not good example of "follow".	Confirming that the investigator, investigator site staff and other parties, and individuals involved in the trial conduct are adequately informed about the trial and working in line with follow the current approved protocol and other protocol-related documents, such as the current Investigator's Brochure and relevant information related to the investigational product and instructions related to their delegated activities.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Quotient Sciences	1303	1308	3.11.4.5.2 (b)	Training of investigators in GCP and the protocol should be tailored to take account of the investigator's experience. Experienced investigators at phase 1 units, who work exclusively on clinical trials, are thoroughly familiar with GCP and standard clinical trial requirements, and so time would be spent more effectively in providing training in aspects specific to the IMP and the trial and not, for example, in the importance of adhering to entry criteria or in identifying serious adverse events (unless the definition of an SAE in the protocol differs from that in GCP).	Please add text in bold: (b) Confirming that the investigator, investigator site staff and other parties, and individuals involved in the trial conduct are adequately informed about the trial and follow the current approved protocol and other protocol-related documents, such as the current Investigator's Brochure and relevant information related to the investigational product and instructions related to their delegated activities. In providing information and training to investigators, sponsors should take into account the experience of the investigator. For example, experienced investigators who work on many clinical trials simultaneously should not need training in basic GCP requirements such as adherence to trial entry criteria or the definition of serious adverse events, and attention should be focussed instead on requirements specific to the trial and investigational product.
	1303	1308	III 3.11.4.5.2	Hospital pharmacists should be added among the experts listed in section III 3.11.4.5.2. In addition, it should be highlighted that the information should be provided in the national language.	(b) Confirming that the investigator, investigator site staff, hospital pharmacists and other parties, and individuals involved in the trial conduct are adequately informed about the trial and follow the current approved protocol and other protocol-related documents, such as the current Investigator's Brochure and relevant information related to the investigational product and instructions related to their delegated activities. The information should be provided in the national language.
Society for Clinical Research Sites	1310	1311	3.11.4.5.2		As referenced in Annex I Item 2.12.10, unlike R2, the draft in Appendix C no longer delineates who, between the sponsor and the investigator, is responsible for which information. Therefore, this section be clarified and thus read "Confirming that the investigator is maintaining the essential records generated by the investigator/institution (see Appendix C)."
EFPIA Consolidated Comments	1313	1314	3.11.4.5.2 (d)	Clarification is requested as to whether such confirmation is not required for "screened" participants is not necessary. Could this be read that you don't need to review the screen failures who would have signed the IC.	Confirming that informed consent was obtained before participation in the trial (see section 2.8), and where appropriate, re-consented in a timely manner, for all enrolled participants at the site.
Fergus Sweeney	1313	1313	3.11.4.5.2.d	There is no requirement for a monitor to check the consent of "all" participants at a site. Firstly only a sample of sites may be visited, and secondly particularly in large scale trials there may be hundreds of participants and it is not a good use of monitor time to check absolutely all consent sheets at the expense of checking other key data. Absolutes should not be used, they are disproportionate and excessively prescriptive.	reword to "Conforming that informed consent was obtained before participation in the trial (see section 2.8)."
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	1313	1314	III 3.11.4.5.2	Confirmation that IC was obtained for all enrolled participants in general, i.e., regardless of trial specifics, doesn't seem proportionate for large trials with a large number of participants and low-risk profile. As for many other aspects a risk-based approach should be allowed (e.g., checking only a sample of ICs at each site).	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
The GCP Unit at Aalborg and Aarhus University Hospital	1313	1314	3.11.4.5.2 (d)	Confirming that informed consent was obtained before participation in the trial for all enrolled participants at the site - does that mean that informed consent should always be monitored 100%?	
Mandy Jackson National Clinical Trials Office Quality Working Group Ireland	1325	1325		Could retention 'rates' be replaced with retention 'numbers' for ease of reporting	
EAHP	1338	1339	III 3.11.4.5.3	Proper storage requirements also need to be observed during the shipment.	(i) that storage and shipment conditions are acceptable and in accordance with the storage requirement specified in the protocol;
Quotient Sciences	1338	1339	3.11.4.5.3 (a) (i)	Storage conditions may be specified in documents other than the protocol, eg the investigational medicinal product dossier.	Please edit as follows: (i) that storage conditions are acceptable and in accordance with the storage requirement specified in the protocol or other trial document(s), e.g., investigational product quality documentation.
EAHP	1341	1342	III 3.11.4.5.3	The label attached by the sponsor should be in compliance with EU GMP Annex 13: Investigational Medicinal Products (https://www.gmp-compliance.org/guidelines/gmp-guideline/eu-gmp-annex-13-investigational-medicinal-products).	(ii) that supplies are sufficient throughout the trial, are used within their shelf-life and the adherence of the label provide by the sponsor complies with EU GMP Annex 13: Investigational Medicinal Products (https://www.gmp-compliance.org/guidelines/gmp-guideline/eu-gmp-annex-13-investigational-medicinal-products);
CARVALHO Carla	1355	1357	3.11.4.5.3.a (v)	For some studies, a reconstitution step at site level is necessary before the administration of the product to the patient. It's important to ensure that the authorized materials and kep reconstitution steps were done adequately to guarantee the quality of the products administrated.	(v) that the receipt, preparation (when applicable), use, return and destruction, or alternative disposition of the investigational product(s) are controlled and documented adequately;
EFPIA Consolidated Comments	1355	1357	III.3.11.4.5.3(v)	It should be clarified that the monitor is not required to double-check and physically verify the investigational product(s) but to ensure appropriate documentation is maintained by the trial site.	that the receipt, use, return and destruction, or alternative disposition of the investigational product(s) are controlled and documented adequately by the investigator and other delegated individuals involved in the trial conduct.
Good Clinical Trials Collaborative, on behalf of supporting organisations	1357	1357	Sponsor (3.11.4.5.3.v)	Modification for consistency: "*documented* ~~adequately~~ *in accordance with the sponsor requirements.*" (Note this is the same concluding text as in the point (vi) (lines 1360-1361).	
EAHP	1359	1361	III 3.11.4.5.3	The disposal should be carried out by the sponsor.	(vi) that the disposition of unused investigational product(s) complies with applicable regulatory requirement(s) and is in accordance with the sponsor requirements carried out by the sponsor;
EAHP	1363	1365	III 3.11.4.5.3	In relation to point (vii) a clarification is needed.	/
Ipsen	1363	1365	3.11.4.5.3vii	Suggest clarification through either defining which of the regulatory requirements are not applicable or at least adding "may not be applicable according to local regulations."	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
CARVALHO Carla	1369	1375	3.11.4.5.4.b	As per the statement, we can understand that we can select a sample of patients or a sample of data or a sample of data in a selected sample of patients. This means that the result of the study can be considered while not 100% of the primary endpoint is verified. In oncology studies, such absence can potentially impact the result of the study (e.g., primary endpoint is the overall survival and based on the date of death. In some country, no certificate of death is generated when a patient is dead).	Checking the accuracy, completeness and consistency of the reported trial data against the source records and other trial-related records and whether these were reported in a timely manner. This can be done on the basis of using samples and supported by data analytics, as appropriate but should ensure that the data collected and considered for the primary endpoint are correct. The sample size may need adjustment based on previous monitoring results or other indications of insufficient data quality. Monitoring should:
Good Clinical Trials Collaborative, on behalf of supporting organisations	1373	1373	Sponsor (3.11.4.5.4.b)	Insert "The sample size *and the types of data or records to be assessed* may need adjustment…" (since in some instances the correct response is to focus on a particular subset of records, participants or data fields which are critical-to-quality or where issues have been detected previously).	
Swedish Monitors attending NORM meeting 2023	1380	1384	3.11.4.5.4 b (ii), and (iii)	As monitors, we feel that this section is difficult to follow. It is not clear what a monitor can/should perform, as this is covering all types of monitroing activities which may or may not be available in a study. For example, not all studies have central monitoring with support from statisticians. The tasks under (ii) and (iii) for example, can only be performed if central monitoring is available with the assisitance of statistician. Without Central monitoring and stat-support, these two point will be almost impossible to monitor.	Add "if possible", or "where / when possible" at the end of the two points (ii) and (iii).
GQMA	1383	1384	III.3.11.4.5.4 b (iii)	In case of a single centre clinical trial, no variability of data can be assessed across sites	Change to: "examine data trends, such as the range, consistency and, variability of data within and, where applicable, across sites;"
Society for Clinical Research Sites	1388	1403	3.11.4.6		We recommend that a sub-section (d) be added that reads "(d) The sponsor should promptly provide a copy of the monitoring report to the investigator/institution." This transparency, especially when done promptly, better enables the investigator/institution to address any negative monitoring findings as well as provide an indication to the investigator/institution where they are performing well. It is key information necessary for the investigator/institutions' resource planning and prioritization.
Society of Quality Assurance (SQA)	1405	1408	3.12.1	Add wording that compliance is required (not optional)	"Compliance with the protocol, SOPs, GCP and/or applicable regulatory requirement(s) by an investigator/institution or by member(s) of the sponsor's staff is required. Noncompliance should lead to appropriate and proportionate action by the sponsor to secure compliance."
Jazz Pharmaceuticals	1413	1413	III.3.12.2	Further guidance is needed to assist interpretation of "confirm their adequacy".	
Association for Clinical Data Management (ACDM)	1414	1417	3.12.2	Is this referring to serious breach of GCP? If yes please provide more detail. If not clarify what is required.	Please add clarification on which are expectations

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Good Clinical Trials Collaborative, on behalf of supporting organisations	1420	1421	Sponsor (3.12.3)	It is not always appropriate for the sponsor to "terminate the investigator's/institution's participation in the trial". The first duty of the Sponsor should be to consider alternative ways to minimise the impact of serious noncompliance on the trial participants and the reliability of the results. Options may include transfer of participants to another centre or a switch to follow-up methods that use information from routine healthcare data systems (which might be at the investigator site or elsewhere).	Consider modifications which highlight the responsibility of the Sponsor to minimise impact on trial participants and reliability of results.
Good Clinical Trials Collaborative, on behalf of supporting organisations	1430	1439	Sponsor (3.13.1)	In the current draft, there is little emphasis on the greater value of regular review of aggregated emerging safety data (3.13.1), and no reference to the importance of comparison to cases in a control group, or the value of utilising a Data Monitoring Committee for assessment.	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-reporting-requirements-inds-investigational-new-drug-applications-and-babe
EFPIA Consolidated Comments	1434	1436	3.13.1	"The sponsor should review the available emerging safety information to assess whether there is any new data that may affect the participant's willingness to continue in the trial, impact the conduct of the trial, or alter the approval/favourable opinion of the IRB/IEC and/or regulatory authority(ies), as applicable." Emerging safety information could be misleading with Emerging Safety Issue definition applicable to Post Marketing Environmenet. Recommendation to provide a clear defination or remove "Emerging".	"The sponsor should review the available emerging safety information to assess whether there is any new data that may affect the participant's willingness to continue in the trial, impact the conduct of the trial, or alter the approval/favourable opinion of the IRB/IEC and/or regulatory authority(ies), as applicable."
Good Clinical Trials Collaborative, on behalf of supporting organisations	1440	1475	Sponsor (3.13.2)	It may be helpful, in the relevant sections, to present the glossary definition within the main text to support consistent and proportionate interpretation i.e. Adverse Event (AE) and Serious Adverse Event (SAE) within section 2.7.2, and Adverse Drug Reaction (ADR) and the specific definitions of i) suspected, ii) unexpected, and iii) serious, as derived from the entry for Suspected Unexpected Serious Adverse Reaction (SUSAR) within 3.13.2.	Incorporate glossary definition of ADRs and the component definitions of SUSARs into section 3.13.2.
Medicines for Europe	1441	1443	3.13.1	Trials with short clinical phase may not require safety updates and updated IBs.	The sponsor should submit to the regulatory authority(ies) safety updates and periodic reports, including changes to the Investigator's Brochure, if applicable, as required by applicable regulatory requirements.
Fergus Sweeney	1443	1443	3.13.2.a	the protocol may have specific requirements for certain trials so should also be referenced	reword to ""…as required by applicable regulatory requirements and in accordance with the protocol."
EFPIA Consolidated Comments	1445	1475	3.13.2	Reference to other ICH Guidelines is welcome as E6 is not the primary guidance for safety reporting. Risk based approach for submissions to IRB/EC is also welcomed but some clarification needed on what constitutes follow up information that needs to be reported in an expedited manner . e.g if only minor information/clarifications on the original reported information are updated ,what should this be reportable ?. RSI is now clearly called out in IB to make determination as to whether event is a SUSAR . Please consider this addition. possibly after b.	Proposal is that the clarification be added: If any follow up information is received that makes the adverse event a SUSAR then this follow up information should be reported immediately.
EFPIA Consolidated Comments	1448	1448	3.13.2b	Typo the first bracket is BOLD before (ADR "of all adverse drug reactions (ADRs)"	of all adverse drug reactions (ADRs)

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Good Clinical Trials Collaborative, on behalf of supporting organisations	1448	1449	Sponsor (3.13.2)	Reword to "all adverse drug reactions (ADRs) that meet three criteria: suspected, unexpected and serious (i.e., SUSARS)" to "all adverse drug reactions (ADRs) that are SUSARS (i.e. suspected reactions, unexpected, and serious; see Glossary)"	
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	1448	1448	III 3.13.2	Formatting error. Incorrect font.	Font of first bracket has to be adjusted: "(ADRs)".
Fergus Sweeney	1449	1449	3.13.2.b	the protocol may have specific requirements as set out in legislation and must be referenced	add at the end of the subsetion "….and serious (SUSARs) unless otherwise specified in the protocol."
Quotient Sciences	1449	1449	3.13.2 (b)	It should be clarified that *suspected* refers to a suspected relationship with the investigational product, and it would also be clearer if the criteria were presented in the order: serious, unexpected, suspected.	Please edit as follows: (b) The sponsor should, in accordance with the applicable regulatory requirement(s) and with ICH E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, expedite the reporting to the regulatory authority(ies) of all adverse drug reactions (ADRs) that meet three criteria: serious suspected, unexpected and serious suspected *to be related to the investigational product* (i.e., SUSARs).
DARQA	1458	1464	3.13.2	Reporting of SUSARs by the Sponsor is described in this section. Responsibility for the investigator to review provided updated safety information is missing in the document.	Recommended to describe in general terms this investigator responsibility
Quotient Sciences	1458	1464	3.13.2 (d)	In the UK, there are plans to remove the requirement to make expedited reports of SUSARs to the REC. So, this section should refer to reporting to both investigators/institutions and RECs in line with regulatory requirements.	Please edit as follows: (d) The reporting of SUSARs to investigator(s)/institutions(s) and to the IRB(s)/IEC(s) should be undertaken in accordance with regulatory requirements and in a manner that reflects the urgency of action required, and should take into consideration the evolving knowledge of the safety profile of the product. Reporting of SUSARs to the investigators/institutions should be made in accordance with regulatory requirements. In some regions, periodic reporting of line listings with an overall safety assessment may be appropriate.
Society for Clinical Research Sites	1458	1464	3.13.2	Unfortunately, many SUSAR reports provided to investigators are events not meeting all three criteria of a SUSAR yet investigators are asked to treat them as such and such frustrations distract from those SUSAR reports that are actually important new knowledge for the investigator.	We request that this section take the opportunity add more direction to call out and facilitate the elimination of the overly burdensome and non-productive practice of requiring that the investigators sign, date and opine upon one or more attestations on each SUSAR report. We do not see this requirement in the guidance yet it seems to be the demanded practice. It would be beneficial for this section to clarify that such reports should not be sent unless all criteria for a SUSAR are sufficiently met.
EFPIA Consolidated Comments	1466	1466	3.13.2 (e)	Urgent Safety Issue needs to link to 3.13.3 to provide clarity on term	....see 3.13.3 on the management of immediate hazards.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUCROF	1466	1467	III. 3.13.2 e)	A definition for urgent safety issues is not available and therefore could be treated differently. Please consider adding definition for urgent safety issues	
GQMA	1476	1484	III.3.13.3	The EU CTR 536 uses another term for 'Immediate Hazard'. Harmonization of the terminology would be beneficial to rule out misunderstandings.	Consider harmonization of the term 'Immediate Hazard' by using the term 'urgent safety measure'.
Kotagiri Srinivasa Rao	1485	1496	3.14	Insurance/Indemnification/Compensation to Participants and Investigators	In some situations sponsor may not providing the insurance they may delegate the activity to institutions/CRO. In such case CRO/Institutions is having the insurance.
Fergus Sweeney	1486	1486	3.14.1	specify this is malpractice of the investigator (not sponsor for example)	add at end of section "….malpractice and/or negligence of the investigator/institution."
Fergus Sweeney	1486	1486	3.14.1	Consider also addiing wording relating to malpractice or negligence by the sponsor or their service providers.	new wording to be added
Society for Clinical Research Sites	1491	1493	3.14.2	We request that this section take the opportunity add more direction to call out and facilitate the elimination of the overly burdensome and non-productive practice of requiring that the investigators sign, date and opine upon one or more attestations on each SUSAR report. We do not see this requirement in the guidance yet it seems to be the demanded practice. Unfortunately, many SUSAR reports provided to investigators are events not meeting all three criteria of a SUSAR yet investigators are asked to treat them as such and such frustrations distract from those SUSAR reports that are actually important new knowledge for the investigator. It would be beneficial for this section to clarify that such reports should not be sent unless all criteria for a SUSAR are sufficiently met.	We understand the sponsor should have clear policies about covering costs for injuries during the study. However, we urge for further enhancements in Annex I Item, specifically: 1)Make the payment conditions from the sponsor clear and unambiguous as to when the sponsor pays and when they do not pay; 2)Ensure these conditions are in the written trial agreement for investigators/sites and in the informed consent for participants. This guarantees consistency between sponsor policies, agreements, and participant promises. If there are differences, what the sponsor pledged in the informed consent should prevail; 3)Keep the policies consistent throughout the trial, unless investigators/sites and participants can withdraw if the sponsor changes reimbursement policies.
Fergus Sweeney	1495	1495	3.14.3	The term "compensation" is used in GCP in different sections to refer either to compensation of trial participants for their travel expenses or time in relation to trial participation and in other sections such as here to refer to compensation for injury which is then linked to insurance/indemnity. These should be clearly differentiated either by using a different term for compensation for reasonable expenses, or by spelling it out in more words. The latter may be easier. The two concepts should not be confused in the same section. Payment for expenses has nothing to do with insurance/indemnity/compensation. Insurance/indemnity/compensation is already a complex issue without mixiing it up with something else	reword to "The approach to compensating trial participants for trial related injury should comply with applicable regulatory requirements"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EAHP	1500	1503	III 3.15.1	Besides the Investigator's Brochure also the Pharmacy binder needs to be included.	The sponsor should ensure that an Investigator's Brochure and a Pharmacy binder are developed and updated as significant new information on the investigational product becomes available. Alternatively, for authorised medicinal products, the sponsor should identify the basic product information to be used in the trial (see Appendix A).
EFPIA Consolidated Comments	1500	1503	3.15.1	The reference to Appendix A with regards to authorized medicinal products is misleading as the appendix contains provisions for the Investigator's Brochure only.	Move reference '(see Appendix A)' to the first sentence related to the IB.
AFI	1504	1504	3.15.2	Regarding IP, it might improve to add clarity on the following points: - introduce the notion of NIMP/AxMP and therefore harmonize with terminology used in other regulatory texts (e.g.GMP) and clarify the scope of ICH-GCP; expectations of AxMPs in terms of traceability's documentation and whether they should be provided free of charge to participants (whether authorized or not) ; specifically for destruction, indicate whether the expectation is to have proof of ACTUAL destruction ; in relation to accountability check done by the monitor, clarify that this can be done remotely (without a on site physical check by the monitor).	
EAHP	1505	1509	III 3.15.2	The labelling should be carried out by the sponsor.	(a) The sponsor should ensure that the investigational product(s) (including active control(s) and placebo, if applicable) is characterised as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP and is coded and labelled by the sponsor in a manner that protects the blinding, if applicable.
AFI	1509	1510	3.15.2	In addition, the labelling should comply with applicable regulatory requirement	Please, clarify what is meant by "regulatory requirements". To remove the sentence in order to standardize the labeling as much as possible avoiding to create huge differences between countries.
EAHP	1512	1517	III 3.15.2	The sponsor needs to guarantee that the temperature is tracked with the support of an electronic record of the temperature during the transport.	(b) The sponsor should determine acceptable storage temperatures and other storage conditions (e.g., protection from light) for the investigational product(s), appropriate reconstitution fluids and procedures, and devices for product infusion, if any. This should be tracked during the transport of the investigational medicinal product through an electronic record of the temperature. The sponsor should inform all involved parties (e.g., monitors, investigators, pharmacists, storage managers) of these determinations.
Mandy Jackson National Clinical Trials Office Quality Working Group Ireland	1512	1514		For academic sponsors would the manufacturer be responsible for determining storage conditions and storage conditions	
EFPIA Consolidated Comments	1514	1515	3.15.2 (b)	appropriate reconstitution fluids and procedures, and devices for product infusion, if any- text may be too specific, propose more general text to encompass broader range of delivery systems (not just for infusions).	appropriate reconstitution fluids and procedures and devices for product infusion preparation and/or administration, if any.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUCROF	1514	1515	III. 3.15.2	"devices for product infusion" is only one example. It could be different aadministration devices, e.g., transdermal systems. Make text more general	"devices for product administration".
EFPIA Consolidated Comments	1524	1526	3.15.2 d (i)	Applicable will cover verious roles which need to be unblinded like bioanalytical managers, uCRAs, etc.	A process to blind the applicable sponsor staff, trial participant and/or investigator as appropriate to the investigational product identity and assignment to prevent and detect inappropriate unblinding
Fergus Sweeney	1542	1543	3.15.2.e	This section has been present for a long time. It is not clear if it is causing any issues but it is very focused on terminology for small chemical products rather then biologicals and advanced therapies where concepts of PK, BE and BA are very different or absent, and where adjustments in formulation may have a broader range rather than a specific set of concentrations.	reconsider the wording and make it more open to wider concepts
Society for Clinical Research Sites	1544	1589	3.15.3		Please specify that instructions for handling and storing the investigational product (IP) are accessible in the primary language of the receiving investigator/participant. Also, the instructions should include conversions for different measurement scales, such as Fahrenheit and Celsius, centimeters and inches, as needed by the recipient.
EAHP	1545	1549	III 3.15.3	It needs to be ensured by the sponsor that the investigational medicinal product is correctly labelled.	(a) The sponsor is responsible for supplying the investigator(s)/institution(s) with the correctly labelled investigational product(s) or, where appropriate, supplying trial participants in accordance with applicable regulatory requirements and after obtaining the required approval/favourable opinion from the IRB/IEC and the regulatory authority(ies) for the trial.
EFPIA Consolidated Comments	1545	1549	3.15.3 a)	supplies could come from a local mechanism.	The sponsor is responsible for supplying the investigator(s)/institution(s) with the investigational product(s) or, where appropriate, supplying trial participants in accordance with applicable regulatory requirements and after obtaining the required approval/favourable opinion from the IRB/IEC and the regulatory authority(ies) for the trial. The supply of investigational products may be made through appropriate local purchasing.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUCROF	1545	1546	III. 3.15.3 a)	"The sponsor is responsible for supplying to the investigator(s)/institution(s) with the investigational product(s) or, where appropriate, supplying trial participants in accordance with applicable regulatory requirements and after obtaining the required approval/favourable opinion from the IRB/IEC and the regulatory authority(ies) for the trial." The responsibility "for supplying" the IP by the Sponsor might be an over-simplification as other rules might apply in case the IP is a marketed product. For example, for investigator initiated trials or physician's choice designs, the normal supply chain is used in many cases. Sometimes the (marketed) IP can be sourced locally by the sites and further be reimbursed by the sponsor. The term "supplying" is very restrictive and might not mirror the actual situation. Additional clarifications are needed. In addition approval/positive opinion by IRB/IEC and regulatory authority(ies) is required in all cases, not only for supplying IP(s) at trial participants' homes. This is a bit misleading in the original text.	After obtaining the required approval/favourable opinion from the IRB/IEC and the regulatory authority(ies) for the trial, the sponsor is responsible for supplying investigational product(s) to the investigator(s)/institution(s). In case of marketed investigational product(s), other rules might apply, in which case the sponsor is responsible for ensuring that applicable regulatory requirements are adhered to (e.g., procurement via the normal supply chain). Where appropriate, trial participants should be supplied with investigational product(s) in accordance with applicable regulatory requirements.
AFI	1561	1564	3.15.3 (c) (i)	To clarify the possibility to deliver investigational product to trial participants home and to provide additional specific point on this with reccomended procedure.	Ensure timely delivery of investigational product(s) to the investigator(s) or, where appropriate, to trial participants home in accordance with applicable regulatory requirements to avoid any interruption to the trial as well as for the continuation of treatment for participants. Reccomeded minimal requirements for home delivery.
Quotient Sciences	1561	1564	3.15.3 (c) (i)	Investigational product may be supplied to investigator or institition and the wording should reflect this.	Please edit as follows: ensure timely delivery of investigational product(s) to the investigator(s)/institutions or, where appropriate, to trial participants in accordance with applicable regulatory requirements to avoid any interruption to the trial as well as for the continuation of treatment for participants.
PPD	1570	1573	3.15 Investigational Product(s)	Clarification of the term "system". Computerised system or a process or approach? It could be both - there must be a physical process to perform and a means of tracking the materials through the process which is usually a computerised system.	Clarify what is meant by "system" through glossary definition (e.g., computerized or process). See Row 17 comment above Define System in Glossary Define Computerized System in Glossary

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
PPD	1575	1576	3.15 Investigational Product(s)	Clarification of the term "system". Computerised system or a process or approach? It could be both - there must be a physical process to perform and a means of tracking the materials through the process which is usually a computerised system.	Clarify what is meant by "system" through glossary definition (e.g., computerized or process). See Row 17 comment above Define System in Glossary Define Computerized System in Glossary
Fergus Sweeney	1589	1589	3.15..3.c	If the investigational product has a marketing authorisation and participants are prescribed product to be received from the pharmacy or investigator/institution many of the requirements of 3.15.3.c cannot be applied or would involve disproportionate use of resource to no useful purpose. An additional subsection should be added as 3.15.3.c.vii to make this clear.	add a new subsection 3.15.3.c.vii "Where an investigational medicinal product that has a marketing authorisation is used and participants are prescribed locally acailable supply from the institution or pharmacy as per normal practice the above requirements may not apply."
EUCROF	1597	1598	III. 3.16.1	"The sponsor should focus their quality assurance and quality control activities and data review on critical data, including its relevant metadata." Data review is part of QC/QA.	"The sponsor should focus their quality assurance and quality control activities on critical data, including its relevant metadata."
Fergus Sweeney	1598	1598	3.16.1.b	The concept of "metadata" is very broad and loosely used. This lack of definition risks a lot of unecessary discussion, work, retention of excess metadata when data are reported on through data acquisition tools and generally disproportionate and inappropriate activity. This is also likely to lead to lots of data being retained but perhaps not the most important due to lack of understanding. There are in essence two groups of metadata: 1) the metadata that explain a data value and are retained with it as it is reported onwards via data acquisition tools (72 for example is a data point and its key metadata are "pulse rate", "beats per minute" "date of measurement" and if needed "time of measurement", "id code of trial participant", "trial visit number". These always travel with the data through to the final report. 2) are metadata that describe the ALCOA elements - who did the measurement and made the record in the system, the time and date of recording in the system, changes to that data point and their time, date and person making the change, if applicable machine id where it is a machine to machine recording (as is for many lab instruments and some clincal ones). These metadata underpinning ALCOA concept stay with the source record and are not moved to the sponsor data acquisition tool/CRF. All this needs to be explained so that people understand, do the right things but dont get lost or overdemand/overcollect metadata that is not needed or can stay on location with the osurce record.	Add the two concepts here as this is where it first arises but also in the glossary and that is perhaps a good place to give each a description and name - e.g. ALCOA metadata and scientific metadata. Those names could then be used elsewhere for clarity. If data are translated during the data acquisition process (e.g. an average of three measurements or a more complex algorithm, then usually the original data points as well as the product should also be retained with their respective metadata of both types).
Fergus Sweeney	1601	1601	3.16.1.c	data collection methods need not be described for every data element in the protocol, the main sponsor data acquisition tools (eCRF, ePRO…) can be described but others may be too detailed or vary across sites or regions. It is also important in avoiding unecessary protocol amendments or protocols that are outdated, which is a key objective of simplifying clinical trials and making them efficient.	add "…collection in the protocol or other trial document.."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Association for Clinical Data Management (ACDM)	1606	1608	3.16.1(d)	Data acquisition tools are fit for purpose. More clarity may be needed. There are systems that may collect more data that the one needed by protocol. Which are expectations for fit for purpose? should sponsor ask to customized tools per protocol? Required by the protocol "only" to be in adequacy with principles of minimization!?	Suggestion to link to the Data minimization principle. And alignment with GDPR The protocol is not defining every single data point…. Suggestion: quality by design, involve all impacted functions in the design (specially DM)
Medicines for Europe	1606		3.16.1 (d)	Some data acquisition tools are not deployed by the sponsor and therefore the sponsor cannot take responsibility for their fitness for purpose.	The sponsor should ensure that data acquisition tools deployed by the sponsor are fit for purpose and designed to capture the information required by the protocol. They should be validated and ready for use prior to their required use in the trial.
DGPharMed e. V. (Deutsche Gesellschaft für Pharmazeutische Medizin)	1613	1614	III.3.16.1	Maintaining the blind is also essential for the role of the investigator/site personnel	Add investigator
AFI	1616	1618	3.16.1 (g)	To guide investigators/providers/participants on the expectation for data capture etc also regarding timelines to keep updated overview on the trial	The sponsor should provide guidance to investigators/institutions, service providers and trial participants, where relevant, on the expectations for data capture, data changes, data retention and data disposal, also referring to timelines.
Association for Clinical Data Management (ACDM)	1616	1618	3.16.1(g)	The FDA appears to be focusing on including this information in the consent document. Is this also the case for other agencies?	Expand to add this is required in the patient consent process.
EFPIA Consolidated Comments	1616	1618	3.16.1 g	useful to reference DG section 4.5	.... See Data Governance Section 4.5
Good Clinical Trials Collaborative, on behalf of supporting organisations	1620	1622	Sponsor (3.16.1.h)	This currently states that "the sponsor should not make changes to data entered by the investigator… unless agreed upon by the investigator." This requirement is unduly rigid. There are some data that are clearly wrong (e.g. entering date of event that is in the future). Some investigators are not available or responsive to communications from the sponsor, some investigators leave, some sites close. In such circumstances, sticking to data that are clearly wrong is not the best way to ensure reliability of results or patient safety. The important thing is that there is a full audit trail (including timestamp, author name, reason for change) that allows any changes to be viewed, and analyses of the results to be conducted both before and after the change.	The current requirement (point 3.16.1.h) should be deleted in entirety.
Association for Clinical Data Management (ACDM)	1624	1627	3.16.1.(i)	More clarity is needed on expectations - if expectations are that changes should be done in a timely manner (and reflected in the audit trail) - any change should have evidence of the request of the change and reason for the change.	Expand on piece 'source records around the time of data entry' - meaning correction of errors should be supported by evidence e.g. documented phone calls or emails very shortly after the data was entered - not weeks or months. Emphasize that participants data corrections should be through investigator. So participant should go to investigator to correct data…
Ipsen	1624	1627	3.16.1i	"The sponsor should allow correction of errors to data, including data entered by participants, where requested by the investigators/participants. Such data corrections should be justified and supported by source records around the time of original entry" It is not clear who is responsible for ensuring that data changes made by participants are accurate, contemporaneous and supported by source records.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	1624	1627	3.16.1 (i)	The wording "around the time of original entry" is vague and the requirement can only be met if supporting information is available	Delete "around the time of original entry"
Fergus Sweeney	1626	1627	3.16.1.i	not every entry in a data acquisition tool will have a related source. This is especially applicable to patient diaries or other PRO tools. Patients dont make source records to support their data submitted. The requirement is understood, but the need for a source in all cases will rule out almost any request for change by a patient.	reconsider the value and need for this requirement
Good Clinical Trials Collaborative, on behalf of supporting organisations	1629	1636	Sponsor (3.16.1.j)	Minor rewording and use of parentheses to aid clarity.	Change to "The sponsor should ensure that the investigator has access to data… including relevant data from external sources (for example, central laboratory data… ePRO data) if they are necessary to enable investigators to make decisions…"
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	1629	1635	III 3.16.1	The investigator should not have access to data collected at other clinical sites, even if they were collected in accordance with the protocol during the course of the trial. The present text does not mention such restriction.	Suggestion: "The sponsor should ensure that the investigator has access to data collected by the investigational site in accordance with the protocol during the course of the trial for patients at the Investigator's site."
Association for Clinical Data Management (ACDM)	1633	1635	3.16.1 (j)	Appreciate the alignment with FDA draft guidance on DHT and DCT	No Action
Association for Clinical Data Management (ACDM)	1638	1639	3.16.1 (k)	This statement is confusing. Investigator should have access to the data - are you referring to that?... Suggest to replace to do not have exclusive access…	We think this means that the investigator should have access to all data associated with their patients at all times for their medical consideration of the patient requirements. This is not clear so please clarify Suggest to merge point k & and also to determine the time (since when until when…)
EUCROF	1638	1639	III. 3.16.1 (k)	"The Sponsor should not have exlusive control of data captured in data acquisition tools" Sould be supplemented with more information to increase understandability.	"The Sponsor should not have exlusive control of data captured in data acquisition tools. Access to the collected data should be guaranteed for the investigator at any time and irrespective of the media used.
Good Clinical Trials Collaborative, on behalf of supporting organisations	1638	1639	Sponsor (3.16.1.k)	Currently states that the sponsor should not have exclusive control of data captured in data acquisition tools. This rigidity is unhelpful. For example, an IRT, central laboratory or central pharmacy may be contracted to the sponsor (as may the data storage provider). There are other ways to adequately protect against inappropriate manipulation of data by the Sponsor including the requirement for full audit trails, the use of electronic signatures, the duplication of records across multiple machines, or contractual controls between the Sponsor and its system supplier. In many other businesses (e.g. banking, airline booking systems, customer relations systems), the data are controlled exclusively by the company (bank, airline, online insurance site) with adequate protections against fraud and inappropriate manipulation.	The principles of having adequate controls, audit trails, etc are covered in the new Section 4. The operational details specified in 3.16.1.k are restrictive, inflexible and largely outdated.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Ollie Östlund	1638	1639	III.3.16.1(k)	It is not clear what this means. Please provide examples of who else may share control, and the purpose this is intended to fill. Potentially this point could cause major problem in for example decentralised trials, where essentially all trial data could be entered directly into a sponsor system. Could "control" be shared with trial participants? What about investigatos-sponsored trials? Trial data is by definition sensitive personal information, so there are imortant ethical and legal confidentiality aspects.	Please provide examples of who else may share control, and the purpose this is intended to fill.
Society for Clinical Research Sites	1638	1639	3.16.1		We agree that the sponsor should not have exclusive control of data captured in data acquisition tools. However, this item does not clarify who else is intended and/or appropriate to have any control and/or exclusive control. Many people other than the investigator and sponsor touch this data during its lifecycle (e.g. the CRO, the technology provider, data intermediaries that clean the data, etc.) and thus we believe there is more to say in this item other than what is drafted.
EFPIA Consolidated Comments	1641	1642	III.3.16.1(l)	Consideration should be given to rephrasing to better reflect the required action.	The sponsor should ensure that the investigator has access to the required data for the period of retention.
Fergus Sweeney	1641	1641	3.16.1.l	"required data" is very vague. The essential is that the investigator has access to the data reported by the investigator, or relied on by them to manage the participant condition or treatment decisions (including no change, all is good)	suggest to add "..in particular access to data reported by the investigator or relied on by them for the management of the participant in the trial, or their care."
GCP-unit, Copenhagen	1641	1642	3.16.1. (l)	Not quite sure what is ment here. Investigator should always have acces to data in concern to his site, not only for retention purpose? I cant find any place in R3 where this sentence from former ICH-GCP is written "The sponsor should ensure that the investigator has control of and continuous access to the CRF data reported to the sponsor" page 60 R2.	Suggest that this sentence or a clear variation is in R3
Good Clinical Trials Collaborative, on behalf of supporting organisations	1641	1642	Sponsor (3.16.1.l)	The stated requirement is for investigators to have access specifically “for retention purposes”. This is unduly rigid. The high level principle is that relevant trial data should be retained. Whether this is done by the sponsor, the investigator or a third party system provider (contracted to either sponsor or investigator) is immaterial.	This requirement should be deleted to retain flexibility now and in the future. The high level principle is covered in the new Section 4.
Society for Clinical Research Sites	1641	1642	3.16.1		The site community is confused as to what this section is requiring. If the sponsor already holds the data, then please clarify the purpose of imposing additional requirements upon the investigator. We recommend removing this item altogether.
EUCROF	1644	1644	III. 3.16.21(m)	"The sponsor should ensure that the investigator receives instructions…"	"The sponsor should ensure that the investigator and appropriate site staff receive instructions and should document such instructions."
Association for Clinical Data Management (ACDM)	1648	1649	3.16.1 (n)	This statement is confusing. What is endorsement? Is this confirmation of review and approval? How would this be documented?	Please carify and expand what is required

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
eClinical Forum	1648	1649	III 3.16.1(n)	This states: The sponsor should seek investigator endorsement of their data at predetermined milestones. What does seek mean? "Seek" does not imply success in obtaining. We believe the correct word here is "obtain".	This section should be revised to state that the sponsor should obtain investigator endorsement.
EFPIA Consolidated Comments	1648	1649	3.16.1 (n)	not clear that this is just at particular trial milestones it is not the overall investigator opinion on the trial conduct or results but rather the sign-off of the reported data to the sponsor	The sponsor should seek investigator endorsement of their reported data at predetermined frequencies and milestones.
Good Clinical Trials Collaborative, on behalf of supporting organisations	1648	1649	Sponsor (3.16.1.m)	Investigator endorsement of data does not necessarily add quality but definitely adds work – there are other ways to address quality as described earlier, in comments on Investigator (2.12.5)	Delete.
Ipsen	1648	1649	3.16.1n	"The sponsor should seek investigator endorsement of their data at predetermined milestones." Suggest adding more rationale to selection of predetermined milestone (e.g based on a risk approach) as stated in the EMA guidance (e.g The acceptable timing and frequency)	
Medicines for Europe	1648	1649	3.16.1 (n)	It's not clear what is meant by "of their data"	
Ollie Östlund	1648	1649	III.3.16.1(n)	Does this include data from external sources? If not, please state that explicitly. Getting investigators to "sign off" on registry data on, for example, hospitalisations at other hospitals, has not added to quality in out registry-based trials.	
Society for Clinical Research Sites	1648	1649	3.16.1		We are confused as to what this section is requiring. The investigator has already signed off on the individual case report forms and any data queries, thus it seems an unnecessary burden to impose upon the investigators to further endorse the data they already attested to. We recommend removing this item altogether.
Association for Clinical Data Management (ACDM)	1656	1659	3.16.1 (p)	Is this restriction to the tool? Or restriction to the data being used for analysis? For example would we expect to prevent participants from creating new diary entries? or just prevent changes to data being analysed? Is this not something that can be accomplished by export of data into analysis datasets?	Please clarify exactly what is required here it is unclear.
Good Clinical Trials Collaborative, on behalf of supporting organisations	1656	1659	Sponsor (3.16.1.p)	The requirement to restrict edit access to the data acquisition tools for the purpose of analysis such as interim analysis is obsolete on many systems – creating snapshots of the database in real-time whilst maintaining live usage can be achieved with some modern technology approaches.	Delete.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Quotient Sciences	1656	1659	3.16.1 (p)	In phase 1 trials, the study database is always locked before final analysis. However, interim analysis to support dose decisions is done to very short timelines, while the trial is ongoing. Minimum datasets to be used for dose decisions are specified in the protocol, e.g., PK data up to at least 24 h after dosing and safety data up to at least 7 days after dosing. Source data may be collected electronically and it is not possible to restrict access to the data collection system while the interim analysis is ongoing because we are continuing to collect data from the participants in real time and we may also need to make corrections to data. A copy of the data is extracted from the database for interim analysis - that copy is not editable by clinic staff. The investigator's team informs the analyst if there are updates to key data (e.g., adverse events) after extraction and before the dose decision meeting. It should not be necessary to restrict edit access to the data collection tool before provision of data for interim analysis in phase 1 trials.	Please edit as follows: (p) Prior to provision of the data for analysis, edit access to the data acquisition tools should be restricted as appropriate to the purpose of the analysis; for example, for interim analysis, restriction may not be appropriate or the restriction may only be temporary or managed differently compared to the final analysis.
EFPIA Consolidated Comments	1661	1667	3.16.1 q	mixing concepts data management versus stats. Have made a proposal here and an additional one in the statistics part under 3.16.2 b	Deviations from the planned statistical analysis or Changes made to the clinical trial database data analysis set after the trial has been unblinded, (where applicable), should be clearly documented. and Such changes should be justified and should only only occur in exceptional circumstances (e.g., data discrepancies that must be resolved for the reliability of the trial results). Data changes should be authorised by the investigator and reflected in an audit trail. Post-unblinding data changes and deviations from the planned statistical analyses should be reported in the clinical trial report.
Good Clinical Trials Collaborative, on behalf of supporting organisations	1665	1665	Sponsor (3.16.1.q)	Data changes should not necessarily need to be authorised by the investigator (see earlier points e.g. Sponsor (3.16.1.h)). Adequate controls against inappropriate data manipulation or fraud can be put in place through other means (in particular the use of full audit trails, etc).	Delete “Data changes should be authorised by the investigator”.
DGPharMed e. V. (Deutsche Gesellschaft für Pharmazeutische Medizin)	1673	1675	III.3.16.1	Should there be a comment on site personnel’s personal data, too?	Add protection of site personnel´s personal data
Quotient Sciences	1673	1675	3.16.1 (s)	To help sponsors respond to data subject rights (within the relevant jurisdiction) efficiently, it can be useful to consider them early on and check computerised systems have mechanisms to assist.	Add text in bold: (s) The sponsor should implement appropriate measures to protect the privacy and confidentiality of personal information of trial participants, and uphold the rights of data subjects, in accordance with applicable regulatory requirements on personal data protection.
GQMA	1685	1687	III.3.16.1. v	As per EU GDPR personal data breaches with high risk to the rights and freedoms of natural persons should be notified.	Change to: "The sponsor should have processes and procedures in place for reporting incidents (including security breaches) that have a significant impact on the trial data or result in a high risk to the rights and freedoms of the trial participants to relevant parties, including regulatory authorities, where relevant."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Fergus Sweeney	1687	1687	3.16.1.v	suggest replace second use of relevant by appropriate for readability	reword "…authorities, where relevant."
Fergus Sweeney	1690	1728	3.16.1.w	This section is detailed and following it will require a lot of work. Great care is needed to keep it proportionate and useful and to avoid collection of endless details, especially about investigator site or lab systems that are not provided by the sponsor. There are expectations that are worded for general application but should really only apply to sponsor used/supplied systems. Be very careful and list separately what is really essential for investigator site systems. Subsection i is utterly unrealistic to demand for every investigator site and should only apply to sponsor (supplied) systems, likewise for ii amd iii. only v and vi are applicable to investigator sites and should better be placed in a separate section.	reword the start of subsection w: "(w) When using computerised systems deployed by the sponsor in a clincial trial, the sponsor should:" then make a new heading "x) When using computerised systems deployed by the investigator site, the sponsor should evaluate them as follows:" and place existing subsections of w, i.e. (v) and (vi) in this new section but move vi service providers to under (w). Alternatively in (w)(i), (ii), (ii) and (iv) each subsection starts "for computerised systems deployed by the sponsor..."
German Pharmaceutical Industry Association (BPI)	1690	1728	3.16.1.(w)	The section applies generally to all computerized systems ("*when using computerised systems in a clinical trial*"). Some of the following subsection (i) to (vi) specify which systems are meant, e.g., in (ii) *computerised systems deployed by the sponsor*. However, other subsections do not specify which computerised systems are meant, and therefore seem to be applicable to all computerised systems. Especially for subsection (iii) "*maintain a record of the individual users who are authorised to access the system, their roles and their access privileges*" this results in a requirement that cannot be fulfilled by the sponsor - e.g. the sponsor cannot have an overview on all users of an electronic data system of a hospital (used as source data within the trial). This missing specifications of which computerized systems are meant makes it impossible for sponsors to fulfill all requirements.	add respective specifications for clarification. e.g.: (iii) maintain *for computerised systems deployed by the sponsor* a record of the individual users who are authorised to access the system, their roles and their access privileges. (iv) ensure that access rights granted to investigator site staff *to computerized systems specifically for the purposes of the clinical trial* are in accordance with the documented delegations by the investigator and visible to the investigator;
Medicines for Europe	1690	1728	3.16.1 (w)	Items (i) (partly), (iii), (iv) should not be under sponsor responsibility if a system deployed by the investigator/institution is used. The proportionality approach is not mentioned in this paragraph, in contrast to chapter 4. It may be useful to revise and shorten this paragraph, avoid overlap with section 4, and refer to section 4, where applicable. This comment is connected with the comment raised for section 3.16.1 (d)	
Society for Clinical Research Sites	1690	1728	3.16.1		This subsection should be amended to also require the reciprocal reporting. It is just as important for participant safety and trial quality that the sponsor report to the investigator(s) any system defects identified or incidents that could potentially constitute a serious non-compliance with the clinical trial protocol, trial procedures or GCP.
Good Clinical Trials Collaborative, on behalf of supporting organisations	1692	1692	Sponsor (3.16.1.w.i)	Modify to add the word "key". Therefore: "have a record of the key computerised systems used in a clinical trial" (since there may be many that perform peripheral or non-critical functions). This change should help avoid over-interpretation.	Change text as proposed.
GQMA	1692	1692	III.3.16.1. w (i)	It is not clear whether this would apply to sponsor-owned systems only or includes also the computerized systems used by investigators/institutions and any trial vendor.	Clarify if this requirement refers only to sponsor-owned or also to contracted systems and/or to systems used by the investigational site.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Quotient Sciences	1692	1697	3.16.1 (w) (i)	It is implied but not specified that this record relates to systems deployed by the sponsor only.	Please clarify, e.g., (i) have a record of the sponsor-deployed computerised systems used in a clinical trial…
Society of Quality Assurance (SQA)	1692	1692	3.16.1(w)(i)	It is not clear where the computer system record is expected. Is it in the trial protocol or as part of CSV documents? It is recommended to provide options or examples to indicate where the computer system applicability could be included.	"Have a record available (ex: in trial protocol or relevant CSV documentation) of the computerized systems used....."
Good Clinical Trials Collaborative, on behalf of supporting organisations	1705	1707	Sponsor (3.16.1.w.ii)	This is the first time in the whole of Point 3.16.1 (which runs from subpoints a-w) that the concept of proportionality is mentioned!	
Quotient Sciences	1709	1710	3.16.1 (w) (iii)	It is implied but not specified that this requirement relates to systems deployed by the sponsor only.	Please clarify, e.g., (iii) maintain a record of the individual users who are authorised to access the sponsor-deployed system….
EUCROF	1710	1710	III. 3.16.1 (w) iii	"...roles and their access privileges:"	"...roles and their access privileges**;**"
AFI	1716	1722	3.16.1.w (V)	When a Sponsor selects Investigator/Site has to take care about validated hospital information systems/electronic health records, too. Unfortunately, there is still no or less understanding of the requirement regarding computerized systems by such providers. Often, providers of such hospital information systems/electronic health records are not trained in GCP and are not familiar with computerized system validation requirements. Similarly, monitors, project managers for Sponsor and investigators for sites are no subject matter experts on computerized system validation and this raises concerns related to responsibilities in validation of computerized systems used at site or assessment of adequacy of validation by site/investigators.	
Association for Clinical Data Management (ACDM)	1716	1722	3.16.1 (w)(v)	Could be wise to cross reference this section under investigator section.	Reference this section in the investigators section so they are linked.
DGPharMed e. V. (Deutsche Gesellschaft für Pharmazeutische Medizin)	1716	1722	III.3.16.1	Due to the large number of several and different computerized systems at trial sites – especially university hospitals - , it is not manageable for the sponsor to assess the qualification of all. This should clearly be an obligation to the investigator/institution. The investigator/institution should provide the sponsor with evidence.	The responsibility shall lie with the investigator/institution
eClinical Forum	1716	1717	III 3.16.1(w)(v)	This clause discusses systems deployed by investigator/ institutions. We would like it to be clear that it does not apply to systems not deployed by investigators/institutions.	Revise to clarify who is responsible for service providers at each point of time. Sites can only be responsible when they directly deploy the service provider.
Good Clinical Trials Collaborative, on behalf of supporting organisations	1716	1722	Sponsor (3.16.1.v)	There is often little influence that the investigator or sponsor can have on the choice of systems deployed at the investigator's institution. It is not particularly valuable to require such systems to be evaluated by the sponsor.	Consider deleting.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	1716	1720	III 3.16.1	Most medical information systems (MIS) used by German hospitals do not meet all requirements, i.e., they lack an audit trail. This is a clear deficit but the sites or the investigators, respectively, have little if any influence on the choice or replacement of MIS. The mitigating measures used for many years are no longer accepted by the (German) inspectorate. This is only to illustrate that "appropriate" may be very subjectively interpreted.	
Society of Quality Assurance (SQA)	1719	1719	3.16.1(w)(v)	When the investigator site owns the system(s), it should be the investigator's responsibility to ensure all their systems are fit for purpose, while sponsor can verify this during their pre-assessment or assessment of the investigator sites. It is recommended to clearly highlight this difference through the suggested wording so that it is not a burden on the sponsors to validate investigator systems.	"...are fit for purpose through verification of appropriate validation/qualification documents or equivalent from the investigator"
AFI	1724	1728	3.16.1 (w) (vi)	Considering ePRO, a process for system defects identified by trial particpants should also be in place	
EFPIA Consolidated Comments	1724	1728	3.16.1 (w)(vi)	Can also prospective notification of the sponsor about system changes rathen than already occurred problems be considered Add a new paragraph	ensure that there is a process in place for service providers and investigator(s)/institution(s) to inform the sponsor of system changes/ upgrades which have significant impact on source records (e.g., new electronic health record system, eConsent tools)
GQMA	1724	1728	III.3.16.1. w (vi)	Whenever there is reporting of (serious) non-compliance, data protection aspects should be included.	Change to: "ensure that there is a process in place for service providers and investigators to inform the sponsor of system defects identified or incidents that could potentially constitute a serious non-compliance with the clinical trial protocol, trial procedures, GCP, or data protection regulations in accordance with section 3.13."
Quotient Sciences	1724	1728	3.16.1 (w) (vi)	Does this apply only to sponsor-deployed systems?	Please clarify.
Medicines for Europe	1734	1737	3.16.2 a)	From the perspective of bioequivalence studies this would be very difficult to achieve. For parallel groups, 2×2×2 cross-overs, and RSABE/ABEL sample size tables were published. Regrettably some contain typos or the number of simulations for RSABE/ABEL was too small for a stable result (see https://bebac.at/articles/Simulations-101.phtml#sabe). We are not aware that anything has been published for Higher-Order crossovers, Balaam's design, ABE in replicate designs, the FDA's ref-er-ence scaling for NTIDs, and Non-Inferiority / Non-Superiority. Therefore it is unclear how this could be implemented in the case of BE studies which are the basis of generic registration and we propose that the text is modified to encompass these scenarios where validation of sample size calculation could not be achieved.	(a) The sponsor should ensure that appropriate and documented quality control of statistical programming and data analysis is implemented (e.g., where appropriate, for sample size estimations calculations, results for IDMC, outputs for clinical trial report, statistical or centralised monitoring).
Medicines for Europe	1734	1737	3.16.2 (a)	In addition to quality control, quality assurance measures should also be mentioned here.	Replace "quality control" by "sponsor oversight"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA Consolidated Comments	1738	1738	3.16.2 a	There should be details on how analysis plan, programming documents are handled as part of statistical programming and datasets section. This text is additional. Could be a separate bullet	Sponsor should ensure statistical analysis plan, programming documents are developed and finalised prior to the corresponding analysis.
EFPIA Consolidated Comments	1739	1740	3.16.2 b	deviations from the SAP are not covered. Please add to b	(b) The sponsor should ensure the traceability of data transformations and derivations during data processing and analysis. Deviations from the planned statistical analysis should be justified, documented and reported in the clinical trial report.
Fergus Sweeney	1742	1742	3.16.2.c	reword to add rationale for the allocation	"…ensure that the rationale for the allocation to…."
Quotient Sciences	1742	1746	3.16.2 (c)	Clarification required.	Please edit as follows: (c) The sponsor should ensure that the criteria for allocation to or exclusion of each trial participant from any analysis set is predefined (e.g., in the protocol or the statistical analysis plan). The rationale for inclusion or exclusion for any participant (or particular data point) should be clearly described and documented.
Dr. C. Wilsher	1744	1744	3.16.2.c	Statistical Analysis Plan is not defined nor in the Glossary.	
CARVALHO Carla	1748	1754	3.16.2.d	Some study design allows cross-over of the patients e.g., blinded study with a open-label portion. When the patient is progressing, it's allowed to unblind the patient. If the patient was on the placebo arm, allow the patient to be take the treatment in the open part. Only limited staff should remain blinded. In order to avoid identifying all staff unblinded for the cross-over part, change of the wording is proposed.	Procedures should be in place to describe unblinding ; these descriptions should include: (i) who was unblinded, at what timepoint and for what purpose they were unblinded for the blinded part of the study; (ii) who should remain blinded in case of cross-over design; (iii) the safeguards in place to preserve the blinding.
EFPIA Consolidated Comments	1748	1749	3.16.2-d	propose to move to data management section, need to add where applicable due to open label	Procedures should be in place to describe unblinding where applicable;
German Pharmaceutical Industry Association (BPI)	1754	1756	3.16.2. d	It is not quite clear why processes with regards to unblinding (who should remain blinded / safeguards to preserve blinding) are mentioned here (again) in a chapter about Statistical Programming and Data Analysis. Or is this specifically adressing interim analysis? Intention of this section is not obvious.	Either delete here or rephrase to make clearer.
Good Clinical Trials Collaborative, on behalf of supporting organisations	1758	1762	Sponsor (3.6.2.e)	Regarding statistcial programming records and data analyses. Add at end "Such records and outputs should be maintained in such a way as to prevent premature or inadvertent unblinding of study results (e.g. the impact of allocated trial treatment on the study efficacy and safety outcomes)."	
Medicines for Europe	1758	1762	3.16.2. (e)	Programming may not be done by sponsor, in such cases sponsor will not retain all records.	The sponsor should retain ensure the retention of the statistical programming records that relate to the

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Fergus Sweeney	1764	1766	3.16.3	absolutes are not needed. Also "in accordance" is the term used generally not "in conformance"	reword "….shoud retain the sponsor specific…..to the trial in accordance with the …"
Society for Clinical Research Sites	1768	1772	3.16.3		This draft item is seemingly introducing a new concept on obliging the service provider to retain records. This is further confusing the issue on who the service providers are supporting and the investigator's role. The draft item does not delineate when service providers are independently responsible for retention of the records they generate, as opposed to the investigator/site (or sponsor) being responsible for those independently generated records. We maintain that in a decentralized environment where sponsors (whether directly or through service providers that they select and contract with) should be the entities responsible for the records they generate, not the investigator/site. We hope that this can be clarified throughout the guidance so that confusion can be decreased and responsibility can be appropriately assigned. In addition, this section should be adjusted to reflect our comments and requested changes in Annex I Item 2.12.11 and Annex C.1.3; after the investigator/site's local regulatory obligations have expired, the records may be transferred to the sponsor's custody in lieu of destruction. This is in the best interest of the ability to reproduce the records in the distant future given the growing incapability of the site/investigator's ability to adequately keep the records. This topic is discussed at length in our comments to Annex I Item 2.12.11 and is of critical importance to all stakeholders that it be assimilated into the final guidance.
CARVALHO Carla	1773	1775	3.16.3.c	In order to avoid any issues regarding the transfer of data ownership, it's important to ensure that the procedural documents used for the conduct of the study are also transfered. Such procedural documents are requested when the product is filed in Japan.	The sponsor should report any transfer of ownership of the essential records to the appropriate authority(ies) as required by the applicable regulatory requirement(s). Such transfer should be controlled and should include the procedural documents used.
Quotient Sciences	1773	1775	3.16.3 (c)	Clarification required.	Please edit as follows: (c) The sponsor should report to the appropriate authority(ies) any transfer of ownership of the essential records to the appropriate authority(ies) as required by the applicable regulatory requirement(s).
EFPIA Consolidated Comments	1776	1780	3.16.4 (a)	Direct access can be remote if all the source records are accessible remotely. We find majority of sites do still have paper source in addition to electronic records. If there is no remote system e.g. eISF, that provides the monitor access to the paper source the monitor cannot access all records. This needs to be called out in the guidance so that sites that prefer remote access only understand their responsiblity to provide remote access to all source including paper source in order to permit direct access and monitoring. If sites cannot provide remote access then they have a responsibility to allow direct access onsite	The sponsor should ensure that it is specified in the protocol or other documented agreement that the investigator(s)/institution(s) provide direct access to source records for trial-related monitoring, audits, IRB/IEC review and regulatory inspection. This may be onsite, remote or a combination of both, in-line with the sponsors risk-based monitoring/audit strategy and the regulatory authority(ies) requirements.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Society for Clinical Research Sites	1776	1785	3.16.4	We have concerns over the use of the term "direct access" (both here as well as in Annex I Items 2.8.11(n), 2.12.12, 3.6.3(d), 3.11.4.1(c), the Glossary and Appendix B.11). The phrase "direct access" (as opposed to "access") is interpretable as supporting an activity that is generally prohibited with established healthcare privacy/security practices and regulations across the globe (i.e. providing login IDs directly into to electronic health records).	We request the deletion of the word "direct" (or change the phrase to "access to view") here and in the other sections referenced to avoid this confusion and that the guidance can recognize the variety of ways source document verification has been accomplished over the past decade without "direct" access (but with "access to view"). This would also bring these sections to be consistent with Annex I Item 3.11.4's requirement that monitors "adhere to data protection and confidentiality requirements in accordance with applicable regulatory requirements, institution policy and established data security standards."
Quotient Sciences	1777	1780	3.16.4 (a)	Many RECs ask us to remove from the ICF statements that the REC could have access to source records because they do not see that as part of their remit. Reference to access by RECs should be in line with local rules and guidance.	Please edit as follows: (a) The sponsor should ensure that it is specified in the protocol or other documented agreement that the investigator(s)/institution(s) provide direct access to source records for trial-related monitoring, audits, IRB/IEC review and regulatory inspection and, in accordance with local regulatory requirements and guidance, IRB/IEC review.
Fergus Sweeney	1780	1780	3.16.4.a	ensure foreign inspections are not hindered	add "…inspection (domestic or foreign)"
Medicines for Europe	1782	1785	3.16.4 (b)	not applicable to healthy volunteers and phase I studies	For phase II-IV studies, the sponsor should ensure that trial participants have consented to direct…
Quotient Sciences	1782	1785	3.16.4 (b)	Many RECs ask us to remove from the ICF statements that the REC could have access to source records because they do not see that as part of their remit. Reference to access by RECs should be in line with local rules and guidance.	Please edit as follows: (b) The sponsor should ensure that trial participants have consented to direct access to their original medical records and other participant-related trial documents for trial-related monitoring, audit, IRB/IEC review and regulatory inspection and, in accordance with local regulatory requirements and guidance, IRB/IEC review as part of the informed consent.
Fergus Sweeney	1785	1785	3.16.4.b	ensure foreign inspections are not hindered	add "…inspection (domestic or foreign)..."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA Consolidated Comments	1787	1787	3.17.1	The case when a regulatory authority terminates a trial is not covered in this section. It is proposed that text from 2.6.3 is moved to here and deleted from 2.6.3	The sponsor may suspend or terminate a trial in accordance with the protocol or any other reason justifying the suspension or early termination. These decisions need to be taken in accordance with Principle 2.3. If the Regulatory Authority terminates or suspends the trial, they will inform the sponsor. In these cases the sponsor should promptly inform the investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC should also be informed promptly and provided with the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, in accordance with applicable regulatory requirement(s).
EUCROF	1790	1793	III. 3.17.1	"The IRB/IEC should also be informed promptly and provided with the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, in accordance with applicable regulatory requirement(s)." Structure of the sentence might be misleading: "suspension by the sponsor" would be a wrong interpretation.	"The IRB/IEC should also be informed promptly by the sponsor or by the investigator/institution and provided with the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s)."
EFPIA Consolidated Comments	1798	1798	3.17.2 (a)	The expression "the regulatory agency(ies)" is used once here instead of the expression 'the regulatory authority(ies) that are used (49 times) in the guideline.	Please see suggested verbiage " Whether the trial is completed or prematurely terminated or an interim analysis is undertaken for regulatory submission, the sponsor should ensure that the clinical trial reports, including interim reports, are prepared and provided to the regulatory authorities as required by the applicable regulatory requirement(s)"
EUCROF	1806	1808	III. 3.17.2 (c)	"Consideration should be given to providing the investigator with information about the final treatment taken by their participants for blinded trials and a brief summary of the overall outcome of the trial." Not clear wht is meant by "final treatment".	Consideration should be given to providing the investigator with information about the treatment allocation for their participants (for blinded trials) and a brief summary of the overall outcome of the trial.
GQMA	1806	1808	III.3.17.2 c	In a blinded trial the sponsor should always inform the investigator about the treatment allocation of their participants. The wording "Consideration should be given to" seems to suggest, that the sponsor may as well decide against providing such information at all.	Change to: "The sponsor shall provide the investigator with information about the final treatment taken..."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Quotient Sciences	1806	1812	3.17.2 (c)	Provision of a lay summary of results to *patient* participants should be encouraged. However, unlike patients, the vast majority of healthy volunteers are not interested in seeing the results of the phase 1 trials in which they have participated – in our experience, having offered volunteers the opportunity to see the results, very, very few volunteers show any interest in them. In phase 1 healthy volunteer trials, it is proportionate to give volunteers a summary of the results on request; it should not be mandatory to provide results to healthy volunteers.	Please edit as follows: (c) Consideration should be given to providing the investigator with information about the final treatment taken by their participants for blinded trials and a brief summary of the overall outcome of the trial. Sponsors are encouraged to provide this information to patient participants. For healthy volunteer trials, sponsors should provide a simple summary of results, and treatment allocation, if requested by participants. Where this information is provided to participants, the language should be non-technical, understandable to a layperson and non-promotional. The sponsor should only supply this information after the trial has been unblinded and all relevant analyses/conclusions have been completed and finalised.
EUCROF	1808	1808	III. 3.17.2.(c)	"brief summary of the overall outcome of the trial". Represents redundancy to point (b): "Investigators should be provided with a summary of the trial results".	
Fergus Sweeney	1809	1809	3.17.2.c	lay people have a much greater ability to understand technical language where it is explaiined, clinical trial reports made available for lay people can certainly include technical language if it is explained. We should not overly downgrade the clarity of published data for lay person use.	add "…language should be non-technical or where used technical terms are used they should be explained, understandable…"
Fergus Sweeney	1811	1811	3.17.c	absolutes are not needed. In addtion the use here could stop or be used as an excuse to stop publication of interim data when that is necessary and justified. In chronic conditions some trials may go on for one or more decades, but the product may be authorised and used or its use adjusted (or ought to be adjusted) based on interim analysis.	reword to "…unblinded and relevant analyses…"
German Pharmaceutical Industry Association (BPI)	1813	1813	4.	data governance: this (new) term should also be explained in the glossary for a better overall understanding of the background of this new chapter	Add "data governance" to the glossary
Good Clinical Trials Collaborative, on behalf of supporting organisations	1813	2029	Section 4	The text in these lines of the new section is helpful and well written. It encourages thoughtful and proportionate application to individual circumstances.	
Good Clinical Trials Collaborative, on behalf of supporting organisations	1813	2029	Section 4	Given that development of information systems (e.g. for the communication, banking, and commerce sectors) is a well-established endeavour with its own standards and guidelines, one sensible option might be to delete the sections on data in the Investigator (Section 2) and Sponsor (Section 3) sections, to retain the new Section 4 and add to it that development of Information Systems for Clinical Trials should follow the principles of relevant, well-established international standards and guidelines (perhaps giving a few examples, such as GAMP, ISO 27001 [quality management systems], ISO 9001 [information security]).	
Fergus Sweeney	1818	1818	4	in general avoid use of versions of ICH guidelines as otherwise the cross references will become outdated	reword to …ICH E8 and.."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
AFI	1819	1821	4	...and support good decision making .	Good decision making of Investigator and Sponsor in terms of product safety and efficacy and in order to suggest reccomandations, if any.
EUCROF	1819	1821	III. 4.	"The quality and amount of the information generated in a clinical trial should be sufficient to address trial objectives, provide confidence in the trial's results and support good decision making." Trial participant protection is missing	"The quality and amount of the information generated in a clinical trial should be sufficient to address trial objectives, provide confidence in trial participant protection and in the trial's results and support good decision making."
German Pharmaceutical Industry Association (BPI)	1819	1821	4.	This sentence refers very generally to *quality and amount of information generated in a clinical trial* , and the consequences (e.g. *good decison making*). This sentence per se is completely correct, however, it does not fit to the chapter "data governance", as governance focusses on the correct handling and protection of data, but not on requirements for the amount of data or consequences out of the data. The sentence at this place therefore makes it more difficult to understand the intention of the chapter.	move the sentence to another chapter of the guideline
AFI	1824	1825	4	Implemented proportionatelly and documented appropriately	Proportional implementation should be documented in the protocol, data management plan and any other appropriate document that should be referred in the protocol. Documented either by Investigators and Sponsor. Documents must be available at site, Investigator's File and in Sponsor' documentaton (Sponsor's File)
EFPIA Consolidated Comments	1824	1836	4	These points were already addressed and discussed above in section 3 - Data. Consider to delete to avoid repetition The following key processes should address the full data life cycle with a focus on the criticality of the data and should be implemented proportionately and documented appropriately: (a) processes to ensure data protection of trial participants' confidential data; (b) processes for managing computerised systems to ensure that they are fit for 1829 purpose and used appropriately; (c) processes to safeguard essential elements of the clinical trial, such as randomisation, dose escalation and blinding; (d) processes to support key decision making, such as data finalisation prior to analysis, unblinding, allocation to analysis data sets, changes in clinical trial design and, where applicable, the activities of, for example, an IDMC.	suggest to remove the duplication from section 3 where it is the same text.
Sandoz AG, Switzerland	1826	1826	4 a)	Reference to applicable/Local laws should be included. Rationale: The compliance should be in line with adherance to any applicable / local law	"confidential data in compliance with applicable laws/regulations"
EFPIA Consolidated Comments	1828	1829	III.4(b)	Software Development Life Cycle and Computer System Validation processes are key in ensuring elements of full data life cycle and data criticality as built into the design of computerised systems throughout their life cycle. It is important to reference these industry accepted processes out to avoid ambiguity.	processes for managing computerised systems (e.g. Software Development Life Cycle and Computer System Validation) to ensure that they are fit for purpose and used appropriately;

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Society of Quality Assurance (SQA)	1828	1828	4(b)	Software development lifecycle (SDLC) and computer system validation (CSV) processes are key in ensuring elements of full data life cycle and data criticality as built into the design of computerized systems throughout their life cycle. It is important to clearly call these industry accepted processes out to avoid ambiguity.	"...managing computerized systems, (e.g. Software Development Life Cycle and Computer System Validation) to ensure ....."
Medicines for Europe	1831	1832	4	Dose administration is an essential element and thus should be added	(c) processes to safeguard essential elements of the clinical trial, such as randomisation, dose administration and dose escalation and blinding;
EUCROF	1834	1835	III. 4. (d)	"processes to support key decision making, such as data finalisation prior to analysis," Data finalisation is not a common term	processes to support key decision making, such as final data cleaning prior to analysis,
Association for Clinical Data Management (ACDM)	1837	1837	4.1	There should be some clarification to potentially unblinding information in external systems and the management of maintaining the blind and unbiased influence, if there is expectations PIs to review various sources	Please asses to include further clarification/recommendation
Medicines for Europe	1837	1837	4.1	Not all trials require a blinded design.	Safeguard Blinding in Data Governance for blinded trials
Association for Clinical Data Management (ACDM)	1838	1839	4.1.1	Suggest a cross reference to section 3.16.1 w) iii).	Reference this section in the investigators section so they are linked.
Quotient Sciences	1839	1839	4.1.1	Typographic error.	Please change " users' account " to " users' account**s** ".
Association for Clinical Data Management (ACDM)	1844	1849	4.1.2	This is a very well written requirement	No Action
CARVALHO Carla	1844	1849	4.1.2	This is not possible for cross-over study. Staff interacting with site who cross-over the patient will have access to the treatment received by the patient and this will have no impact in the trial result.	Roles, responsibilities and procedures for access to unblinded information should be defined and documented by all relevant parties according to the protocol; this information may also be included in the data management plans and statistical analysis plans. For example, in blinded trials with no cross-over, sponsor staff or designated third parties who are involved in operation of the trial and directly or indirectly interact with site investigator staff should not have access to unblinding information. For blinded trials wth a cross-over portion, the staff that will be in direct contact with the site will be informed about the treatment allocated after the unblinding due to the cross-over.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA Consolidated Comments	1844	1849	4.1.2	"Roles, responsibilities and procedures for access to unblinded information...according to the protocol;" It is not uncommon for the protocol to refer to other instructions/manuals.	….according to the protocol and/or other trial instructions/manuals;"
Quotient Sciences	1844	1849	4.1.2	Rarely, in phase 1 trials in healthy volunteers, sponsors unblind treatment allocation for one or a few participants to investigate a potential side effect and guide decisions on progress of the trial. The investigator is not unblinded in those circumstances. For small sponsors, it might not be possible to ensure that all sponsor staff who interact directly or indirectly with investigators do not have access to any unblinding information.	Please edit as follows: 4.1.2 Roles, responsibilities and procedures for access to unblinded information should be defined and documented by all relevant parties according to the protocol; this information may also be included in the data management plans and statistical analysis plans. For example, in blinded trials, sponsor staff or designated third parties who are involved in operation of the trial and directly or indirectly interact with site investigator staff should, wherever possible, not have access to unblinding information. Where that is not possible, suitable controls must be in place to prevent unblinding of investigator staff.
Good Clinical Trials Collaborative, on behalf of supporting organisations	1849	1849	Section 4 - Data Governance	Add at end "Provisions should be put in place to protect blinding in the context of monitoring, audit or inspection activities." (To guard against the paradox of processes intended to maintain or assess quality, inadvertently damaging quality.)	
AFI	1851	1853	4.1.3	Any planned….to the trial results.	The locaton of unblinding documents should be documented and the documents should not be availabe for blinded personnel involved in the trial.
EFPIA Consolidated Comments	1852	1853	4.1.3	consideration for actions post discovery. Clarified the differences between planned and unplanned	Any planned or unplanned unblinding, including accidental or emergency unblinding, should be documented. Accidental and emergency unblinding should also be assessed for the impact to trial results, and the need for corrective and/or preventative actions to be taken based upon the outcome of assessment.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Society for Clinical Research Sites	1854	1964	4.2-4.4		Line 1867 references a "responsible party" (as do Lines 1936, 1947, 1953, 1960, 1965 and 1991) and it is not stated who that refers to. It seems that the "responsible party" would be the one (whether the sponsor or investigator) contracting for the service, thus we request that it be clarified. This would be consistent with Lines 1927-1929 (indicating that the sponsor is responsible for the computerized systems they put in place). Lines 1932-1935 should be slightly clarified that the investigator is responsible for the electronic systems that they "put into play". Simply leaving it as what the investigator "deploys" could lead to confusion that the investigator is accountable for the technology the sponsor put in play simply because the investigator used it. Specific to Annex I Item 4.3, while we appreciate the recommendation that the intended participant population and healthcare professionals are involved in the design of the computerized system that they may use, we additionally request that the investigator/site also be added to this list as 1) they are often the end users of the products; and 2) they can also provide the best information of their local population to assure that the right diversity of participant population and healthcare professionals are represented in the design.
AFI	1855	1855	4.2	Procedure should …	In the Study Protocol, it should be indicated where the procedure is specified
Association for Clinical Data Management (ACDM)	1857	1860	4.2.1 (a)	Although this requirement seems reasonable, it stems from GMP and might require additional clarifications in order to be understood in a clinical trial conduct setting.	Clarify so requirement is clearly understood with reference to correct sections e.g. 3.16.1
Association for Clinical Data Management (ACDM)	1857	1864	4.2.1 (a) (b)	Data Life Cycle for data verification will be satisfied if also prevented from CSV side.	So we would suggest to also "introduce this terminology at section 3.16.1 as well. Presume at w), i) An same with section 4.2.2, etc… to allow correct reading of people
EUCROF	1857	1857	III. 4.2.1 (a)	"The requirements for and extent of data verification…"	"The requirements for and the extent of data verification…"
EFPIA Consolidated Comments	1859	1860	4.2.1 (a)	Verbiage in Section 4.2.1 Data Capture (a) is "The requirements for and extent of data verification, when data captured onpaper or in an electronic health record are manually transcribed into a computerised system, should take the criticality of the data into account. Refer to section 4.2.3 for data entered directly in data acquisition tools"Reference to section 4.2.3 is incorrect in the above sentence sentence .Section 4.2.3 refers to Review of Data and MetaData . Apologies we could not find the correct reference.	Remove reference to 4.2.3
GCP-unit, Copenhagen	1859	1860	4.2.1 (a)	"Refer to section 4.2.3 for data entered directly in data acquisition tools" it should refer to 4.2.2 (a) (iii) ? Or what section? 4.2.3 does not make sence in this concern	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Mandy Jackson National Clinical Trials Office Quality Working Group Ireland	1860	1893	Data capture	Line 1860 states to refer to 4.2.3 (line 1893) with regards to data entered directly in data acquistion tools but 4.2.3 does not have any detail on data entered directly just review of data.	Could statement be clarified, guidance included for data entered directly into data acquistion tools
AFI	1861	1864	4.2.1 b	…controlled and documented.	Controlled and documented by Sponsor's Personnel or delegate.
Association for Clinical Data Management (ACDM)	1861	1864	4.2.1. (b)	What is considered relevant?	Please define what is required metadata.
Fergus Sweeney	1861	1861	4.2.1.b	This sentence illustrates why is it essential to be more clear about which metadata should be accompanying data points via data acquisition tools. ALCOA metadata do not typically accompany data reported onwards but remain in the source, as they do with medical records, paper or otherwise. The scientific metadata do go forward via that data acquistion (eCRF etc) reporting tools to the sponsor and for analysis. The second sentence on automated data validation checks is a separate topic that should be in its own subsection though it could be questioned whether GCP needs this detail	reword to be more clear about metadata and which may be "relevant". Split into a separate subsection or delete the automated data check concept.
Ludger Wienbrede	1861	1864		"Acquired data from any source should be accompanied by relevant metadata. At the point of data capture, automated data validation checks should be considered as required based upon risk, and their implementation should be controlled and documented." This should be deleted or modified in a way that makes it technology-open. Sometimes data are still captured on paper or in a way that imply no metadata or do not allow automated data validation checks. Even in trials with eCRFs there might still be paper questionnaires which are the point of data capture.	
Fergus Sweeney	1866	1892	4.2.2	This section needs to be much clearer to avoid disproportionate or simply confused or incorrect retention and onward reporting metadata. The concepts of ALCOA metadata and scientific metadata should be clear. This section is all about ALCOA metadata only and should make that clear. The scientific metadata are essential and have to move forward with the data points they relate to. Much of CDISC work is on scientific metadata.	reword to make very clear that there are various forms of metadata.
Fergus Sweeney	1866	1892	4.2.2	This section implies that in future very extensive work and records may be demanded of researchers. A strong sense of proportionality is needed. Audit trails may be reviewed from time to time but not constantly nor with detaield records of that being done.	reword to be much clearer and to avoid excess demands on investigator sites
Fergus Sweeney	1866	1892	4.2.2	However much this may be achieveable for sponsor systems, for healthcare systems there needs to be a much more cautious expectation of what will be present. If healthcare systems have been developped for and are considered fit for use for healthcare, they are unlikely to be modifed to meet added GCP requirements. Regulating for the unachievable can lead to a more general disregard for/frustration with requirements and a lot of unecessary work trying to work around established healthcare systems. They may or may not record workflow actions for instance, but only the outcome.	review the section carefully with respect to its applicability in all its detail to healthcare systems

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GCP-unit, Copenhagen	1867	1868	4.2.2	Not sure what "the responsible party" refers to. Later (in line 1936) its written "The responsible party should ensure that those developing computerised systems (…)" so its a third party? Not sponsor and not the ones develping? The term is used many times in this section, and mayby need a definition.	
Sandoz AG, Switzerland	1867	1867	4.2.2	The definition of "responsible party" in context of Sec. 4 must be defined to avoid confusion. Rationale: Within a clinical trial setup, several roles and responsibilities exist wherein a Sponsor may outsource to CRO which may also further sub-contract its work. Ultimately, responsibilities may vary based on individual setups wherein to identify the right responsible party, whereas sponsor retains the overall responsibility.	Addition of "responsible party" definition
Fergus Sweeney	1872	1872	4.2.2.a.i	the requirement may seem laudable but is it really something that most systems do? If it isnt it will not be at all easy to achieve, may never be achieved. Do not regulate for the unachieveable.	consider deletion of this subsection
Charles River Labs	1875	1878	4.2.2	should be rephased so that there is a clear requirement for a reason for change to data, and if absent a risk-based evaluation is required.	systems are designed to permit data changes in such a way that the initial data entry and any subsequent changes or deletions are documented, including, where appropriate, having a risk-based evaluation in place if the reason for the change is not implicit;
Sandoz AG, Switzerland	1878	1878	4.2.2 ii)	Changes are to be considered implicit especially in case the changes in the system are due to change of data from a "source system" Rationale: Data changes originating from a different source should have the rationale for changes at the source and not at the transmitted data system.	Addition: "e.g. data changes from a different source / system"
SGS Health Sciences	1882	1884	4.2.2	allowing disabling or modification of an audit trail 'in rare circumstances and only if a log of such action and justification is maintained' creates opportunities for disabling or modifying an audit trail for whatever reason, also to cover up mistakes, or signs that the system was not performing as intended. Suggestion to either remove this second part, or to specify in which rare circumstances this would be allowed e.g. to maintain confidentiality of the trial participant or a relative of the trial participant? Example: it has already occurred that in a CRF comment personal data (identifiers) had been entered by the site by mistake. Even if it was corrected afterwards by the site, in the audit trail you could still see what was entered originally, and how it was modified. Or in case data of a trial participant were accidentally entered in a CRF of the wrong trial? (may happen for sites conducting multiple trials concurrently) We can't think of any other examples where it could be allowed to disable or modify the audit trail, except for reasons of malpractice.	Ensuring that audit trails, reports and logs are not disabled or modified except to maintain confidentiality of a trial participant or a representative or relative of the trial participant. in rare circumstances and only if a log of such action and justification is maintained;
Association for Clinical Data Management (ACDM)	1886	1887	4.2.2 (c)	Think term decipherable needs clarification. Many people say the audit trial must be readable by a human, while others say it simply needs to be appropriate for a program to read.	Clarify what is meant by decipherable.
Dr. C. Wilsher	1886	1886	4.2.2	"(c) Ensuring that audit trails and logs are decipherable and can facilitate analysis". Is "decipherable" the same as "human-readable"?	(c) Ensuring that audit trails and logs are in human-readable format and can facilitate analysis

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA Consolidated Comments	1886	1886	III.4.2.2(c)	The concept of "decipherable" is subjective and technical. It is recommended that this be clarified.	"Ensuring that audit trails and logs are decipherable possible to interpret and can facilitate analysis.
Fergus Sweeney	1886	1886	4.2.2.c	Audit trails should permit review but "facilitating analysis" is over-reach and increasing expectation beyond what is reasonable.	reword to "…decipherable and can support review."
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	1886	1886	III 4.2	It is unclear how audit trails cloud facilitate analysis. Also, it is unclear what is meant by "decipherable". If "decipherable" means "human readable" the wording should be adaped.	
Society of Quality Assurance (SQA)	1886	1886	4.2.2(c)	The word decipherable is subjective. It is recommend to replace with something like easy to interpret or human readable and understandable.	"Ensuring that audit trails and logs are easy to interpret and can facilitate analysis".
Association for Clinical Data Management (ACDM)	1888	1890	4.2.2 (d)	Transfer/interface in general. Time stamp for data acquisition tool is restrictive. At least any inbound data transfer must have audit trail so we can fully trace E2E the data life cycle ! do not restrict to data acquisition tool, to consider any data transfer interface)	Agree with co-ordinated universal time. Also add that the end to end data transfer from source to final data sets must be unambiguous.
SHIONOGI	1889	1890	4.2.2(d)	Abbreviation UTC seems to be incorrect compared to the clarifying text: coordinated universal time (CUT)	consider to replace UTC with CUT
EFPIA Consolidated Comments	1892	1892	III.4.2.2(e)	Determination of which of the identified metadata require review and retentions should be risk-based.	Determining, using a risk-based approach, which of the identified metadata require review and retention.
Society of Quality Assurance (SQA)	1892	1892	4.2.2(e)	Determination should be risk-based.	"Determining, using a risk-based approach, which.....
EFPIA Consolidated Comments	1894	1896	4.2.3	Suggest that the review of audit trails should be updated to reflect a risk based approach focused on the criticiality of the data	Procedures for review of trial- specific data , audit trails and other relevant metadata should be in place. It should be a planned activity , the extent and nature should be risk based ,adapted to the individual trial and adjusted based on experience during the trial
EUCROF	1894	1895	III. 4.2.3	"Procedures for review of trial-specific data, audit trails and other relevant metadata should be in place. It should be added whether the review of data and meta data is sponsor or investigator task. See also General comments.	
AFI	1895	1896	4.2.3	It should be a planned…	...planned by Sponsor
Association for Clinical Data Management (ACDM)	1897	1901	4.2.4	Should there be clarification that only authorized individuals can make data changes (example site staff, subject)	Add confirmation that any making the changes should be confirmed through user name, role , training etc

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EFPIA Consolidated Comments	1897	1901	4.2.4	It is not clear what the entity is so made proposal	There should be processes to correct data errors that could impact the reliability of the trial results. Corrections should be attributed to the entity (person or computer generated) making the correction, justified and supported by source records around the time of original entry, and performed in a timely manner.
AFI	1898	1901	4.2.4	…process to correct ..	Allowed only to Investigators
Medicines for Europe	1899	1901	4.2.4	According to the Guideline on computerised systems and electronic data in clinical trials (EMA/INS/GCP/112288/2023), coming into effect on 07 September 2023, data should be attributable to the person and /or system generating the data. We suggest to maintain the same wording to ensure alignment between documents.	Corrections should be attributed to the person and /or system entity making the correction, justified and supported by source records around the time of original entry, and performed in a timely manner.
Fergus Sweeney	1900	1900	4.2.4	The data in the system may be the source data so it may sometimes be challenging for certain data corrections	consider if this requirement is generally applicable e.g. for PRO tools or other direct data capture
Quotient Sciences	1902	1907	4.2.5	Technologies that transfer personal data out of its original jurisdiction may increase its disclosure e.g., to authorities within the new jurisdiction.	Add text in bold: 4.2.5 Data Transfer, Exchange and Migration Validated processes or other appropriate processes such as reconciliation should be in place to ensure that electronic data transferred between computerised systems retains its integrity and preserves its confidentiality. The transfer process should be documented to ensure traceability, and data reconciliation should be implemented as appropriate. Responsibilities for identifying situations where electronic transfer of personal data will include transfer of data to new jurisdictions, and for ensuring that such transfers will be lawful, must be clear.
EFPIA Consolidated Comments	1903	1907	4.2.5	Item "Data Transfer, Exchange and Migration" does not account for data transfers expectations during the study conduct from service providers such as labs, eCOA providers, etc. Consider to include in 3.16 or here in 4.2.5 the expectation about test transfer, data transfer agreements, QC activities before finalization of the data for analysis.	Validated processes and/or other appropriate processes such as reconciliation should be in place to ensure that electronic data, including metadata, transferred between computerised systems (e.g., between a service provider and a sponsor) retains its original content, integrity and preserves its confidentiality. The data exchange / transfer or system migration process should be documented to ensure traceability, and data reconciliation should be implemented as appropriate, to avoid data loss and modifications.
GCP-unit, Copenhagen	1903	1903	4.2.5	Maby a better word than "reconciliation". Sorry to say, but I think the understandig is desturbed of to many foreign word	Perhaps this sentence "Validated processes or other appropriate processes to verify the accuracy and consistency of data should be in place (..)"
Fergus Sweeney	1905	1905	4.2.5	data transfer should preserve the required confidentiality for the transfer not an absolute confidentiality	reword "…and preserves the required level of confidentiality."

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Association for Clinical Data Management (ACDM)	1909	1912	4.2.6	Omissions cannot be "rectified" in datasets prior to analysis. We cannot impute raw data. Imputation of missing values may be tolerable in late phase research - but in Phase I-III and in view of a marketing authorisation, such activities can only be done as sensitivity analysis on analysis (ADaM) datasets.	Recommend to replace "omission". Clarify this rectification of omitted data must be before the data is extracted into data sets.
Charles River Labs	1909	1913	4.2.6	Point (a) is unclear. Recommend rephrasing line 1912 to state that review/verification of data is done to ensure the reliability of trial results. Recommend removing implication that reviewers can decide the impact of errors and data omissions that are not the investigator.	Update text as you see fit.
Association for Clinical Data Management (ACDM)	1914	1919	4.2.6 (a)	Unless the data exists at the source, we should not be imputing them in SDTM datasets for Submission.	Clarify this rectification of omitted data must be before the data is extracted into data sets.
AFI	1915	1916	4.2.6 b	…should be confirmed and documented ….	…should be confirmed and documented by Sponsor or delegate….
GCP-unit, Copenhagen	1917	1918	4.2.6 (b)	"These activities may include reconciliation of entered data and data sets or reconciliation of relevant databases" Difficult to understand the meaning of this and how to handle it	
AFI	1922	1923	4.2.6 c	…and should be documented.	…and should be documented by Sponsor.
German Pharmaceutical Industry Association (BPI)	1924	2029	4.3.-4.8.	Structure ist not logical. 4.3 is a general chapter on Computerised Systems. However, all following chapters (4.4 - 4.8.) seem to refer also to Computerised Systems. Thus, they should not be separate chapters but subchapters of a large section "computerized Systems" to facilitate reading and understanding of these further chapters.	Restructure; i.e. make chapters 4.4.-4.8 to subchapters of section 4.3 Computerized Systems, i.e., 4.3.3 - 4.3.7.
IFCT	1927	1932	4.3	precise that is attended. What can the sponsor do ? How ?	Give details.
Society of Quality Assurance (SQA)	1927	1927	4.3	It is important to highlight that these responsibilities related to computerized systems are clearly documented through existing agreements or contacts.	"…trials should be clear and documented. The responsibilities of the sponsor, investigator, and other parties with respect to computerised systems used in clinical trials should be clear and documented as part of existing agreements. In summary,...".
DGPharMed e. V. (Deutsche Gesellschaft für Pharmazeutische Medizin)	1930	1933	III.4.3	That is an undue obligation to the sponsor. Furthermore, it appears that institutions will not allow sponsors to audit their systems for standard care. This should clearly be an obligation to the investigator/institution. The investigator/institution should provide the sponsor with evidence/ documentation.	The responsibility shall lie with the investigator/institution

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EFPIA Consolidated Comments	1930	1932	4.3 Computerised Systems	Suggest to exchange the sequence for describing the responsibility of Sponsor and Investigator/institutions on the systems to be used by investigator/institution. The main responsibility to ensure the institution systems' qualification lies with Investigator/institutions, and the system qualification should fulfill both the clinical routine practice and clinical trial specific requirements. Phrase on investigator moved earlier on in paragraph. moved text. The investigator/institution should ensure that the expectations for computerized systems are proportionately addressed and implemented,	The investigator/institution should ensure that the expectations for computerized systems are proportionately addressed and implemented, including the systems used for electronic health records and other record keeping systems for source data collection, and other systems deployed specifically for the purposes of conducting clinical trials by investigator/institution. The sponsor should review whether the systems used by the investigator/ institution are fit for purpose in the context of the trial.
SGS Health Sciences	1930	1935	4.3	ambiguity related to the responsibility for assessing fitness for purpose of electronic health records systems for source data collection, if for the investigator it is specified that it's about systems deployed specifically for the purposes of conducting clinical trials. Electronic health records systems are usually deployed by the hospital the site is part of, and as such not deployed specifically for the purpose of conducting trials, yet may be used by the investigator for source data collection. In this case, how it is stated now, it would be the sponsor's responsibility to assess if the system is fit for purpose, and to assess fitness for purpose and compliance with the regulatory requirements - this does not seem right. 1. The sponsor can not be held responsible for a system implemented at a site, for which the site has no other choice than using it because it's hospital policy. 2. the sponsor representatives visiting the sites may not be subject matter experts in computerized system validation and/or the regulatory requirements. If this would need to be done as part of site (pre)qualification by an audit team including SMEs, this would require many more sponsor site qualification audits. For CROs, delegated with site qualification/selection, it may not be feasible to do this for every site. 3. the sponsor representatives may not get access to the EHR due to hospital policy, and as such, can not assess/verify compliance with all the regulatory This may result in more source data being entered directly into the CRF, and then the question pops up again how trial participants will be able to access their trial data, if not part of their EHR.	In the event that the investigator/institution deploys systems specifically for the purposes of conducting clinical trials, the investigator/institution should ensure that the expectations are proportionately addressed and implemented.
German Pharmaceutical Industry Association (BPI)	1932	1935	4.3.	"In the event that systens are deployed by the investigator specifically for the purpose of the trial, investigator should ensure that the expectations are adressed…." It is not clear in this context, what the term "expectations" refers to. Which expectations, whose expectations? It can only be assumed that the terminology should be the same as earlier in this section for the sponsor responsibilities (line 1928-1929: "*expectations for computerized systems as described in this section*")	add respective terminology: *In the event that the investigators/institution deploys systems specifically for the purposes of conductiong clinical trials, the investigator/institution should ensure that the expectations for computerized systems as described in this section are proportionately addressed and implemented"*
Ludger Wienbrede	1936	1938		"The responsible party should ensure that those developing computerised systems for clinical trials are aware of the intended purpose and the regulatory requirements that apply to them." This is often impossible to implement. Line 1814 defines the responsible parties as investigators and sponsors. Sponsors and inesvtigators often use off-the-shelf products, which might allow some tailoring to a specific trial, but investestigators and sponsors have no possibility to influence the development of computerised systems directly.	
AFI	1939	1941	4.3	…involved in the design of the system...	…involved in the general design of the system…

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Dr. C. Wilsher	1939	1941	4.3	This new "recommendation" will require lot more work documenting this. There is no definition of what "recommendation" means. Suggest removing this.	When designing a system, it should be ensured that, where relevant, computerised systems are suitable for use by the intended user population
PPD	1939	1941	III. Annex I 4. DATA GOVERNANCE – INVESTIGATOR AND SPONSOR 4.3 Computerised Systems	This does not sound like a practical recommendation. This requires further explanation with regards to how this could possibly be achieved. Does this mean at a study specific level?	Recommendation to remove this text. While understanding the importance of the patient perspective, the relevance of the text is unclear in this context (e.g., for the Sponsor). How would this be practically applied? 'Where relevant' is a broad term for interpretation. Suggest removing it as it is already stated elsewhere in the need/fit for purpose for the trial.
Quotient Sciences	1939	1941	4.3	Involvement of healthy volunteers in design of participant-facing computerised systems will not usually be necessary.	Please edit as follows: It is recommended that representatives of intended patient participant populations and healthcare professionals are involved in the design of the system, where relevant, to ensure that computerised systems are suitable for use by the intended user population.
Society of Quality Assurance (SQA)	1939	1940	4.3	It will be a challenging ask on industry to ensure that intended participant populations are involved in design of the systems, especially with so many COTS systems being utilized in the clinical trial space. Involvement of healthcare professionals during the user acceptance testing stage plays a role in ensuring that the systems are suitable for the intended user. It is recommended to add wording around healthcare professional testing, as well as allowing end user feedback, obtained as a result of using the system, to be used to make appropriate updates.	"It is suggested that representatives of intended healthcare professionals are consulted in the design and/or testing of the system, where relevant, to ensure that computerised systems are suitable for use by the intended user population. It is suggested that feedback from participants and healthcare professionals who actively use the system be leveraged to update the system, as appropriate."
AFI	1947	1948	4.3.2	..trained in their use.	..trained in their use. Training should be documented.
Association for Clinical Data Management (ACDM)	1949	1949	4.4	General comment to this section: For future reference, the FDA draft DCT and DHT guidance put security responsibility directly on sponsor, but also seem to focus more on ensuring participants are aware of risk. Also FDA references their cybersecurity policy provided by the CDRH Digital Health Centre of Excellence at https://www.fda.gov/medical-devices/digital-health-centre-excellence/cybersecurity	No Action
AFI	1953	1958	4.4.2	…should be considered.	…should be considered and properly documented.
Association for Clinical Data Management (ACDM)	1953	1958	4.4.2	Clarification is needed as to the responsible party. Is this the sponsor who is responsible for all delegated activities? Does this include the investigator for site specific systems?	Please clarify what roles could be the responsible party.
Charles River Labs	1953	1960	4.4.2	the use of the phrase "responsible party" should be clarified. There is some ambiguity as to who the responsible party is, as it could change depending on the context (investigator vs vendor vs developer).	Update text as you see fit.

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Medicines for Europe	1953	1955	4.4.2	Further clarification on the security breaches would be necessary through defining the term in the glossary section.	
Association for Clinical Data Management (ACDM)	1960	1960	4.4.3	Clarification is needed as to the responsible party. Is this the sponsor who is responsible for all delegated activities? Does this include the investigator for site specific systems?	Please clarify what roles could be the responsible party.
EFPIA Consolidated Comments	1962	1963	III.4.4.4	Procedures should also address business continuity. Suggest to include some in training to clarify.	Procedures should cover the following: system security measures, data backup, and disaster recovery and business continuity.
AFI	1964	1965	4.5.1	Validation of computerized systems", can we further clarify who the responsible party is in Section 4.5? Also does the agency has any plans to issue a more detailed guidance about validation of computerized systems as this can help sponsors better understand the requirements for such a validation?	
Association for Clinical Data Management (ACDM)	1964	1964	4.5	General comment to this section: For future reference the FDA draft guidance on DHT seems to be taking a very risk based approach to validation. Example is line 823 "fit-for-purpose: In the context of use of a DHT in a clinical investigation, a conclusion that the level of validation associated with a DHT is sufficient to support its context of use."	No Action
Fergus Sweeney	1964	2006	4.5	This may be achieveable for most sponsor systems though even then for those purchased and plugged in as such an on site testing may be possible but all the demands here may not be reasonable. For investigator sites they often work using systems that have been at some point purchased or installed by their institution or even the broader healthcare framework. They are bought, and installed with configuration as needed within the context of the healthcare infrastructure and are used to record data for healthcare purposes and are judged fit for that purpose. All of these requirements for documentation of validation, lifecycle development etc of healthcare systems at investigator sites cannot simply be imposed on or demanded as documentation from investigators.institutions. Teh developpers adn IT personnel in hospitals will have done much of this but that is different fro expecting the investigator to produce all this documentation. In many cases it may lead to sites simply giving up on research due to excess demands. Consider all this detail and its imposition on sites and healthcare very carefully. GCP is there to enable research not to bind it up in detail which may have been addressed in the process but is not readily available for investigators or their institutions, to produce to sponsor monitors and auditors or to inspectors.	reconsider the need to have one set of requirements for sponsor and investigator site, adn instead consider a redused set of key points for investigator site/healthcare systems with less prescriptive detail
AFI	1965	1970	4.5.1	The responsible party is responsible for the validation status of the system throughout its life cycle. The approach to validation of computerised systems should be based on a risk assessment that considers the intended use of the system; the purpose and importance of the data/record that is collected/generated, maintained and retained in the system; and the potential of the system to affect the well-being, rights and safety of trial participants and the reliability of trial results	The validation should be documented and specified if periodicity check should be applied
Kotagiri Srinivasa Rao	1975	1976	4.5.3	Systems should be appropriately validated prior to use with adequate change control procedures implemented.	The validity period of the validation aldo to be clearly mentioend. If any major changes that may effect out thenonly validation to be done for existing system.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Fergus Sweeney	1991	1994	4.5.7	Who is to keep this - the investigator? This as an example of just how complicated this is for investigator sites. It is dramatic over reach by GCP	completely reconsider what is applied to investigator sites and restrict to an absolute minimum
German Pharmaceutical Industry Association (BPI)	1991	1994	4.5.7.	Further guidance is needed for the computerized systems developed by other parties with respect to common office programs like MS office.	
Charles River Labs	2004	2005	4.5.10	In section 4.5.10 it is not clear what is meant by lines 2004-2005. Is the meaning of "implemented" conveying that trial-specific systems cannot even be installed/validated until clinical trial approvals have been received?	n/a
Society of Quality Assurance (SQA)	2004	2006	4.5.10	There needs to be consideration given for emergency trial specific configuration changes that are sometimes required to avoid direct impact to participant safety. In such cases waiting for necessary approvals from IRBs or Health Agencies may not be possible as it could put the participant at risk. In addition, for companies that use global systems across multiple regions, it is sometimes not possible to wait for approval from all health agencies to implement changes within a global system. It is recommended to account for such situations.	"The trial specific systems (including updates resulting from protocol amendments) should only be implemented to enable the conduct of the trial by the investigator after all necessary approvals for the clinical trial have been received. In cases where trial specific configurations are made as a result of protocol amendments that may have direct impact to participant safety, these configurations may be released to site users on an exception basis without waiting for necessary approvals provided appropriate justification is documented".
Society for Clinical Research Sites	2007	2009	4.6		We agree that contingency procedures should be in place, but the draft is unclear on who is responsible to develop and/or assure those contingency procedures. We believe this should be clarified in that if there is a service provider supplying a solution, it should be the service provider's obligation (with their contracting entity being the one ultimately accountable) to provide the alternate strategy should the technology fail (e.g. in the case of a service provider supplying an electronic consent platform, they (or their contracting entity) should provide paper forms, a website, extra tablets, etc.). This section should be clarified such that the sponsor bears the ultimate responsibility for assuring the contingencies for the technology they provide (directly or through service providers) and the investigator bears the ultimate responsibility for the contingencies of the technology that they provide.
eClinical Forum	2011	2014	III 4.7.1	This section states; …. there should be periodic review of these cumulative issues to identify those 2014 that are repeated and/or systemic. It does not mention what should be done about repeated or systemic issues.	Revise this section to state what is to be done with these issues.
EFPIA Consolidated Comments	2011	2014	III.4.7.1	This section addresses review of cumulative issues within systems however it is also possible that changes within systems that could drift from original intended use. As such, it is recommended that the principle of computerized system periodic review be included, in alignment with EU GMP Annex 11 requirements. Hpwever the additional text would fit best under 4.5.7	Computer systems should be reviewed periodically to ensure that they remain in a validated state and that cumulative changes and issues (e.g. raised by users) observed for the systems do not impact the original intended use.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Ludger Wienbrede	2011	2014		"Where appropriate, there should be mechanisms (e.g., help desk support) in place to document, evaluate and manage issues with the computerised systems (e.g., raised by users), and there should be periodic review of these cumulative issues to identify those that are repeated and/or systemic. " This is usually not under the control of sponsors and investigators. If ICH GCP is intended to implement such requirements, it should explicitly introduce software developers as a party beside sponsors, investigtors, ethics committees. This applies also to other sections of ICH GCP that addresses software development and maintenance.	
Society of Quality Assurance (SQA)	2011	2014	4.7.1	This part only talks about reviewing cumulative issues within systems but often times it is the changes within systems that could drift from original intended use. It is recommended to introduce the principle of computerized system periodic review in alignment with Annex 11 requirements. This principle could be added as line item under this section.	"Where appropriate, there should be mechanisms in place to document, evaluate and manage issues with the computerized systems (e.g. raised by users). Computer Systems should be reviewed periodically to ensure they remain in a validated state, and cumulative changes and issues (e.g. raised by users) observed for the systems do not impact the original intended use".
DARQA	2013	2013	4.7.1	The term "periodic review" is used in a different way than by other industry guidelines such as GAMP and the EMA Guideline on Computerised Systems in Clinical Trials, which may cause confusion	"Periodic review" to be changed into "regularly reviewed".
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	2019	2022	III 4.8.1	It is unclear whether the second sentence refers only to the aforementioned access control or is generally meant. This would be the advice for example to use a two-factor authorization only if a high level of security is really needed. If the sentence is meant more generally it is of little help without practical examples as the given requirements regarding computerized system inevitably will impact user-friendliness.	Please phrase the paragraph unambiguously: "The security measures regarding access control should be selected..." or "Generally, security measures should be selected...". If it is a general recommendation, please add an example.
Fergus Sweeney	2021	2022	4.8.1	The strive for user friendliness is laudable but is it necessary in GCP? If a less friendly system is used will that be declared non-compliant?	
Association for Clinical Data Management (ACDM)	2025	2026	4.8.2	Access rights should be revoked "when or as soon as " they are no longer needed	Please clarify
EFPIA Consolidated Comments	2025	2026	III.4.8.2	It is important to highlight the need for periodic review of access rights to enable execution of this requirement. In large clinical trial settings where user roles are likely to change from one trial to another, access rights typically do not get revoked but instead need to be altered depending upon the user role in the trial. Therefore, the suggested wording will give the required flexibility to be able to meet the practical expectation around fit for purpose trial specific system access.	Access rights should be revoked or altered on a timely basis when they are no longer needed.
EFPIA Consolidated Comments	2025	2026	4.8.2	We recommend including a statement indicating the investigator or delegated staff member should notify the sponsor when access should be revoked for an individual no longer supporting the clinical trial. This would best fit under 2.3.3.	"The investigator or delegated staff member should notify the sponsor when an individual is no longer supporting the clinical trial in order for access to systems to be revoked."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Society of Quality Assurance (SQA)	2025	2026	4.8.2	It is important to highlight the need for periodic review of access rights to enable execution of this requirement. In large clinical trial settings where user roles are likely to change from one trial to another, access rights typically do not get revoked but rather need to be altered depending upon the user role in the trial. Therefore, the suggested wording will give the required flexibility to be able to meet the practical expectation around fit for purpose trial specific system access.	"Access rights should be reviewed periodically and rights should be altered for role changes and revoked when no longer needed."
EFPIA Consolidated Comments	2030	2336	GLOSSARY additional terms to include	Fit for purpose is also not clear. Clinical Trial Database Trial Master file Source data review and verfication would benefit from clarity in a glossary term	Fit for purpose: The suitability of the system or process to provide an appropriate level of reliability of trial results. Clincal Trial Database: The consolidated collection of the clinical trial data required by the protocol and applied for statistical analysis by the sponsor and used to produce the data analysis sets which will be part of the Clinical Trial Report. Trial Master file: The identified information repositories where essential records are maintained and retained, by the sponsor and the investigator. The TMF is usually composed of a sponsor TMF, held by the sponsor organisation, and an investigator TMF held by the investigator/institution. The investigator TMF is often referred to as the investigator site file (ISF) or regulatory binder. See also essential records. Source Data Verification: The process by which data within the Case Report Form (CRF) or other sponsor data acquisition systems are compared to the original source records (e.g., patient medical records). This process assures accurate transcription of data by investigational site staff and can happen on-site or remotely as appropriate. Source Data Review: The review of source records to check their quality, to confirm appropriate investigator involvement and delegation, to check compliance with the protocol and GCP, and to help assess data integrity and that the critical processes are adequate. This process can happen on-site or remotely as appropriate.
EUCROF	2030	2336	GLOSSARY	It would be very helpful to have the terms numbered in order to be able to reference in an easier way. The terms in the former Glossary were numbered. See also General Comment.	
Fergus Sweeney	2030	2030		It is important to give the glossary a section number to maintain a consistent structure across the document. Or give it a separate title page of its own if it is to be valid across the principles and annexes	Give Glossary section 5 if this is its location. Or give it a title page of its own
Good Clinical Trials Collaborative, on behalf of supporting organisations	2030	2336	GLOSSARY	Clarify if the Glossary applies to the whole document (and can be updated in future when new Annexes are added) or just to Annex 1.	
GQMA	2030	2030	Glossary	The guideline uses the words investigator-initiated trial and sponsor-investigator in section A.1.1, but only sponsor-investigator is defined in the Glossary.	Add a new term to the glossary and a definition for "investigator-initiated trial" and refer to sponsor-investigator in Glossary line 2307.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
GQMA	2030	2030	Glossary	If the suggestion is followed to implement some wording on auxiliary medicinal products in this E6 revision, it would be good to add a respective definition to the glossary.	Add a new term to the glossary and define it for "auxiliary medicinal products", in case respective wording is introduced into the guideline
Ipsen	2030		Glossary	Missing definitions: Subcontracted Service Provider or Third Party, security breach, Prescreening, important protocol deviation, incident	
Quotient Sciences	2030	2336	Glossary	Please add definitions for *important protocol deviation* and *serious breach* .	Please add definitions of *important protocol deviation* and *serious breach* .
SHIONOGI	2030	2336	Glossary	Missing definitiation on what is understood as 'enrolment in a clinical trial'. This is an industry and CRO wide discussion topic. Is a subjected enrolled in a clinical trial as of: a) signing of the informed consent (regardless the design of the clinical trial - e.g. if there is a wash-out period/screening phase during which subjects may be drop-out because of exclusion criteria) or b) randomization (in case of a randomized clinical trial) or assigning the investigational product (in case of an open-label study) or c) first dosing	Suggest to add provide a definition of what 'participant enrolment in a clinical trial' means with all the terms and options listed in cell F23
EUCROF	2032	2032	GLOSSARY	Adverse Event (AE): Any unfavourable medical occurrence in a trial participant. What is the rationale of leaving out "administered a medicinal product" like we have in other AE definitions? I.e.: "Any unfavourable medical occurrence in a trial participant administered a medicinal product."	
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	2032	2033	Glossary	In this changed definition the administration of a pharmaceutical product is not anymore part of the Adverse Event definition. This differs from the Adverse Event definition in the European legislation (EU CTR). How should we deal with this discrepancy in the EU?	
Mithra Pharmaceuticlas SA PV	2032	2033	Glossary	no longer aligned with GVP definition where it says "Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. So is this a new definition to encompass pre IMP events? And is there no definiton for non-treatment emergent adverse events?	
Good Clinical Trials Collaborative, on behalf of supporting organisations	2034	2068	GLOSSARY	The following edits to glossary definitions will aid rational and appropriate interpretation.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Good Clinical Trials Collaborative, on behalf of supporting organisations	2034	2045	GLOSSARY - Adverse Drug Reaction	Add (before the two bullet points) a simple definition that is easy to remember, explain and operationalise: "An Adverse Event that is believed with a reasonable probability to be caused by the study treatment"	Change as described.
EFPIA Consolidated Comments	2035	2044	Glossary ADR	The Draft Guideline states: Line 2035-2037 : "in the pre-approval clinical experience … unfavourable and unintended…" Line 2045-2046: "for marketed medicinal products …noxious and unintended" The Draft Guideline references ICH E2A. Is it intentional to utilize different terminology for pre-approval / marketed settings, *unfavourable* / *noxious*, respectively? E2A states "noxious and unintended" (Section II.A.2.). While it is understood that E2A was adopted in 1994 and may be outdated, consistent terminology would be preferable wherever possible and unless there is reason for different terminology.	Proposed change: If there is not a reason for use of different terminology suggest aligning with E2A. Line 2035-2037 : "in the pre-approval clinical experience … unfavourable noxious and unintended…"
Quotient Sciences	2035	2043	Glossary, Adverse Drug Reaction (ADR)	1. Typographic error (" symptoms " should read " symptom "). 2.The ADR definition is likely to be reproduced in protocols. So please remove the last 2 sentences of the first bullet from the definition and add them as a footnote or elsewhere in the guideline.	Please edit as follows: * in the pre-approval clinical experience with a new investigational product or its new usages (particularly as the therapeutic dose(s) may not be established): unfavourable and unintended responses, such as a sign (e.g., laboratory results), symptoms or disease related to any dose of a medicinal product where a causal relationship between a medicinal product and an adverse event is a reasonable possibility. The level of certainty about the relatedness of the adverse drug reaction to an investigational product will vary. If the ADR is suspected to be medicinal product-related with a high level of certainty, it should be included in the reference safety information (RSI) and/or the Investigator's Brochure (IB). * for marketed medicinal products: a response to a drug that is noxious and unintended and that occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of diseases or for modification of physiological function. (See ICH E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Note that the level of certainty about the relatedness of the adverse drug reaction to an investigational product will vary. If the ADR is suspected to be medicinal product-related with a high level of certainty, it should be included in the reference safety information (RSI) and/or the Investigator's Brochure (IB).
EUCROF	2041	2043	GLOSSARY	"If the ADR is suspected to be medicinal product-related with a high level of certainty, it should be included in the reference safety information (RSI) and/or the Investigator's Brochure (IB)." The text is not conclusive as the IB represents the RSI.	If the ADR is suspected to be medicinal product-related with a high level of certainty, it should be included in the reference safety information (RSI), e.g., the Investigator's Brochure (IB) or other product information defined as RSI.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Good Clinical Trials Collaborative, on behalf of supporting organisations	2041	2043	GLOSSARY - Adverse Drug Reaction	Delete "If the ADR is suspected to be medicinal product-related with a high level of certainty, it should be included in the reference safety information (RSI) and/or the Investigator's Brochure (IB)" since this is not relevant to the definition.	Change as described.
Ludger Wienbrede	2042	2043		"… it should be included in the reference safety information (RSI) and/or the Investigator's Brochure (IB)". According to the definition of lines 2277 - 2279, the RSI might be a part of the IB. Here in line 2042 is appears to be that the RSI could be the IB or something separate. In ICH E2F, the RSI was a whole document, either the IB or the "label" (e.g. the summary of product characteristics). It is appreciated that the concept of RSI has developed and meant something different in 2010 than it might mean in 2023. However, within one document as ICH GCP the term should be used for the same concept. Ideally this concept is as described in lines 2277-2279, with some more precision: it is a list contained in the IB or the "label". See and adapt also lines 2061 - 2063.	
EFPIA Consolidated Comments	2050	2056	Glossary, SAE definition	The definition of SAE is missing the Important Medical event criteria	Other medically important event
German Pharmaceutical Industry Association (BPI)	2050	2056	Glossary SAE	ICH E2A classifies important medical events also as serious.	A reference to ICH E2A is included, but the addition of medical important events in the SAE definition would be helpful here.
Mary Stapleton, Pharmacovigilance Consultant, Ireland	2050	2056	Glossary	The Serious Adverse Event (SAE) definition. It is commonly accepted that there are six criteria that define an adverse event as serious. The five listed here and the adverse events that are considered 'medically significant' or 'medically important'. The additional criterion was not in the previous versions of ICH E6 but the reference to ICH E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (where the concept is explained and examples are given) was separate from the last criterion listed and more striking. It is important that it is known that certain adverse events e.g. disease or endpoint defining laboratory results can be subject to the same sponsor reporting timeline as the other SAE criteria.	At a minimum, the ICH E2A reference should be more stand-alone but it would also be useful to mention 'medically important' as a separate SAE criterion.
Quotient Sciences	2050	2056	Glossary, Serious Adverse Event (SAE)	Please can the opportunity be taken to align ICH E6 and ICH E2A, and include in E6 the guidance from E2A on interpretation of 'life-threatening' and important medical events that may jeopardise the participant or require intervention to prevent a serious outcome.	Please include additional information from ICH E2A.
Society for Clinical Research Sites	2050	2056	Glossary		We believe there is a missing "or" in the list of criteria that should be added.
Good Clinical Trials Collaborative, on behalf of supporting organisations	2057	2068	GLOSSARY - Suspected Unexpected Serious Adverse Reaction (SUSAR)	Amend "Suspected" and its definition to "Suspected reaction: There is a reasonable ~~possibility~~ probability that the drug caused the adverse ~~drug reaction~~ event."	Change as described.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Quotient Sciences	2057	2058	Glossary, Suspected Unexpected Serious Adverse Reaction (SUSAR)	Could SUSARs please be referred to as serious unexpected suspected adverse reactions? It would make it clearer that a SUSAR is an event that is *suspected* to be a *reaction* rather than an event that is *suspected* to be *unexpected* .	Please edit as follows: Suspected Serious Unexpected Serious Suspected Adverse Reaction (SUSAR): an adverse reaction that meets three criteria: serious suspected, unexpected and serious suspected to be related to the investigational product. Please also reverse the order of the 3 bullets that follow.
Quotient Sciences	2062	2066	Glossary, Suspected Unexpected Serious Adverse Reaction (SUSAR)	It would be helpful to clarify that the RSI is based on prior clinical experience. There is potential for confusion, as an adverse event that might be *expected* to occur, based on the pharmacological activity of the investigational product, is classed as *unexpected* if it has not previously been reported. For clarity, the reference to the glossary term should be placed in parentheses. The final sentence of the definition would be better placed in the RSI glossary entry.	Please edit as follows: * Unexpected: An adverse reaction, the nature or severity of which is not consistent with prior clinical experience as documented in the applicable product information (e.g., the RSI, [see glossary term] contained within the Investigator's Brochure or alternative documents according to applicable regulatory requirements. Refer to ICH E2F Development Safety Update Report for more information about RSI.
EFPIA Consolidated Comments	2063	2066	Glossary SUSAR	Edit: parenthesis are used but the closing parenthesis is missing ')' which impacts the reading of the rest of the section	
EUCROF	2063	2063	GLOSSARY	...with the applicable product information (e.g., the RSI, see glossary term contained … Bracket is missing	with the applicable product information (e.g., the RSI, see glossary term**)** contained
Dr. C. Wilsher	2070	2074	Glossary	Why has "signed & dated" been removed? By signing & dating, parties show their intent and when that agreement was made.	A document or set of documents describing the details of any arrangements on delegation or transfer, distribution and/or sharing of activities and, if appropriate, on financial matters between two or more parties. This could be in the form of a signed and dated contract. The protocol may serve as the basis of an agreement
Society for Clinical Research Sites	2070	2074	Glossary		The term "Agreement" recognizes that in lieu of a single contract, there could be a set of documents that constitute an "agreement." We encourage that this definition reflects that when there are multiple documents that 1) there are internal consistencies between those documents; 2) that there is a mechanism to address what document reigns supreme in the event of a conflict. For example, the promise made by a sponsor in an informed consent document should reign supreme over what they state in their reimbursement policies. Record retention is a regulatory matter, not a scientific matter, thus the agreement should overrule the protocol. It is not uncommon to have statement along the lines of "in the event of a conflict, the protocol shall govern matters related to science, the informed consent shall govern in matters related to promises made trial participants and the clinical trial agreement shall govern all other matters."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Ludger Wienbrede	2072	2073		"The protocol may serve as the basis of an agreement." What does that practically mean except for: The agreement has to be compliant with the contract? If it means more, this should be explained. If it means just compliance, that should be stated explicitly. In practice, agreements only refer to the protocol, but only the budget section might reflect the visits described in the protocol. Most of the agreement concerns responsibilities, financing, legal requirements, liability, data protection, protection of intellectual property and not topics of the study protocol. Therefore, the statement "The protocol may serve as the basis of an agreement." makes little sense.	
EFPIA Consolidated Comments	2076	2077	Glossary Applicable regulatory requirements	applicable regulatory requirements regulations that directly address the conduct of clinical trials, but ALSO other inherent regulations as for example privacy regulations. If the glossary is not changed then at least in some sections privacy regulations should be mentioned explicitly. Therefore, suggest to slightly expand this definition	Any law(s) and regulation(s) which may have an impact on the conduct of interventional clinical trials of investigational products, for example data privacy, artificial intelligence, healthcare provisions, good manufacturing practice.
EUCROF	2076	2077	GLOSSARY	"Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products." It is not only about laws and regulations addressing clinical trials, there are relevant laws with a wider scope but applicable also to clinical trials, for example, laws and regulations on data protection.	
Fergus Sweeney	2078	2080		Does the concept of Assent also apply to adults with impaired understanding where a legally acceptable representative is consenting?	discuss if assent should also apply to adults with impaired understanding where a legally acceptable representative is consenting
Mandy Jackson National Clinical Trials Office Quality Working Group Ireland	2078	2080	Glossary	Definiton of assent refers to 'Affirmative agreement of a minor to participate in clinical trial'	Should defintion of assent also include reference to adults who cannot provide legally valid consent.
Quotient Sciences	2078	2080	Glossary, Assent	Please add that assent is also appropriate for adults with diminished capacity, e.g., learning difficulties.	Please edit as follows: Affirmative agreement of a minor or adult with diminished capacity (e.g., adult with learning difficuties) to participate
EFPIA Consolidated Comments	2089	2089	Glossary Audit Certificate	States an audit certificate as "*A declaration of confirmation by the auditor that an audit has taken place*". Preparation of the audit certificate is not necessarily done by an auditor.	Recommend removing "" . A declaration of confirmation by the auditor that an audit has taken place.
Fergus Sweeney	2092	2097		Audit trail. Refer to this as ALCOA metadata. It would also be better to start by simply explainig audit trail and then explaining that it consists of metadata, and the actual data point also.	use the term ALCOA metadata or equivalent for the metadata referred to here. It would also be better to start by simply explainig audit trail and then explaining that it consists of metadata, and the actual data point also.
Ludger Wienbrede	2092		xxx	Metadata records that allow reconstruction of the course of events by capturing details on actions (manual or automated) performed relating to information and data collection and, where applicable, to activities in computerised systems. The audit trail should show activities, initial entry, and changes to data fields or records, by whom, when and, where applicable, why. In computerised systems, the audit trail should be secure, computer generated and timestamped.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUCROF	2093	2093	GLOSSARY	"Metadata records ..." The history is contained in metadata however tha current values are contained in data. The new entries are also part of the audit trail (to reconstruct the course of events). Shouldn't the definition of audit trail refer to data and metadata?	"Data and metadata records …."
Society of Quality Assurance (SQA)	2096	2096	Glossary	In the 'Audit Trail' definition, it is recommended to add clarity around the when the reason for change (the "why") is applicable. It is recommended that the applicability of the 'why' be determined via a risk-based evaluation of the scenario and whether the reason for change is implicit as part of the process. In most cases, this could pose a challenge and even nuisance to introduce the reason for change field for every data change especially when it could be quite implicit why data is being changed.	"....and where applicable, why, based upon risk based evaluation if reason for change is not implicit."
Quotient Sciences	2099	2102	Glossary, Blinding/Masking	Please clarify definition of double blind.	Please edit as follows: A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the participant(s) being unaware, and double-blinding usually refers to the participant(s), and investigator(s) and/or other trial staff, as appropriate, being unaware of the treatment assignment(s).
EFPIA Consolidated Comments	2100	2102	Glossary Blinding	Sponsor staff is omitted in the double-blinding for unknown reason. Please add.	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the participant(s) being unaware, and double-blinding usually refers to the participant(s), investigator(s) or other trial staff, including sponsor staff working on the trial, as appropriate, being unaware of the treatment assignment(s).
EUCROF	2100	2100	GLOSSARY	"Single-blinding usually refers to the participant(s) being unaware, …" There are studies where it is exactly the other way around, i.e. the investigator remains blinded but the participant is not blinded. The text should be kept more neutral.	"Single-blinding usually refers to either the participant(s) being unaware, or the investigator being unaware.
Ludger Wienbrede	2100	2102		"Single-blinding usually refers to the participant(s) being unaware, and double-blinding usually refers to the participant(s), investigator(s) or other trial staff, as appropriate, being unaware of the treatment assignment(s)." This should be deleted and replaced by a statement like: Note: There are no unequivocal concepts for single-blinded, double-blinded etc.. Therefore, each protocol should define who is blinded in what way. Rationale: See articles like: M Thorlund Haahr and A Hróbjartsson: Who is blinded in randomized clinical trials? A study of 200 trials and a survey of authors. Clin Trials 2006;3(4):360-5. P J Devereaux et al.: Physician interpretations and textbook definitions of blinding terminology in randomized controlled trials. JAMA 2001 Apr 18;285(15):2000-3. T A Lang and D F Stroup: Who knew? The misleading specificity of "double-blind" and what to do about it. Trials 2020 Aug 5;21(1):697.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Ludger Wienbrede	2107	2110		"Certified copy: A copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information as the original, including relevant metadata, where applicable." This definition has several shortcomings: 1. What is an original? E.g. if an ethics committee sends a fax or if an online portal produces an approval letter or if the an online portal produces no approval letter but you just try to print out the screenshot: What is the original? Is the first fax received by the applicant the original (because the applicant has no access to the paper original in the ethics committee's office)? Is the letter produced by the online portal the original - but can there be more than one original and is the letter fabricated by the portal actually a correct original reflecting some information that is hidden somewhere inside the portal? 2. In the cases described before: Who might actually be able to certify the process from the paper original to the fax, from the online portal to the fabricated letter? I reality, you will not easily find anyone who could be made responsible for that or do that. 3. It is harder to define what a copy is than this definition conveys. See for example: Amrei Bahr: Was ist eine Kopie? (Meiner, 2022). 4. The part "including relevant metadata, where applicable" is problematic, too: Who defines what metadata are relevant? What does "where applicable" mean: If there are any metadata? If you print an electronic file on paper, e.g. for the still commonplace paper investigator site file, you might loose some metadata. Is this acceptable? ICH GCP should in a annex define which metadata are relevant for which kind of document. Otherwise, the community of auditors and inspectors will invent rules for this or leave it open to their random decision during the next audit or inspection. This would result in filing of huge und useless amount of metadata, because you can never be sure which of the are regarded as relevant. --- Effectively, because a definition of a copy is difficult, either define it better or omit it.	
Fergus Sweeney	2109	2109		The text states "(i.e. by a dated…". i.e. implies these are the only approaches, it is possible there are others?	Should this be so restrictive?
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	2111	2116	Glossary	Please take into account, that this definition of clinical trial differs from the definition of clinical trial according to the EU CTR. According to EU CTR the definition in ICH E6 means a clinical study. How should we deal with this discrepancy in the EU?	
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	2117	2121	Glossary	It should be added that CSR according to ICH E3 is only applicable for trials intended to use for marketing authorisation.	
EUCROF	2122	2124	GLOSSARY	"Comparator: An investigational or authorised medicinal product (i.e., active control), placebo or standard of care used as a reference in a clinical trial." Sometimes "no treatment/intervention" is used as a comparator. See also Declaration of Helsinki No. 33.	Comparator: An investigational or authorised medicinal product (i.e., active control), placebo, standard of care or no treatment/intervention used as a reference in a clinical trial.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	2122	2124	Glossary	A comparator product may also be the product used as absorption standard in a bioequivalence trial (as defined in ICH M13. Therefore this definition should be broad enough to include this concept as well.	An investigational or authorised medicinal product (i.e. for example, an active control or a product used to compare against the test product in a bioequivalece trial), placebo or standard of care used as a reference in a clinical trial.
Good Clinical Trials Collaborative, on behalf of supporting organisations	2126	2126	GLOSSARY - Compliance (in relation to trials)	Amend definition of Compliance as follows: "Adherence to the protocol and other trial-related requirements, the Principles of GCP, requirement and the applicable regulatory requirements."	
Ludger Wienbrede	2131	2133		"An investigator assigned the responsibility for the coordination of investigators at different investigator sites participating in a multicentre trial (if appropriate)." There are some problems with the concept of the coordinating investigator: 1. There might be more than one. In some countries there has to be a national coordinating investigator. If a trial is conducted in more than one of such countries, there is more than one coordinating investigator. These coordinating investigators have no coordinating role in study other countries. This is not actually a problem, it should just be noted. 2. It is not clear what the coordinating investigator actually coordinates. In most settings, there is no actual coodination of anything. It might be that the central ethics committee is determined by the seat of the coordinating investigator. It might be that the sponsor develops the protocol with the coordinating investigator, i might be that the national legislation requires one - often without defining any tasks. ICH guidelines and EU legislation attribute the function of signing the report to this person. All of this is just fine, but little of this is coordination. Perhaps ICH GCP should introduce another name. 3. If the only function of the coordinating investigator or coordinating investigators is to sign the study report, ICH GCP might call this investigator "investigator responsible for the study report". This is a cumbersome name, but a honest and transparent one.	
EUCROF	2133	2133	GLOSSARY	"if appropriate" is not adding value here and should be deleted	
EFPIA Consolidated Comments	2143	2151	Glossary DAT	An electronic transfer of data cannot be a data originator - in this case the data originator would be a machine	The data originator may be a human (e.g., the participant or trial staff) or a machine (e.g., wearables, and sensors)., including in the case of or an electronic transfer of data from one system to another [e.g., such as an extraction of data from an electronic health record or laboratory system]).
SHIONOGI	2143	2151	DAT	Ensure consistency in terms used: PROs and COAs, whereas the rest of the guidline refers to electronic versions of these systems - ePRO and eCOA	recommend to replace Pros and COAs with ePROs and eCOAs
EUCROF	2146	2148	GLOSSARY	"The data originator may be a human (e.g., the participant or trial staff), a machine (e.g., wearables and sensors) or an electronic transfer of data from one system to another (e.g., extraction of data from an electronic health record or laboratory system)." The logic in the sentence is not conclusive as the electronic data transfer is not a data originator, but the data in the former system that have been transerred to a new system.	"The data originator may be a human (e.g., the participant or trial staff), a machine (e.g., wearables and sensors) or an electronic system of which data gets transferred to another system (e.g., extraction of data from an electronic health record or laboratory system).

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
FVR-Finnish Vaccine Research	2146	2148	Glossary (DAT)	In the Introduction, innovative trial designs and technologies and stakeholder/health care provider's perspectives are welcomed. The use of health registers could be mentioned, e.g., here.	The data originator may be a human(e.g., the participant or trial staff), a machine (e.g., wearables and sensors) or an electronic transfer of data from one system to another (e.g., extraction of data from an electronic health record, a health register, or laboratory system).
Fergus Sweeney	2150	2150		This is about PRO and COA applications not the reports	reword as "…(PRO applications)….(COA applications).."
EFPIA Consolidated Comments	2152	2158	Glossary Direct Access	It is unclear whether direct access covers "over the shoulder" access or if direct access implies that access must be granted to enable full review of specific records without over the shoulder limitations (e.g., over the shoulder access should not hinder the activities of the monitor/auditor/inspector that are pertinent to the trial). EFPIA recommends clarifying the definition of direct access to confirm if 'over the shoulder' access is included in this definition, or if direct access must be access granted to enable full review of specified records without over the shoulder limitations.	maybe performed in person or remotely, or where appropriate via over the shoulder of a user.
Society for Clinical Research Sites	2152	2158	Glossary		We have concerns over the use of the term "direct access" (both here as well as in Annex I Items 2.8.11(n), 2.12.12, 3.6.3(d), 3.11.4.1(c), 3.16.4(a), 3.16.4(b), the Glossary and Appendix B.11). The phrase "direct access" (as opposed to "access") is interpretable as supporting an activity that is generally prohibited with established healthcare privacy/security practices and regulations across the globe (i.e. providing login IDs directly into to electronic health records). We request the deletion of the word "direct" (or change the phrase to "access to view") here and in the other sections referenced to avoid this confusion and that the guidance can recognize the variety of ways source document verification has been accomplished over the past decade without "direct" access (but with "access to view"). This would also bring these sections to be consistent with Annex I Item 3.11.4's requirement that monitors "adhere to data protection and confidentiality requirements in accordance with applicable regulatory requirements, institution policy and established data security standards." Alternatively, if the term "direct access" must be used, then the same issue can be accomplished by changing the definition herein to delineate that the term does not require login access when alternative methods of source document verification are available (e.g. via certified copies or "over-the-shoulder" viewing). However, we believe that this is not as strong a solution to the problem as dropping "direct" altogether or changing it to "access to view".

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Quotient Sciences	2153	2158	Glossary, Direct Access	The wording could be improved.	Please edit as follows: Permission to examine, analyse and verify, in person or remotely, records that are important to the evaluation of a clinical trial and may be performed in person or remotely. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of participants' identities and their data and of sponsor's proprietary information.
Good Clinical Trials Collaborative, on behalf of supporting organisations	2157	2157	GLOSSARY - Direct Access	Insertion *"maintain the confidentiality of participants' identities and their data, the reliability of the study results (including avoiding premature unblinding), and sponsor's proprietary information."* Since it is important that the efforts of regulatory authorities, monitors and auditors that are intended to evaluate trial quality do not negatively impact quality.	
Dr. C. Wilsher	2160	2165	Glossary	The notion of the ability to "reconstruct" the conduct of the trial is missing and was a powerful way of explaining to people why essential records were necessary.	Essential records are the documents and data (and relevant metadata), in any format, associated with a clinical trial that facilitate the ongoing management of the trial and collectively allow the reconstruction of events and evaluation of the methods used, the factors affecting a trial and the actions taken during the trial conduct to determine the reliability of the trial results produced and the verification that the trial was conducted in accordance with GCP and applicable regulatory requirements (see 2164 Appendix C. Essential Records for the Conduct of a Clinical Trial).
EUCROF	2163	2164	GLOSSARY	"… trial conduct to determine the reliability of the trial results produced and the verification that the trial was conducted in accordance with GCP and applicable regulatory requirements" There is some redundancy in this sentence as "reliability of trials results" is already part of GCP. Delete "the reliability of the trial results produced"	"… trial conduct to determine that the trial was conducted in accordance with GCP and applicable regulatory requirements"
Fergus Sweeney	2164	2164		conduct of the trial in accordance with the protocol is the core of what essential records should show and protocol is not mentioned	reword to "….in accordance with the protocol, GCP.."
Dr. C. Wilsher	2166	2169	Glossary	"Integrity & Confidentiality" have been taken out. Proposes re-inserting them so make it crystal clear to anyone who only goes to the glossary for information .	A standard for the planning, initiating, performing, recording, oversight, evaluation, analysis and reporting of clinical trials that provides assurance that the data and reported results are reliable and that the rights, integrity, confidentiality, safety and well-being of trial participants are protected.
EUCROF	2166	2166	GLOSSARY	Good Clinical Practice: The definition should also include "archiving" like the definition of GLP. Archiving has become a very important topic.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Ludger Wienbrede	2166	2169		"Good Clinical Practice (GCP): A standard for the planning, initiating, performing, recording, oversight, evaluation, analysis and reporting of clinical trials that provides assurance that the data and reported results are reliable and that the rights, safety and well-being of trial participants are protected." See comment to lines 2-3.	
Quotient Sciences	2167	2169	Glossary, Good Clinical Practice (GCP)	Why has 'confidentiality' been removed from the definition in GCP R2?	Please reinstate "confidentiality" of trial participants.
Fergus Sweeney	2170	2170		should impartial witness also include where the participant cannot understand the language being spoken and needs an interpretor?	suggest reword to include where an interpretor is used as well as where the participant cannot read.
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	2177	2180	Glossary	What is meant by "to assess at intervals … the critical efficacy endpoints"? Interim efficacy analyses have to be pre-specified in the protocol and statistical analysis plan, and may affect power and therefore sample size calculation. It is the task of IDMCs to assess results of planned interim analyses, but surely not to look regularly into efficacy data. Or is meant that the the IDMC should assess completeness and data quality of efficacy endpoints (which makes sense)?	
Ollie Östlund	2182	2190	III Glossary	See comments on line 586-774 on conflating informed consent (confirming willingness to participate), which is what this glossary term should contain, with archiving documentation of informed consent (obtaining written or electronic signatures).	Remove the sentence "Informed consent is documented…".
FVR-Finnish Vaccine Research	2188	2190	Informed Consent	The explicit request of written or electronic signed and dated informed consent is conflicting with the current European Clinical Trials Regulation (Regulation (EU) No 536/2014), which allows obtaining informed consent by described simplified means in low-interventional cluster trials under defined conditions (Article 30).	Obtaining informed consent by simplified means in low-interventional cluster trials should be allowed under conditions defined in the Regulation (EU) No 536/2014, Article 30.
Mandy Jackson National Clinical Trials Office Quality Working Group Ireland	2190	2190	Informed consent	Who would determine when it is appropriate to obtain consent remotely. Is it expected certain criteria/circumstances should be applied in determining this.	
Fergus Sweeney	2192	2192		ensure foreign inspections are not hindered	add "…authorities (domestic or foreign)…"
EUCROF	2196	2196	GLOSSARY	"Some aspects of the inspection may be conducted remotely" There are inspection (also after the COVID pandemic) that are conducted fully remotely.	"Some or all aspects of the inspection may be conducted remotely"
Fergus Sweeney	2196	2196		There needs to to be the potential for a complete inspection to be conducted remotely where needed and feasible. To do otherwise is to stick in the past.	reword to "An inspection or some aspects of it may be conducted remotely, at the discretion of the inspecting authority."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUCROF	2202	2202	GLOSSARY	"… constituted of medical professionals and non-medical members …" the non-medical members are in most cases also professionals. Exception might be the layperson or patient representatives, however there are lawyers, statisticians, etc.	"… constituted of medical professionals and non-medical professionals and members"
Fergus Sweeney	2209	2209		suggest reword - allow is permissive whereas enable is more active	reword to "…but should enable the IRB/IEC to…"
Fergus Sweeney	2211	2211		ICH E8 uses study to include non-interventional/observational studies whereas E6 only relates to interventional clinical trials. Study should be deleted and only Clinical Trial Report used	reword "Clinical Trial Report"
EFPIA Consolidated Comments	2212	2213	Glossary Interim Clinical Trial Report	Clarify that the intermediate analysis needs to be predefined.	A report of intermediate results and their evaluation based on analyses performed during the course of a trial at a predefined timepoint.
Medicines for Europe	2214	2218	Glossary	In some regions, the term "reference product" has a legal definition that may be different from what the text intends to cover in this section. Confusion should be avoided and the term "comparator" should be used instead.	Investigational Product A pharmaceutical form of an active ingredient or placebo being tested or used as a comparator reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Society for Clinical Research Sites	2221	2228	Glossary	To be clear, investigators support trial decentralization and recognize sponsors' role in creating infrastructure for decentralized aspects. However, when accountability is placed on investigators without corresponding authority, it becomes a significant concern as sponsors assume tasks previously handled by investigators. We hope R3 maintains consistency, emphasizing investigators' accountability only for directly controlled matters, especially with multiple investigators and service providers overseen by the sponsor or an external coordinating investigator.	The guidance should clarify the meaning of Lines 2222-2223, especially regarding when an investigator is responsible for trial participants and when they are not. For example, if a participant is in a study phase with interactions solely between them and the sponsor (or selected service provider like a mobile health or telemedicine company), some argue that the sponsor becomes responsible for those participants as the ones overseeing the trial. This aligns with the idea that the sponsor, acting as the "coordinating investigator," leads the team, assigning local investigator(s) tasks at different sites.
Medicines for Europe	2227	2228	Glossary	it should be clear when the guideline is refering to investigator and when to institution. The sentence "Where required by the applicable regulatory requirements, the "investigator" should be read as "investigator and/or the institution." is rather missleading.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA Consolidated Comments	2234	2235	Glossary Investigator site	should definition be expanded to cover more flexible designs and decentralized trials as investigator's tasks may be delegated e.g., to local HCPs/nurses? Per this definition, a patient's home may be considered the investigative site if the PI is observing and directing (via, say, a telehealth portal) a study visit being performed by an OHP. This lack of clarity may have monitoring implications (site selection, routine monitoring). We have already had these issues raised. Our position - it should be made clear that the home (e.g.) is not part of the study site re: site activities such as monitoring and inspection	The location(s) at which trial-related activities are conducted or from where they are coordinated under the investigator's/institution's supervision, for example the trial participant's home, mobile medical units, or other local venues. Where activities are undertaken at the participant's home, this would not be included as a location for monitoring, auditing or inspecting.
Fergus Sweeney	2239	2243		clealry explain here that metadata inlcudes those elements used to support the ALCOA principles and those scientific attributes used to define the data point	reword to explain the two kinds of metadata
eClinical Forum	2240	2240	Glossary	The definition of metadata is too broad as it appears to encompass technical data created solely for the general health of a computerized system, such as an API log.	Please provide a clarification in the definition of metadata such that it "excludes technical data created for the general health of the computerized systems such as API logs"
EFPIA Consolidated Comments	2240	2243	Glossary Metdata	It is recommended that examples of metadata, in the context of a clinical trial, be included to provided clarity and to avoid ambiguity between raw data, metadata and source data.	The contextual information required to understand a given data element. Metadata is structured information that describes, explains or otherwise makes it easier to retrieve, use or manage data. For the purpose of this guideline, relevant metadata are those needed to reconstruct the trial conduct. Metadata is an integral part of the source record or reported data and facilitates reconstruction of contextual information, such as when and by whom the data value was entered or revised (e.g timestamps on the lab reports, audit trail in the computerized system).
Society of Quality Assurance (SQA)	2243	2243	Glossary	In the 'Metadata' definition, it is recommended to include examples of metadata in the context of a clinical trial, for better clarity and to avoid ambiguity between raw data, metadata and source data.	Add "Metadata is different from raw data. Information captured in tools such as electronic case report forms (eCRFs) and Interactive Response Technologies (IRTs) would be raw data but when/by whom that information is captured would be the metadata. Audit trails within computerized systems are also considered metadata."
EFPIA Consolidated Comments	2244	2247	Glossary Monitoring	The definition of Inspection specifies that some aspects of the inspection may be conducted remotely, suggesting that an inspection cannot be entirely remote. How about monitoring - can we have fully remote monitoring, while inspections will always have an on-site component? Please unify the approach and specify the same parameters for the quality assurance and quality control interventions	Some aspects of monitoring maybe conducted remotely.
EUCROF	2252	2252	GLOSSARY	"A documented report following site and/or centralised monitoring activities." The sentence could be more precise.	"A documented report following on-site , and/or remote and/or centralised monitoring activities. See also 3.11.4.1 (a) and (b) and 3.11.4.2
Quotient Sciences	2252	2252	Glossary, Monitoring Report	The wording could be improved.	Please edit as follows: A documented report following <u>of</u> site and/or centralised monitoring activities.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Ludger Wienbrede	2253	2254		"Multicentre trial: A clinical trial conducted according to a single protocol but at more than one investigator site." It is usual practice that protocols differ slightly between study countries just because authorities of ethics committees have asked for slight modifications of the protocol in some countries that are not implemented in others. This is not a preferred situation, but it is so common that a note should be added like: Protocols might differ slightly between counties. Such protocols are still regarded as a single protocol if they originate from the same unique protocol and if the differences have no substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial.	
GQMA	2264	2265	Glossary	The term 'amendment' is used throughout the document, but the EU CTR 536 uses the term 'modification'. This could produce misunderstandings.	Assess the harmonization of ICH and EU terminology regarding the term for a protocol change or include 'modification' in the definition for 'amendment' as alternative term.
Quotient Sciences	2264	2265	Glossary, Protocol Amendment	Amendments may be made to any approved trial document, and not all amendments affect the protocol. For example, an amendment may be made to the IMP specification in the IMP dossier or to the participant payment in the ICF that do not affect the protocol. Also, the EU (and UK) are introducing the term 'modification'. Please consider adding 'Amendment/Modification' to the glossary.	Please add to the glossary a definition of Amendment/Modification (not limited to *protocol* amendments). Please also edit line 2264 as follows: Protocol Amendment/Modification
Fergus Sweeney	2268	2268		conduct of the trial in accordance with the protocol is the core of what essential records should show and protocol is not mentioned	reword to "…in compliance with the protocol, GCP…"
EUCROF	2271	2272	GLOSSARY	"The operational techniques and activities undertaken to verify that the requirements for quality of the trial-related activities have been fulfilled." To emphasise that QC is in-process quality control	"The in-process operational techniques and activities undertaken to verify that the requirements for quality of the trial-related activities have been fulfilled."
EFPIA Consolidated Comments	2274	2275	Glossary Randomisation	suggest a more general term than treatments since in early phase the term treatment is avoided.	The process of deliberately including an element of chance when assigning participants to groups that receive different treatments/ products in order to reduce bias.
EFPIA Consolidated Comments	2276	2279	Glossary RSI	Advise updating for consistency with the other references to RSI within the document to include both the IB and alternative documents, in accordance with applicable regulatory requirements (see line 1453 through 1454 as an example wherein allowance is made for RSI to be contained within the IB or other documents).	The RSI is included in the Investigator's Brochure or can be found in alternative documents such as the basic product information.
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	2276	2279	Glossary	Please add or specify, that the RSI may also be a SmPC in case of clinical trials with trial medication used according to standard care.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	2276	2279	Glossary	The definition of RSI, it should be indicated that the RSI is included in the Investigator's Brochure or, in case the trial includes the use of an authorised medicinal product, in the Summary of Product Characteristics of the Comparator.	Contains a cumulative list of ADRs that are expected for the investigational product being administered to participants in a clinical trial. The RSI is included in the Investigator's Brochure or, in case the trial includes the use of an authorised medicinal product, in the Summary of Product Characteristics of this product.
EUCROF	2277	2279	GLOSSARY	"Contains a cumulative list of ADRs that are expected for the investigational product being administered to participants in a clinical trial. The RSI is included in the Investigator's Brochure." RSI definition is incomplete. It should refer to the IB "or alternative documents", similar to the information in the body text of the guide.	"The RSI is included in the Investigator's Brochure or alternative documents (e.g. Summary of product characteristics), as applicable"
FVR-Finnish Vaccine Research	2277	2279	Reference Safety Information	The guidance remains unclear if there are several investigational products used in the trial with different safety profiles and "expected ADRs". It should be clarified what to report as unexpected reactions (SUSARs) if the reaction is unexpected for one IP, but not for another IP in a blinded trial.	
Quotient Sciences	2277	2279	Glossary, Reference safety information (RSI)	It would be helpful to clarify that the RSI is based on prior clinical experience. There is potential for confusion, as an adverse event that might be *expected* to occur, based on the pharmacological activity of the investigational product, is classed as *unexpected* if it has not previously been reported. The definition should be aligned with that within the SUSAR definition and the final sentence of the 'Unexpected' bullet within that SUSAR definition would be better placed in the RSI glossary entry.	Please edit as follows: Contains a cumulative list of ADRs that are expected, based on prior clinical experience, for the investigational product being administered to participants in a clinical trial. The RSI is included in the Investigator's Brochure or alternative documents according to applicable regulatory requirements. Refer to ICH E2F Development Safety Update Report for more information about RSI.
Good Clinical Trials Collaborative, on behalf of supporting organisations	2278	2279	GLOSSARY - Reference Safety Information (RSI)	Add: "The RSI is included in the Investigator's Brochure or the Summary of Product Characteristics." Since some products may have a marketing authorisation already.	
Ipsen	2278	2279	Glossary	For marketed drugs, there can be no longer IB developed by the MAH and the RSI can be included in the SmPC or alternative documents	The RSI is included in the Investigator's Brochure or alternative documents
Ludger Wienbrede	2278	2279		"The RSI is included in the Investigator's Brochure." This should be amended by "for non-authorised medicinal products or for authorised medicinal products that are not used according to the authorisation. For authorised medicinal products the RSI is included in the authorised product information. If the authorised product information differs between trial countries, the sponsor selects one product informtion to define the RSI."	
Fergus Sweeney	2279	2279		RSI for authorised products can be in the SmPC	reword to add"..or for authorised products in the Summary of Product Characteristics."
The GCP Unit at Odense University Hospital, OPEN	2279	2279	Glossary	The RSI is included in the Investigator's Brochure, but SPC should be mentioned too	The RSI is included in the Investigator's Brochure or if relevant SPC.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUCROF	2281	2282	GLOSSARY	"Bodies having the power to regulate, including those that review submitted protocols and clinical data and those that conduct inspections." Clinical data is not sufficient, as non-clinical data is also reviewed when a protocol is assessed.	"Bodies having the power to regulate, including those that review submitted protocols, non-clinical and clinical data and those that conduct inspections.
Dr. C. Wilsher	2284	2287	Glossary	Line 2284 does not mention "subcontracting" in the definition of service provider. However section 3.6.10, line 1013 does mention subcontracting. ("3.6.10 The sponsor should ensure appropriate oversight of important trial-related activities that are transferred to service providers and further subcontracted"). Also the previous version R2 5.2.2 addendum explicitly includes "subcontractors" . But the present draft definition of Service Provider does not mention subcontractors. To be internally consistent, the definition should explicitly state whether subcontractors are included.	Service Provider A person or organisation (commercial, academic or other, including any parties that may have been subcontracted) providing a service used during the conduct of a clinical trial to either the sponsor or the investigator to fulfil one or more of their trial-related activities.
Unicancer	2284	Glossary	2284	A person or organisation (commercial, academic or other) providing a service used during the conduct (…) to fulfil one or more of their trial-related activities. The choice and implementation of a central lab, a n independant review/adjudication committee is done bt the sponsor, activities are trial related but not 'sponsor-related'.	A person or organisation (commercial, academic or other) providing a service used during the conduct (…) to fulfil one or more of the trial-related activities.
EFPIA Consolidated Comments	2285	2287	Glossary Service provider	Examples would be helpful for clarity	(e.g. central laboratory, central endpoint assessment, biomarker analysis laboratory, home nurse)
PPD	2288	2290	III. Annex I GLOSSARY	It is unclear what is meant by "authenticate". This is true for electronic signatures where there is a means to identify who was supposed to have applied the signature based on their logged data, but if a signature is manually/digital, how would it be authenticated? It seems it would require that a printed name accompany the mark, to provide an audit trail to the person who was supposed to sign.	This is the FDA definition of a handwritten signature: "the scripted name or legal mark of an individual handwritten by that individual and executed or adopted with the present intention to authenticate a writing in a permanent form." The text seems to indicate it can go beyond handwritten. Perhaps align the definition more closely to the FDA one? Clarification of how authentication would work in practice.
EFPIA Consolidated Comments	2289	2290	Glossary Signature	It should be mentioned that signatures may be electronic if allowed by local laws and regulations.	A unique mark, symbol or entry which may be electronic in nature in line with applicable regulatory requirements and/or practice to show expression of will and allow authentication of the signatory.
FVR-Finnish Vaccine Research	2293	2298	Source Records	One process in creating original trial documents is the direct electronic data entry into electronic CRFs by trial staff. This should be mentioned as an example.	From row 2294: This may include trial participants' medical/health records/notes/charts; direct entry of trial records into electronic case report form (eCFR); data provided/entered by trial participants…
Fergus Sweeney	2301	2306		The sentences from "A clinical trial may have one or several sponsors.." is not correct. The correct text is in section 3.6.12	update the text regarding having several sponsors so it is the same as that in 3.6.12 which is the correct version

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	2307	2312	Glossary	Please delete the term "Sponsor-Investigator" from the Glossary. This industry-coined term should not officially be introduced in GCP, as it suggests that a physician as an individual is capable of being responsible for a clinical trial. This is very questionable for liability reasons alone and also with regard to the safety of patients in such a trial and should not be supported here.	
GQMA	2308	2310	Glossary	Since the term sponsor-investigator is explained, it would be good to outline in the given definition the term investigator-initiation trial, to link both terms.	Change to: "An individual who both initiates and conducts, alone or with others, a clinical trial (a so-called 'investigator-initiated trial'), and under whose immediate direction the investigational product is administered to, dispensed to or used by a participant."
EFPIA Consolidated Comments	2320	2322	Glossary Trial Participant	Revert to order of wording from R2 Subject/Trial Subject, so here Participant/Trial Participant Trial Participant does not include individual(s) on the clinical trial stages such as screening, screening failure, withdrawal, follow-up, etc	Participant/Trial Participant An individual who signs an informed consent and is screened and /or enrolled either as a recipient of the investigational product(s) or as a control .
EUCROF	2320	2322	GLOSSARY	Trial Participant: An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control. This definition is incomplete as a trial participant could also be a screening failure (has given informed consent, has undergone trial procedures (e.g., diagnostic procedures which are part of the trial) and - with this - has become a trial participant). Screening failures are not randomized, but might deliver important information, they are part of the trial (e.g., trial participants). In addition, reciving the comparator also means receiving investigational produc(s). This means participating as a control might not be doistinct from reciving IP.	Trial Participant An individual who participates in a clinical trial, either resulting to be a screening failure, or as recipient of the investigational test product(s) or as a control.
Fergus Sweeney	2327	2327		Add a definition of Unexpectrd ADR	Add "Unexpected ADR ……"
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	2327	2327	Glossary	"Vulnerable Participants" are defined in the glossary but are not mentioned elsewhere in the guideline.	
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	2327	2336	Glossary	This definition of "vulnerable participants" goes far beyond what is understood as vulnerable for example in the EU Regulation 536/2014. There it is about vulnerable persons such as persons not capable of giving consent, minors, pregnant women/breastfeeding mothers. In the context of clinical trials, describing persons in an professional hierarchy as vulnerable means excluding them from research in a specific case or depriving them of a treatment option. In our opinion, this is not justifable.	Please rephrase
Fergus Sweeney	2336	2336		Reinstate the definition of Well-being from the ICH E6 R2	Reinstate "Well-being (of the trial participants) The physical and mental integrity of the participants in a clinical trial."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Good Clinical Trials Collaborative, on behalf of supporting organisations	2337	2832	APPENDICES	Make it clear that Appendices A, B and C are Appendices to Annex 1 (not to the whole document). This is particularly important for Appendix C (Essential Records) since the details in this appendix may well not apply to other trial designs in the future (e.g. those without investigator sites).	
DGPharMed e. V. (Deutsche Gesellschaft für Pharmazeutische Medizin)	2339	2541	Appendix A	General note: Same wordings in that chapter give rise to the need that the Sponsor has to develop/supply/adapt trial specific parts of IBs. In the context of investigator-initiated trials often (standard) IBs of the MAH/manufacturer are used. The individual adaption of those IBs for minor details (e.g. line 2358/2359, 2384, 2408/2409, 2411) is an undue effort for IITs. Alternative solutions should be possible: e.g. supplements, appendices	Instead of adapting trial specific parts of Ibs, alternative solutions should be possible (e.g. appendices)
Sandoz AG, Switzerland	2340	2341	A.1	The footnote on the definition of "investigational product(s)" does not include drug-device combination products, which should however fall into this category as well, and be added for better clarity.	Add in the footnote "drug-device combination products".
Regeneron Pharmaceuticals, Inc	2367	2377	A.1.2 A.3.6 (b)	Section 1.2 of the CTFG Q&A on Reference Safety Information states "The content of the RSI should include a clear list of 'expected SARs' to the IMP(s)." Additionally, Question 10 of the Clinical Trial Facilitation Group (CTFG) Q&A on Reference Safety Information states "In these cases, a clearly defined section of the IB called RSI should still be present, followed by a brief text stating that no SARs are considered expected by the sponsor for the purpose of expedited reporting and identification of SUSARs." In line with these clarifications, industry stakeholders and authors expect that the Reference Safety Information (RSI) section of the Investigator Brochure (IB) includes information (e.g., a clear list of expected serious adverse reactions) used as a reference point for expedited reporting of a suspected serious adverse event reaction (SUSAR). The Risk-Benefit Assessment section includes information that enables clinicians to assess risk-benefit and appropriateness of a trial for a participant As such, we propose seperate and distinct sections within the guideline. Combining them in Section A.1.2 "Reference Safety Information and Risk-Benefit Assessments" creates a lack of clarity for authors of the IB and investigators utilizing it. To assist both users and authors of the IB, Regeneron proposes moving line 2370 to 2377 into it's own section, " Risk-Benefit Assessment" Section (A.1.3) . In it's place, we propose inserting the contents of line 2510 to 2518 of A.3.6 (b) "Safety and Efficacy" into the "Reference Safety Information" section line 2370. These changes will better align with current safety guidelines.	[CURRENT WORDING] A.1.2 Reference Safety Information and Risk-Benefit Assessment The reference safety information (RSI) contained in the IB provides an important reference point for expedited reporting of suspected unexpected serious adverse reactions (SUSARs) in the clinical trial. The IB also provides insight to support the clinical management of the participants during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced and non-promotional form that enables a clinician or potential investigator to understand it and make their own unbiased risk-benefit benefit risk assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should be involved in the generation of an IB, but the contents of the IB should be approved by the disciplines that generated the described data. PROPOSED CHANGES/RECOMMENDATIONS A.1.2 Reference Safety Information [PROPOSAL TO MOVE "RISK-BENEFIT Assessment" to it's own section following this one] The reference safety information (RSI) contained in the IB provides an important reference point for expedited reporting of suspected unexpected serious adverse reactions (SUSARs) in the clinical trial. The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. There should be a list of adverse reactions, clearly identified as the reference safety information section, including information on their frequency and nature.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Regeneron Pharmaceuticals, Inc	2367	2377	A.1.2 A.3.6 (b)	Section 1.2 of the CTFG Q&A on Reference Safety Information states "The content of the RSI should include a clear list of 'expected SARs' to the IMP(s)." Additionally, Question 10 of the Clinical Trial Facilitation Group (CTFG) Q&A on Reference Safety Information states "In these cases, a clearly defined section of the IB called RSI should still be present, followed by a brief text stating that no SARs are considered expected by the sponsor for the purpose of expedited reporting and identification of SUSARs." In line with these clarifications, industry stakeholders and authors expect that the Reference Safety Information (RSI) section of the Investigator Brochure (IB) includes information (e.g., a clear list of expected serious adverse reactions) used as a reference point for expedited reporting of a suspected serious adverse event reaction (SUSAR). The Risk-Benefit Assessment section includes information that enables clinicians to assess risk-benefit and appropriateness of a trial for a participant As such, we propose seperate and distinct sections within the guideline. Combining them in Section A.1.2 "Reference Safety Information and Risk-Benefit Assessments" creates a lack of clarity for authors of the IB and investigators utilizing it. To assist both users and authors of the IB, Regeneron proposes moving line 2370 to 2377 into it's own section, " Risk-Benefit Assessment" Section (A.1.3) . In it's place, we propose inserting the contents of line 2510 to 2518 of A.3.6 (b) "Safety and Efficacy" into the "Reference Safety Information" section line 2370. These changes will better align with current safety guidelines.	This list should be used for determining the expectedness of a suspected serious adverse reaction and subsequently whether it needs to be expedited in accordance with regulatory requirements. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s). A.1.3 Risk-Benefit Assessment [PROPOSAL TO ADD THIS "NEW" SECTION] The IB also provides insight to support the clinical management of the participants during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced and non-promotional form that enables a clinician or potential investigator to understand it and make their own unbiased risk-benefit benefit risk assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should be involved in the generation of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.
Regeneron Pharmaceuticals, Inc	2367	2377	A.1.2 A.3.6 (b)	Section 1.2 of the CTFG Q&A on Reference Safety Information states "The content of the RSI should include a clear list of 'expected SARs' to the IMP(s)." Additionally, Question 10 of the Clinical Trial Facilitation Group (CTFG) Q&A on Reference Safety Information states "In these cases, a clearly defined section of the IB called RSI should still be present, followed by a brief text stating that no SARs are considered expected by the sponsor for the purpose of expedited reporting and identification of SUSARs." In line with these clarifications, industry stakeholders and authors expect that the Reference Safety Information (RSI) section of the Investigator Brochure (IB) includes information (e.g., a clear list of expected serious adverse reactions) used as a reference point for expedited reporting of a suspected serious adverse event reaction (SUSAR). The Risk-Benefit Assessment section includes information that enables clinicians to assess risk-benefit and appropriateness of a trial for a participant As such, we propose seperate and distinct sections within the guideline. Combining them in Section A.1.2 "Reference Safety Information and Risk-Benefit Assessments" creates a lack of clarity for authors of the IB and investigators utilizing it. To assist both users and authors of the IB, Regeneron proposes moving line 2370 to 2377 into it's own section, " Risk-Benefit Assessment" Section (A.1.3) . In it's place, we propose inserting the contents of line 2510 to 2518 of A.3.6 (b) "Safety and Efficacy" into the "Reference Safety Information" section line 2370. These changes will better align with current safety guidelines.	A.3.6 Effects in Humans (b) Safety and Efficacy A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy and dose response that was obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed. The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. There should be a list of adverse reactions, clearly identified as the reference safety information section, including information on their frequency and nature. This list should be used for determining the expectedness of a suspected serious adverse reaction and subsequently whether it needs to be expedited in accordance with regulatory requirements. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s). (REMOVE AND INSERT THE STRIKETHROUGH LINES IN THIS SECTION TO INTO SECTION A.1.2)

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Fergus Sweeney	2369	2369		RSI is used to identify unexpectedness, not to expedite per se	reword "..reference point for identification of unexpected ADRs, in order to determine which are SUARSs..."
GQMA	2396	2397	A.3	It is unclear why literature references should be placed specifically at the end of each section. The main point is that there should be literature references given in the document.	Change to: "The IB should contain the following sections, each with literature references (publications or reports) included, where appropriate;…"
Sandoz AG, Switzerland	2396	2397	A.3	The general sentence on IBs is too specific for the location of literature references - it is irrelevant where the literature references are located in the document. Suggest to remove "at the end of each chapter".	"The IB should contain the following sections, each with literature references (publications or reports) included at the end of each chapter, where appropriate.
Quotient Sciences	2404	2420	A.3.3-A.3.4	Some regulatory authorities publish IBs, but not IMP quality documentation (e.g., IMPD). The chemical name of the IMP, it's structural formula and physical, chemical and pharmaceutical properties are commercially sensitive. That information in the IB could be replaced with a cross-reference to the IMP quality documentation to protect commercial confidentiality. The IB should reference the class/mechanism of action and the type of formulation, and information on solubility of orally-administered products would be helpful to aid assessment of the likely importance of the effect of food on absorption. But, for all other chemical, physical and pharmaceutical information, cross reference could be made to IMP quality documentation. Excipients are not always listed in the IB.	Please specify that, aside from class/mechanism of action, solubility and type of formulation, all other information may be presented in a separate document containing quality information about the investigational product.
Sandoz AG, Switzerland	2405	2406	A.3.3	The section talks about the introduction which should contain the "chemical name" of the investigational product; In my view, this should be extended to "chemical/compound" name, as for biologics, which do not have a specific chemical structure, this may not be feasible.	"A brief introductory statement should be provided that contains the chemical/compound name (...) of the investigational product(s);
Sandoz AG, Switzerland	2413	2414	A.3.4	This section also focuses on the chemical structural formula, whereas it may not be possible to describe it in such a way for a biologic.	"A description should be provided of the investigation product substance(s) (including the chemical and/or structural formula(e), as applicable), ...
Quotient Sciences	2452	2453	A.3.5, Introduction	Please add that human equivalent dose (HED) may also be used to make comparisons, as it is commonly referenced in IBs supporting first in human trials.	Please edit as follows: Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis; human equivalent doses may also be used to compare doses among species.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Jazz Pharmaceuticals	2510	2518	A.3.6(b)	There are challenges related to providing a single "list of adverse reactions….clearly identified as the reference safety information." The guideline should clarify how sponsors are to communicate adverse reactions which do not meet current CTFG guidance for inclusion in the RSI. Current regional regulatory guidance requires that the RSI must conform to specific parametric requirements which may not apply to all adverse reactions. Some adverse reactions may not meet criteria for inclusion in the RSI. Sometimes pharmaceutical companies address this issue by including two tables in their IBs—one a table of adverse reactions, and the second, a table of expected SARs which is the reference safety information. The guideline should address this practice and provide advice on the requirement here.	
Quotient Sciences	2510	2518	A.3.6 (b)	Typographic error (change " experiences " to " experience ") and wording could be improved.	Please edit as follows: line 2511: ...on the basis of prior experiences… line 2515: …whether it needs to be reported in an expedited manner in accordance with regulatory rquirements.
Fergus Sweeney	2516	2516		the protocol may specifiy particular requirements as mandated by legislation	reword to "..in accordance with the protocol and regulatory requirements."
Regeneron Pharmaceuticals, Inc	2535	2541	A.3.7	There are different approaches across industry to the formatting of *The Guidance to the Investigators* section of the Investigators Brochure. Some organizations chose to include only important risks and others include a full compilation of all risks identified. The current wording of the sentence seems to suggest all possible risks related to the IMP/IP should be covered in this section**.** However, if the intention is to communicate only the important risks we should explicitly state what is important rather than leaving this open to interpretation. The benefit of conveying important risks to investigators allows them to understand what is most important in managing patients and prevents an exhaustive list of risks which could distract attention from important risks, potentially creating greater confusion in an investigator's understandng of how best to manage and treat trial participants.	The overall aim of this section is to provide the investigator with a clear understanding of the possible important risks and adverse reactions of the specific tests, observations and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological and clinical information on the investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions that is based on previous human experience and on the pharmacology of the investigational product.
IPFA, International Plasma and Fractionation Association	2542	2683	Appendix B. CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)	Comment: appendix B provides a template of the protocol with instructions regarding the content. Furthermore, this section refers to other ICH guidelines such as ICH E8(R1) and ICH E9. However, a draft guideline ICH M11 and a draft protocol template on protocol were issued in 2022. How will this guideline and the protocol template be used in relation to the proposed by ICH E6?	
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	2542	2583	B	The structure and content slightly differ from the ICH M11 Guideline. It would be more helpful if ICH M11 Guideline is referenced here. This would avoid any discrepancies between the guidelines.	Suggestion: Reference to ICH M11 Guideline and delete additional information in Appendix B.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Quotient Sciences	2546	2547	Appendix B	Please clarify, that it is usually not appropriate to involve healthy volunteers in development of protocols for phase 1 healthy volunteer trials. * Healthy volunteers are fit and well and do not have special needs that might not be fully understood by personnel designing or managing the trial (e.g. mobility, diet). Personnel designing protocols and writing information sheets for phase 1 trials are all potential healthy volunteers, and may have actually taken part in phase 1 trials. * Looking after the needs of volunteers is central to the success of phase 1 trials and phase 1 units. We review the participant information sheet and protocol from the point of view of a participant and consider aspects of the design that may cause unnecessary discomfort or inconvenience, e.g, avoid discharge of volunteers late in the evening or prolonged fasting. * The design of phase 1 trials must comply with international guidelines and be appropriate to the safety profile, pharmacokinetics and pharmacodynamics of the IMP. The schedule of procedures and sampling is usually very intensive. We aim to minimise inconvenience, but we must ensure volunteer safety and data quality. So, for example, if we must interrupt volunteers' sleep to do procedures, or if volunteers must remain in bed or fast for prolonged periods, we ensure that we inform them of all the burdens and inconvenience of participation. It's in our best interest to do that because not doing so would risk a high withdrawal rate, which would increase the cost of the trial, extend its timelines and potentially lead to exposure of additional volunteers, which has ethical implications. With respect to phase 1 healthy volunteer trials, participant involvement is achieved by obtaining retrospective feedback on participant-facing documents, processes and facilities.	Please edit as follows: Protocol development processes should incorporate input from relevant stakeholders, where appropriate. For example, involvement of patients in design of phase 2/3 patient trials is recommended, whereas involvement of healthy volunteers in design of phase 1 healthy volunteer trials is not usually appropriate.
AdjuTec Pharma; Bjørg Bolstad	2576	2585	Appendix B	Trial Objective and endpoints fit together under the same heading.	Suggests to move B.4.1 to B3.
EFPIA Consolidated Comments	2577	2580	B.3	Since estimands are the foundation and influence trial design, conduct, and analysis. Since these elements are to be described in the protocol, estimands should be described in the protocol as well. Subsequently, trial design, conduct and analysis can be described in alignment with the choice of the estimands. Therefore it would be better to describe estimands in B4.	A clear description of the scientific objectives and the purpose of the trial. Information on estimands, where appropriate, if not included in any other trial-related document, see ICH ICH E6(R3) Guideline E9(R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials.
Quotient Sciences	2577	2578	B.3	Estimands are not applicable for exploratory phase 1 healthy volunteer trials, in which efficacy is not an objective. Please clarify that there is no expectation for estimands to be included in exploratory phase 1 healthy volunteer protocols.	Please edit as follows: Information on estimands, where appropriate (i.e., in pivotal trials, but not in exploratory, trials), if not included in any other trial-related document
AdjuTec Pharma; Bjørg Bolstad	2581		Appendix B	Schedule of events belongs under Trial design.	Add schedule of events in senction B4. Trial Design
EFPIA Consolidated Comments	2584	2585	B4.1	Please consider the reference to E9 R1 here. Additional text proposed.	A description of the estimands, where applicable, to enable reliable estimation of the targeted treatement effect. See ICH Guideline E9(R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA Consolidated Comments	2586	2589	B.4.2	Externally controlled and single arm trials should be added as an example.	A description of the type and design of trial to be conducted (e.g., double-blind, placebo-controlled, parallel design, adaptive design, platform/umbrella/basket, externally-controlled trials, single arm trials, trials with decentralized elements) and a schematic diagram of trial design, procedures and stages.
AdjuTec Pharma; Bjørg Bolstad	2590	2592	Appendix B	Randomisation and Blinding better explained under section B7 treatment and interventions for participants	Suggests to move to B.7
EFPIA Consolidated Comments	2590	2590	B.4.3	not all trials are randomized or blinded. Suggest adding if applicable	A description of the measures taken to minimize/avoid bias, if applicable, including,:
AdjuTec Pharma; Bjørg Bolstad	2593	2595	Appendix B	Drug handling, packing etc much better under section B7 treatment and interventions for participants	Suggets to move to B.7
Quotient Sciences	2598	2600	B.4.6	This section should specify that all stopping criteria - participant dose stopping criteria and withdrawal criteria; dose escalation stopping criteria; and trial stopping criteria be located in a single clearly labelled section, to facilitate compliance. It is also essential that there be a clearly labelled section (Dose Escalation Criteria) that contains all dose escalation criteria for a first in man trial. The rules for escalating the dose must be clear, be together in one place, and be easy to locate, or compliance may be compromised.	Please replace lines 2598-2600 with the following: B.4.6 A description of criteria for: dose escalation (in early phase 1 trials) or dose adjustment/titration (where applicable). In addition, a single, clearly labelled section should contain all applicable stopping rules, including: criteria for stopping dosing, or interrupting or adjusting the dose, in individual participants; criteria for withdrawal of individual participants from the trial; criteria for stopping dose escalation; and criteria for halting, stopping or terminating the trial.
AdjuTec Pharma; Bjørg Bolstad	2601	2602	Appendix B	Drug accountabiolity belongs much better under section B7 treatment and intnterventions for participants	Suggests to move to B.7
AdjuTec Pharma; Bjørg Bolstad	2603	2603	Appendix B	code envelopes procedure for breaking the codes much better under section B7 treatment and interventions for participants	Suggests to move to B.7
EFPIA Consolidated Comments	2603	2603	B.4.8	not all trials are randomized or blinded. Suggest adding if applicable	Maintenance of treatment randomization codes and procedures for breaking codes, if applicable.
Dr. C. Wilsher	2607	2607	B.5.3	"Pre-screening" is mentioned here but not defined. There is a need for a definition as ideas about pre-screening differ widely.	Define pre-screening in glossary. Pre-sceening are activities that happen before consent of the participant is gained. These activities can only include; informing the participant about the trial and answering questions; and activities that would normally occur as a consequence of normal clinical care of the participant. Pre-screening activities cannot include any protocol required activities until after the participant has given consent.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	2608	2618	Appendix B	The section "Withdrawal of Consent or Discontinuation of Participation" should include the information that it needs to be stated in the protocol that the subject can withdraw the consent at any time.	The investigator may choose to discontinue the participant or the participant may withdraw their consent. The protocol should specify: (a) that the participant can withdraw their consent at any time without specific reason; (b) when and how to discontinue participants from the trial/investigational product; (c) the type and timing of the data to be collected for withdrawn/discontinued participants, including the process by which the data are handled, in accordance with applicable regulatory requirements; (d) whether and how participants are to be replaced; (e) the follow-up for participants who have discontinued the use of the investigational product.
Fergus Sweeney	2615	2615	B.6	add a subsection on continued use of data already collected.	add "B.6.e Continued use of data already collected"
AdjuTec Pharma; Bjørg Bolstad	2627		Appendix B	Section B.7, suggests to add two sections which are useful during a clinical trial.	Add section with supportive care guidellines and emergency treatments; Add a section on treatment compliance
Alasdair Breckenridge[+], Jeffrey K. Aronson, Terrence F. Blaschke, Dan Hartman, Carl C. Peck, Bernard Vrijens	2627	2627	B.7.3	As for section 6.3, we propose adding a question of this form after the text at section B.7.3 (see next column).	Modification of section B.7.3: Strategies to monitor the participant's adherence to treament. Specifically, trialists should be asked "What reliable method is to be used to measure patient adherence in the trial?"
ESPACOMP	2627	2627	B.7.3	ESPACOMP is the international Society for Medication Adherence (www.espacomp.eu). In 2012, ESPACOMP has endorsed the taxonomy for medication adherence (1) resulting from the EU-funded ABC project (www.abcproject.eu). In 2018, ESPACOMP has published the ESPACOMP Medication Adherence Reporting Guideline (EMERGE) (2), developped as part of the EQUATOR network for Enhancing the QUAlity and Transparency Of health Research. As one of the key criteria of EMERGE is about the measurement of medication adherence, we believe that the criteria should complement section B.7.3. of the ICH E6 (R3) guidance about the monitoring of adherence to treatment. (1) Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, Dobbels F, Fargher E, Morrison V, Lewek P, Matyjaszczyk M, Mshelia C, Clyne W, Aronson JK, Urquhart J; ABC Project Team. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol. 2012 May;73(5):691-705. doi: 10.1111/j.1365-2125.2012.04167.x. PMID: 22486599; PMCID: PMC3403197. (2) De Geest S, Zullig LL, Dunbar-Jacob J, Helmy R, Hughes DA, Wilson IB, Vrijens B. ESPACOMP Medication Adherence Reporting Guideline (EMERGE). Ann Intern Med. 2018 Jul 3;169(1):30-35. doi: 10.7326/M18-0543. Epub 2018 Jun 26. PMID: 29946690; PMCID: PMC7643841.	Modification of section B.7.3.: Strategies to monitor the participant's adherence to treament. The methods employed to monitor a participant's adherence to the treatment regimen (e.g., self-report, claims data, blood sampling, and electronic monitoring) should be described in the protocol or a separate document. Each phase of adherence (i.e., initiation, implementation, and persistence) should be taken into consideration, providing detailed information on the performance of these measures, where applicable (e.g., validity, reliability, and potential bias).

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
WestRock Corporation	2627	2627	B.7.3	In an article published in 2017 in Nature Reviews Drug Discovery, the authors delineated the adverse implications of poor medication adherence in clinical trials. They proposed that regulators should tackle the problem by requiring that all applications for marketing authorization of medicinal products should require an informed response to the question "What reliable method was used to measure patient adherence in this trial?" and that trialists should be required to include objective methods of measuring patient adherence in their trial designs. Breckenridge A, Aronson JK, Blaschke TF, Hartman D, Peck CC, Vrijens B. Poor medication adherence in clinical trials: consequences and solutions. Nat Rev Drug Discov. 2017 Mar;16(3):149-150. doi: 10.1038/nrd.2017.1. Epub 2017 Feb 3. PMID: 28154411. Indeed, medication adherence in clinical trials has been a recognized global regulatory priority for many years. In its Guidance documents, the U.S. Food and Drug Administration has repeatedly encouraged the use of digital health technology, such as "Smart Packaging", as an innovation to both encourage medication adherence ("[sic] so that nonadherent patients can be encouraged to perform better") and to inform product development. FDA-2012-D-1145, Guidance Document: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products, Guidance for Industry, (March 2019) No. FDA-2021-D-1128, Draft Guidance Document: Digital Health Technologies for Remote Data Acquisition in Clinical Investigations, Guidance for Industry, (December 22, 2021).	We propose to add a qualifier to indicate that strategies deployed should be "validated subject-centered strategies" with a reference to one such validated strategy, and that they be designed to "improve" as well as monitor the participant's adherence to treatment. We also propose to add a question of "What reliable method was used to measure patient adherence in this trial?"after the text at section B.7.3. "Modification of section B.7.3: Validated subject-centered strategies to improve and monitor the participant's adherence to treatment such as smart packaging. Specifically, trialists should be asked what reliable method was to be used to measure patient adherence in the trial."
WestRock Corporation	2627	2627	B.7.3	Smart Packaging has been shown to capture robust and highly reliable dosing history data through electronic medication event monitoring, and this type of indirect method for estimating when and how much drug is ingested has been validated in the scientific literature. Vrijens B, Tousset E, Rode R, Bertz R, Mayer S, Urquahart J.; J Clin Pharmacol 2005 Apr;45(4):461-7; Savic RM, Barrail-Tran A, Duval X, Nembot G, Panhard X, Descamps D, et al.; Clin Pharamcol Ther 2012 Oct 3; Rubio A, Cox C, Weintraub M. Prediction of diltiazem plasma concentration curves from limited measurements using compliance data. Clin Pharmacokinet 1992; 22:238-46. Further, from an adherence improvement perspective, the use of Calendared Blister Packaging (specifically Westrock's Adherence Platform) has been validated to improve both medication adherence and associated health outcomes. Zedler BK, Kakad P, Colilla S, Murrelle L, Shah NR. Does packaging with a calendar feature improve adherence to self- administered medication for long-term use? A systematic review Clinical Therapeutics 2011; 33(1): 62-73; Zedler BK, Joyce A, Kakad P, Harpe SE, A Pharmacoepidemiologic Analysis of the Impact of Calendar Packaging on Adherence to Self-Administered Medications for Long-Term Use Clinical Therapeutics 2011:33(5): 581–597; Dupclay L, Eaddy M, Jackson J, Raju A, Shim A. Real-world impact of reminder packaging on antihypertensive treatment adherence and persistence. Patient preference and adherence. 2012; 6:499-507. doi:10.2147/PPA.S31417; Bosworth H, Brown J, Danus S, Sanders L, McCant F, Zullig L, Olsen M. Evaluation of a Packaging Approach to Improve Cholesterol Medication Adherence Am J Manag Care. 2017 Sep 1;23(9):e280-e286.	We propose to add a qualifier to indicate that strategies deployed should be "validated subject-centered strategies" with a reference to one such validated strategy, and that they be designed to "improve" as well as monitor the participant's adherence to treatment. We also propose to add a question of "What reliable method was used to measure patient adherence in this trial?"after the text at section B.7.3. "Modification of section B.7.3: Validated subject-centered strategies to improve and monitor the participant's adherence to treatment such as smart packaging. Specifically, trialists should be asked what reliable method was to be used to measure patient adherence in the trial."
Fergus Sweeney	2630	2630	B.8.2	typo	corect to "…analysis of efficacy.."
AdjuTec Pharma; Bjørg Bolstad	2635		Appendix B	Miss a section regarding demographic information, or is it considered sufficient to be mentioned in schedule of events?	Add a section on demographic information

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Fergus Sweeney	2642	2642	B.9.3	ICH E9 R1 is not relevant here	delete "see ICH E9(R1)"
Quotient Sciences	2645	2646	B.10.1	Stopping criteria for phase 1 healthy volunteer trials are typically based on medical considerations and exposure data, and those stopping criteria should be in a separate section, along with all other stopping rules, so that they are easy for the investigator to locate. If the intention here is to include in the statistics section details of any statistical analysis and criteria used to determine whether stopping criteria have been met in large, later phase trials, that should be clarified. However, reference to stopping criteria is also made on B.10.4, so it may be better to delete it from B.10.1.	Please edit as follows: Please consider deleting from section B.10.1 reference to statistical criteria for stopping the trial, as they are also covered in B.10.4. Alternatively, if reference to stopping criteria will be retained in B.10.1, please edit as follows: B.10.1 A description of the statistical methods to be employed, including timing and purpose of any planned interim analysis(ses) and the <u>any statistical</u> criteria for the stopping of the trial.
EFPIA Consolidated Comments	2646	2646	B.10.1	stopping rules are repeated in B 10.4 so remove from here.	....and the criteria for the stopping of the trial.
Ludger Wienbrede	2646			"and the criteria for the stopping of the trial": This should be deleted here because is appears again in line 2652.	
EFPIA Consolidated Comments	2648	2648	B.10.2	Not clear what is intended by "reflections on". Also, many trials are sized for an appropriate precision around the estimated effect. Suggest reflecting this in the statement. Brings in reference to the estimands from earlier.	The number of participants planned to be enrolled and the reason for the choice of sample size, including a statement on or calculations of the power of the statistical test including reflections on or calculations of the power of the trial and clinical justification.
EFPIA Consolidated Comments	2652	2652	B.10.4	"The criteria for termination of the trial and the criteria for the stopping of the trial." These two criteria could be used interchangeably. For additional clarity, we recommend stating that the contents of a trial protocol includes the criteria for interim analysis decision making, including stopping the trial for success or termination due to futility What about the criteria for the stopping of a treatment arm?	The criteria for the termination of the trial or arm of a trial, and the criteria for the stopping of the trial including stopping the trial for success or termination due to futility.
Quotient Sciences	2652	2652	B.10.4	As above, please clarify that this section refers to any statistical analysis and criteria used to determine whether stopping/termination criteria have been met in large, later phase trials.	Please edit as follows: B.10.4 The <u>Any statistical</u> criteria for the termination <u>or stopping</u> of the trial and the criteria for the stopping of the trial.
Sandoz AG, Switzerland	2652	2652	B.10.4	The criteria for stopping of the trial were already mentioned in B.10.1 and this is therefore a duplication.	Suggest to remove "criteria for stopping of the trial" from B.10.4., and leave it only in section B.10.1
EFPIA Consolidated Comments	2653	2656	B.10.5	ICH E9(R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials introduced intercurrent events. This thinking is not reflected here. Consider rewording to reflect the thinking in ICH E9(R1), e.g., regarding events likely to affect the interpretation or existence of data. The procedures to account for missing data (see definition in ICH E9(R1)) or data affected due to intercurrent events should be chosen in alignment with the objective. Some of the examples referring to the selection of participants, e.g. "all evaluable participants" may no longer be compatible with the estimand thinking.	The selection of participants to be included in the planned analyses (e.g., Full Analysis Set, Per Protocol Set all randomised participants, all dosed participants, all eligible participants, all evaluable participants).

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Fergus Sweeney	2655	2655	B.10.5	consider adding "…,intention to treat, per protocol, etc"	consider adding "…,intention to treat, per protocol, etc"
Ludger Wienbrede	2656			"Procedures for accounting for missing, unused and spurious data." This should be shortened to "Procedures for accounting for missing data." Rationale: It is not clear what "unsued data" might be and why they exist. It is also not clear why "spurious" data exist after monitoring. It appears that most people in the clinical trial community have no idea how to address these issues in a clinical trial protocol. In 200 plus protocols I have never seen that these issues were addressed. If protocols work without these issues and if hardly anyone know how to implement them into protocol texts, these issues should be deleted from this guideline.	
EFPIA Consolidated Comments	2658	2658	B.10.7	clinical tria should be there instead of and clinical study"	...clinical study trial report.
AdjuTec Pharma; Bjørg Bolstad	2659	2672	Appendix B	These three sections are difficult, it might be better to put them all under one heading. Seems to have left out a section regarding investigator's responsibility. I believe it is important to highlight what is the investigator's responsibility.	Suggest to add investigator responssibility, and keep B.11 as a subtitle under investigator's responsbility.
Society for Clinical Research Sites	2659	2663	B.11	We have concerns over the use of the term "*direct access*" (both here as well as in Annex I Items 2.8.11(n), 2.12.12, 3.6.3(d), 3.16.4(a), 3.11.4.1(c), 3.16.4(b), the Glossary and Appendix B.11). The phrase "direct access" (as opposed to "*access*") is interpretable as supporting an activity that is generally prohibited with established healthcare privacy/security practices and regulations across the globe (i.e. providing login IDs directly into to electronic health records).	We request the deletion of the word "direct" (or change the phrase to "access to view") here and in the other sections referenced to avoid this confusion and that the guidance can recognize the variety of ways source document verification has been accomplished over the past decade without "direct" access (but with "access to view"). This would also bring these sections to be consistent with Annex I Item 3.11.4's requirement that monitors "adhere to data protection and confidentiality requirements in accordance with applicable regulatory requirements, institution policy and established data security standards."
Quotient Sciences	2660	2663	B.11	Many RECs ask us to remove from the ICF statements that the REC could have access to source records because they do not see that as part of their remit. Reference to access by RECs should be in line with local rules and guidance.	Please edit as follows: The sponsor should ensure that it is specified in the protocol or other documented agreement that the investigator(s)/institution(s)/service provider(s) will permit trial-related monitoring, audits, institutional review board/independent ethics committee (IRB/IEC) review and regulatory inspection(s), and, in accordance with local regulatory requirements and guidance, institutional review board/independent ethics committee (IRB/IEC) review, providing direct access to source records.
Fergus Sweeney	2663	2663	B.11	ensure foreign inspections are not hindered	reword "…inspection(s) (domestic or foreign)
Fergus Sweeney	2665	2666	B.12.1	Including identified quality factors in the protocol could freeze their further review and update or lead to multiple unecessary protocol amendments which is counter to an efficient approach and to keeping the protocol simple. It also precludes that these are identifiied post finalisation of the protocol, particularly those which may be process related or drive from experience.	reword or delete. If reworded state "High level Indication of significant, identified, quality factors, updates to these and their associated risks should be dcoumented separetely to the protocol"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Quotient Sciences	2665	2666	B.12.1	Should mitigation not also be included?	Please edit as follows: B.12.1 Description of identified quality factors and associated risks and mitigation in the trial unless documented elsewhere.
Sandoz AG, Switzerland	2665	2666	B.12.1	Suggest to change to "Critical to quality factors" in line with the terminology used in ICH guideline E8 (R1) on general considerations for clinical studies.	"Description of identified critical to quality factors and associated risks in the trial unless documented elsewhere."
EFPIA Consolidated Comments	2667	2668	B.12.2	Such description of the monitoring approaches part of the quality control process can be difficult to include in a large trial and increase the size of the protocol. Flexibility should be allowed to have this information provided elsewhere.	Proposed change: "Description of the monitoring approaches that are part of the quality control process for the clinical trial unless documented elsewhere."
Fergus Sweeney	2667	2667	B.12.2	avoid unecessary detail so state "High level description.." to ensure a simple protocol, limitation of protocol amendments if monitoring approach is adjusted	reword "High level description…"
AFI	2669	2670	B	As this is required in Appendix C (B.12.3), reccomended a cross reference, to clarify that it should be reported in the protocol	Description of the process for the handling of non-compliance with the protocol or GCP with definition of important deviations (i.e., those that impact the rights, safety and well-being of trial participants and the reliability of results).
EFPIA Consolidated Comments	2669	2670	B.12.3	Such description of the process for the handling of non- compliance with the protocol or GCP can be difficult to include in a large trial and increase the size of the protocol. Flexibility should be allowed to have this information provided elsewhere.	..... unless documented elsewhere
Fergus Sweeney	2669	2669	B.12.3	avoid unecessary detail so state "High level description.." to ensure a simple protocol, limitation of protocol amendments if approach is adjusted	reword "High level description…"
Ludger Wienbrede	2671			"Description of ethical considerations relating to the trial". It might be useful to give some examples. Usually this section is filled with a description of the interaction with the ethics committees, which is a bit strange.	
Medicines for Europe	2674	2675	B.14.1	Further elaboration on how much details should be provided in the protocol seems necessary.	
Quotient Sciences	2676	2677	B.14.2	For phase 1 healthy volunteer trials, source documents are typically identified in a separate agreement, not in the protocol. Please clarify that source records may be identified in a separate document.	Please edit as follows: B.14.2 The identification of records to be recorded directly into the data acquisition tools (i.e., no prior written or electronic record of data) and considered to be source data, unless documented elsewhere.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Good Clinical Trials Collaborative, on behalf of supporting organisations	2684	2832	Key theme	Key theme #4: Essential Records. The section on Essential Records lacks emphasis on the need for proportionality. It must be re-drafted to reduce rigidity and discouraging a tendency of documentation for documentation's sake that may then distract attention from other activities that may be more fundamental to trial quality.	Points C.1 – C.3 are a serious threat to the ambitions of this ICH revision and threaten to grossly undermine the stated focus on Principles, proportionality, fitness-for-purpose, flexibility, and focus on issues that have a material impact on safety and wellbeing of participants and reliability of study results. Examples follow.
Quotient Sciences	2684	2832	Appendix C	We do not support the changes to the section on essential documents. The lack of clarity resulting from an attempt to increase flexibility will lead to confusion, disagreements, and errors and will increase rather than decrease the burden on investigators.	
EFPIA Consolidated Comments	2686	2689	C1.1	Edit: use of 'nature ' in reference to trials records in this context is not clear. (does nature here mean e.g., electronic vs paper, or something else) In this section, what is meant by 'proportional approaches', if this is related to risk suggest using the term risk-proportional'	The purpose, format and... risk-proportional proportional approaches....
Good Clinical Trials Collaborative, on behalf of supporting organisations	2694	2703	C.1.3	The current wording over-emphasises the role of essential records. They do not "serve to demonstrate the compliance of the investigator and sponsor". They are just one means to help assess such compliance (others can include, checking the plausibility of the data, interviewing staff, reviewing feedback from trial participants, etc). Indeed just because something is not documented does not mean that it was not done well – and just because something is documented does not mean that all is satisfactory. The sponsor's audit function and inspections by regulatory agencies should not be focused on documentation but take a more holistic view based on the context and nature of the specific trial.	The current draft text is in stark contrast to the recommendations of the G7 that "The Good Clinical Practice for clinical trials guidance should be revised to focus on what matters for the generation of actionable information about effects of an intervention, rather than what is easy to check but less relevant, placing an emphasis on principles and purpose rather than process."
Society for Clinical Research Sites	2694	2703	C.1.3		This section should be clarified, in line with our recommendations in Annex I Items 2.12.11 and 3.16.3(b) as "The investigator/institution should have access to and the ability to maintain and retain the essential records generated by the investigator/institution before, during and after the trial in accordance with applicable regulatory requirements. After the retention period for investigators/institutions under applicable regulatory requirements have expired the investigator/institution may either destroy the records or transfer the records to the sponsor's custody. In the event the investigator/institution becomes unable to maintain the records during their regulated time period, they may ship the records to the sponsor's custody in accordance with applicable regulatory requirements." This topic is discussed at length in our comments to Annex I Item 2.12.11 and is of critical importance to all stakeholders that it be assimilated into the final guidance.
Fergus Sweeney	2696	2696	C.1.3	conduct of the trial in accordance with the protocol is the core of what essential records should show and protocol is not mentioned	reword to "…and sponsor with the protocol, standards of GCP…"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
AFI	2700	2703	C.1.3	The investigator/institution should have access to and the ability to maintain and retain the essential records generated by the investigator/institution before, during and after the trial.	It would be advisable to provide details about retention timelines of essential records.
Association for Clinical Data Management (ACDM)	2700	2703	C.1.3	Appreciate the emphasis, maybe it would help to insist onto this.	Add " Including for the applicable retention timeline"
EFPIA Consolidated Comments	2700	2703	C1.3	Recommend incorporating that essential documents serve to also demonstrate compliance with internal procedures. Please add. The essential records need to be retained after the trial per applicable regulatory record retention requirements. Consider that the IRB might also utilise them and monitors would most definitely use them	The essential records permit and contribute to the evaluation of the conduct of a trial and the reliability of the results produced. They serve to demonstrate the compliance of the investigator and sponsor with the standards of Good Clinical Practice (GCP), procedural documents, and applicable regulatory requirements. The essential records are used as part of the sponsor oversight or investigator supervision of the trial. These records are used by the sponsor's independent audit function, monitors, by the IRB/IEC for review at the investigator site when required and during inspections by regulatory authority(ies) to assess the trial conduct and the reliability of the trial results. The investigator/institution should have access to and the ability to maintain and retain the essential records generated by the investigator/institution before, during and after the trial per applicable regulatory record retention requirements.
Quotient Sciences	2700	2703	C.1.3	GCP R2 stated that the investigator must retain control of the essential records generated by the investigator/institution before, during and after the trial. GCP R3 does not explicitly say that the sponsor must not have control of those documents. While it is acknowledged that sponsors sometimes arrange for investigators' records to be archived, the investigator must control access to the records. Please reinstate the clear statement from GCP R2 that the investigator must retain control of the investigator's records.	Please delete: The investigator/institution should have access to and the ability to maintain and retain the essential records generated by the investigator/institution before, during and after the trial. and replace it with: The investigator/institution should have control of all essential records generated by the investigator/institution before, during, and after the trial.
Ludger Wienbrede	2703			The following should be added: C.1.4 Not all of the repords produced during a clinical trials are essential records. Usually, most of the records producded during a clinical trial are no essential records and should not be handled as such. If every record of communication, shipment, question, answer is handled as an essential record, this would impair the handling of actually essential records. It would impair the quality of clinical trials, would make them expensive, unnecesarily complex and burdensome and would not increase patient safety and reliability of results but effectively put patient safety and scientific reliability at risk, because resources would be rerdistributed to useless record-handling.	
AFI	2705	2707	C.2.1	Records should be identifiable and version controlled, and should include authors, reviewers and approvers as appropriate, along with date and signature (electronic or wet ink), where necessary.	It should be clarified that all previous versions should be retained in TMF/ISF as well

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
eClinical Forum	2709	2712	c.2.2	This section states; For activities that are transferred or delegated to service providers by the sponsor or investigator/institution respectively, arrangements should be made for the access and management of the essential records throughout the trial and for their retention following completion of the trial. There should be some acknowledgment that these essential records are distributed across all of the players in the clinical trial.	Revise this section to say; ….arrangements should be made for the access and management of the distributed essential records throughout the trial …….
Society for Clinical Research Sites	2709	2712	C.2.2		This section should have the minor clarification added to assure that the party delegating to the service provider is the one accountable for access and management of the essential records that service provider is responsible for. Specifically change it to read "…delegated to service providers by the sponsor or investigator/institution respectively, arrangements should be made by the delegating party for the access and management of the essential records throughout the trial and for their retention following completion of the trial."
SHIONOGI	2714	2717	C.2.3	current text is ambiguous. It now reads 'These essential records should be maintained in or referred to from repositories, including, for example, the trial master file (TMF) or investigator site file (ISF). The TMF is held by the sponsor or by the investigator; in the latter case, it is often called the ISF.' The last portion of the text 'TMF is held by the sponsor or the investigator' my confuse people.	Recommend to rephrase into: These essential records should be maintained in or referred to from repositories, including, for example, the trial master file (TMF) or investigator site file (ISF). The TMF is held by the sponsor or by the sponsor/investigator; the ISF is held by the investigator.
Society for Clinical Research Sites	2714	2717	C.2.3		This section seems confusing. The investigator would almost certainly never maintain the entire trial TMF. They only maintain, until such time they can destroy or transfer custody of the documents to the sponsor, the TMF applicable to their site (a.k.a. the ISF). We request this to be reworded to clarify the very limited obligations of the investigator/site of being responsible for the essential documents that they or their subcontractors create.
GQMA	2715	2717	C.2.3	The TMF consists of two parts: one part maintained by the sponsor and another part maintained by the investigator, in accordance with the previous ICH E6 guideline and the EU TMF guideline. Using the term 'or' would describe the current practice wrongly and would apply to sponsor-investigators only.	Change to: "The TMF is held by the sponsor and by the investigator; in the latter case, it is often called the ISF."
Quotient Sciences	2715	2717	C.2.3	The TMF is held jointly by the sponsor and investigator. This section could be interpreted to mean that only one party need hold the TMF.	Please edit as follows: …. The TMF is held jointly by the sponsor or by and investigator; in the latter case it the investigator's file is often called the ISF.
EFPIA Consolidated Comments	2716	2717	C2.3	We would recommend to change the sentence to the proposed as it is ambiguous in relation to the investigator 'TMF'. We would also like to include TMF and investigator site file as a definitions in the glossary.	These essential records should be maintained in or referred to from repositories located at the investigator/institution or the sponsor.....

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Society for Clinical Research Sites	2719	2722	C.2.4		We have concerns over the draft requirement to include source records in the storage system(s) that "should provide for appropriate identification, version history, search and retrieval of trial records". As trials become more decentralized and necessitate the need for more non-investigator healthcare providers to perform routine care services, there is little to no control over how and where those independent parties manage their source documentation. We request that source documents be removed from this requirement.
Society for Clinical Research Sites	2724	2726	C.2.5		As this draft has removed who is responsible for what files and it is unrealistic for an investigator to be asked to assure the sponsor adheres to the sponsor's obligations, this section should be modified to read "The sponsor and investigator/institution should ensure that their respectively created essential records are collected and filed in a timely manner…"
Ludger Wienbrede	2726			In the sentence "The sponsor and investigator/institution should ensure that the essential records are collected and filed in a timely manner, including those required to be in place prior to the trial start, which can greatly assist in the successful management of a trial.", the element "which can greatly assist in the successful management of a trial" can and should be deleted without any loss of meaning. Rather, this enthusiastic relative clause appears like foreign matter in the ICH GCP guideline which, for good reasons, is technically oriented.	
Association for Clinical Data Management (ACDM)	2727	2730	C.2.6	Alteration may appear negative. I would guess "any change to the essential records should be traceable"	Alteration may appear negative. Revise to "any change to the essential records should be traceable"
EFPIA Consolidated Comments	2727	2730	C2.6	Should there also be a reference to making essential document directly accesible to monitors and auditors. Now it only mentions RA.	....and are directly accessible upon request by regulatory authorities, IRB/IEC or the sponsor's representatives, for example monitors and auditors.
Society for Clinical Research Sites	2727	2730	C.2.6		As similar to our suggestion in Appendix C.2.5, to clearly delineate the proper responsibility, this section should be modified to read "The sponsor and investigator/institution should retain their respectively created essential records in a way that ensures…"
Ludger Wienbrede	2729			"Alteration to the essential records should be traceable." This should be deleted. While traceabilty in eTMFs is easy to establish, in paper TMFs it is burdensome without generating considerable benefit. It only generates a playing field for auditors and inspectors who regard trial documentation as a crime scene.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
QA Clinical Studies, Charité - Universitätsmedizin Berlin	2732	2734	C.2.7	In the course of digitisation and national requirements, patient paper records are now being digitised (replacement scanning) in clinics. In this process, the paper original is replaced by a digital copy (certified copy). There are local regulatory opinions that worksheets, consents of a specific trial may not be substitute scanned. This approach contradicts complete digitalization and continues to cause cost-intensive parallel paper-based solutions. It would be great if the new R3 would allow replacement scanning regardless of the type of document. If done properly, then digitised records are more secure and have better integrity.	The original version of the essential record should be retained by the responsible party (sponsor or investigator). When a copy is used to permanently replace the original essential record, the copy should fulfil the requirements for certified copies regardless of the type of document (e.g. informed consent, worksheets).
Society for Clinical Research Sites	2732	2734	C.2.7		This section states "The original version of the essential record should be retained by the responsible party (sponsor or investigator)" however the Appendix does not delineate which party is the responsible party for which essential document. Without clarity, there will be confusion and unnecessary duplication of effort. Perhaps this was intended to mean the party from whom the essential record generated from (e.g. a protocol or IB would be the sponsor's responsibility where a signed informed consent document would be the investigator/Institution's responsibility).
Dr. C. Wilsher	2736	2742	C.2.8	The sponsor and service providers and investigators may need access depending upon the type of records and service porovided and to whom.	In order to fulfil their responsibilities in the conduct of the trial, the sponsor, service providers and investigator/institution may need access to or copies of one another's relevant essential records before, during and after the trial is completed
Fergus Sweeney	2740	2740	C.2.8	overinterpretation of data privacy requirements and imprecise wording on these are having a stifling effect on research and legitimate data use. It is important that data reported in clinical trials is ultimately traceable. There is no need for vague and uninterpretable phrases such as "..careful consideration.."	reword to "Records relating to trial participants should be shared in accordance with data protection prequirements and use participant codes." separate the unblinding point into a separate sentence as this has nothing to do with data privacy.
EFPIA Consolidated Comments	2745	2748	C2.9	Some essential records are also related to the product and are not specific to a trial (for example the investigator brochure) Typo/missing character – need a comma between "procedures" and "validation"	Certain essential records may not be specific to a trial but may be related to the investigational product, systems, facilities and processes involved in running multiple trials and retained outside the trial-specific repositories (e.g., standard operating procedures, validation records, master services agreements, investigator's brochure).
Medicines for Europe	2745	2748	C.2.9	It seems that a comma is missing between "procedures" and "validation".	Certain essential records may not be specific to a trial but may be related to the systems and processes involved in running multiple trials and retained outside the trial-specific repositories (e.g., standard operating procedures**,** validation records, master services agreements).
Good Clinical Trials Collaborative, on behalf of supporting organisations	2759	2759	C.3.1.d	Lacks emphasis on important trial procedures.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Ludger Wienbrede	2759			"Documents the conduct of relevant trial procedures": This should be deleted or supplemented with a note as it opens the opportunity for auditors and inspectors to classify any document as somenthing that documents the conduct of relevant trial procedures. A suggestion for a note: This must not be interpreted as "might document the conduct of relevant trial procedures" as this would make any document ever produced in a clinical trial to fall into this category. Records can only be regarded as documenting the conduct of relevant trial procedures if the sponsor or investigator could reasonably assume that this is the case when he records are produced. Records that document everyday and routine trial procedures are usually not records that document the conduct of relevant trial procedures.	
Good Clinical Trials Collaborative, on behalf of supporting organisations	2762	2764	C.3.1.f	Lacks emphasis on key aspects of compliance.	
Good Clinical Trials Collaborative, on behalf of supporting organisations	2768	2770	C.3.1.h	Should emphasise proportionality by qualifying that only critical non-trial-specific systems should be assessed.	
PPD	2768	2770	III. Annex I Appendix C. ESSENTIAL RECORDS FOR THE CONDUCT OF A CLINICAL TRIAL C.3 Essentiality of Trial Records	The meaning of trial-specific and non-trial-specific is not clear. This section is specific for "Essentiality of Trial Records" and criteria for determining essentiality. It seems to imply that validation documents are essential but only as they relate to trial-specific systems. Many of our systems are not trial-specific. Is validation not required for non-trial-specific systems?	Clarification required (e.g., examples) of both trial-specific and non-trial-specific systems. This area may also be covered through future training, proposed at the panel discussion during recent ICH E6 R3 conference.
Society for Clinical Research Sites	2768	2770	C.3.1 h		We request that the systems that need validation can be better defined in this line item, especially defining what is a “non-trial specific system”, when does a “non-trial specific system” need a fit-for-purpose assessment and a fit-for-purpose assessment looks like. For example, when would the use of Microsoft Excel be determined a “non-trial specific system” (and thus needing a fit-for-purpose assessment) as opposed to being used for general operational support (and not needing such a formal assessment)? Can an investigator rely on a sponsor’s fit-for-purpose assessment completed by the sponsor when the sponsor supplies the technology?
Good Clinical Trials Collaborative, on behalf of supporting organisations	2771	2772	C.3.1.i	Suggests that anything that is signed by the sponsor and/or investigator to confirm review or approval (of anything) is an essential document. There is no concept of how material such documents are to participant safety or reliability of results.	Lacks any proportionality.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Ludger Wienbrede	2776			"Documents ... that participants' informed consent was appropriately obtained and maintained": It is not clear how to document that consent was maintained. What is expected here?	
Fergus Sweeney	2781	2784	C.3.1.m	Current GCP E6 R2 only requires the CV of the investigator. To extend a requirement to other members of the investigator team is a major increase in documentation requirements and burdens without any added value. This is disproportionate and will lead to a race to the bottom in documenting CVs of everyone involved. A huge workload for no benefit. If ever the information is needed the sites will have records of their staff.	reword to apply only to the investigator CV as is currently the case
Centre for Human Drug Research	2785	2786	C.3	n) Porpose to specify what metadata, as this is open ended. Current wording may be interpreted that any minor detail of the trial is required as metadata to reconstruct the trial. Specifying could be by stating e.g. information described in protocol and local SOPs.	metadata (information described in protocol and local SOPs)
eClinical Forum	2785	2786	C.3.1	This section states "Contains the data as well as relevant metadata that would be needed to be able to reconstruct the trial".	Recommend additional clarity on any requirement that data/metadata may be needed to recommission inactive computerised systems, used during clinical trial conduct, but with due consideration of technical challenges associated with the aging and retirement of old infrastructure, platforms and applications over long periods of time, in order to meet Retention requirements.
Good Clinical Trials Collaborative, on behalf of supporting organisations	2785	2786	C.3.1.n	Suggests that it should be possible to "reconstruct" the trial – that is a meaningless and unachievable phrase that drives excessive documentation and distracts from what really matters to quality.	Instead it should emphasise the need to retain records that enable demonstration of key activities critical to patient rights, safety and wellbeing and the reliability of study results.
DARQA	2791	2792	C.3.1(p)	Line refers to documents that service providers are suitably qualified. A service provider qualification activity has not been described in the document.	
DARQA	2791	2792	C.3.1(p)	Laboratories are service providers for a study. The document does not describe how this particular service provider should be managed. It is our expectation that ICH GCP should contain more guidance regarding laboratory managment. Especially taking EMA Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples - EMA/INS/GCP/532137/2010, from GCP Inspectors Working Group, into consideration.	Add a paragraph to the document on how sample management should be done.
AFI	2795	2795	C.3.1.(r)	Documents sponsor oversight of investigator site selection	It would be advisable to have some further details about site selection process and related records to retain in TMF. If, as an example, it's necessary retraininig correspondence with non selected sites and reasons for their exclusion. In some countries, the process for site selection or exclusion is clearly traceable compared to other where it is not. It would be useful to have clarification from Regulatory Authorities concerning their expectations on this process.
GCP-unit, Copenhagen	2795	2798	C.3.1 (r)	Only bullet where "monitoring" is mentioned. Could wish a more clear sentence about monitoring activity	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Good Clinical Trials Collaborative, on behalf of supporting organisations	2799	2801	C.3.1.s	Does not include any indication of proprotionate practice. Procedures for management of analyses and generation of reports can first be judged by the output (are the analyses competent, are they reproducible, are they traceable to the underlying trial data) and secondly by some quite simple documentation (e.g. a statistical analysis plan that was finalised prior to unblinding of the study results).	
CARVALHO Carla	2805	2806	C.3.1.v	Documentation of the preparation of the product before administration at site level is recommended.	Provides information about the shipment, storage, packaging, preparation, dispensing, randomisation and blinding of the investigational product;
EFPIA Consolidated Comments	2805	2806	C.3.1(v)	Reference to "destruction" should be included in order to align with C.3.1(w) in this same section.	Provides information about the shipment, storage, packaging, dispensing, destruction or alternative disposition, randomisation and blinding of the investigational product;
Medicines for Europe	2813	2813	C.3.1 y	This seems to be only applicable to blinded trials.	Documents processes and activities relating to unblinding, if applicable;
Ludger Wienbrede	2814			It remains unclear why "pre-trial screening" activities need to be part of what constitutes essential clinical trial records. Therefore, the wording should be rephrased to read: "Documents the recruitment and consenting process of trial participants and their identity and chronological enrolment as appropriate;"	
Quotient Sciences	2814	2814	C.3.1 (z)	What is meant by 'pre-trial screening'?	Please clarify.
DGPharMed e. V. (Deutsche Gesellschaft für Pharmazeutische Medizin)	2817	2818	C.3	To categorise source records as part of the essential records of the investigator/ institution causes the need for deviant archiving obligations compared to clinical routine. That causes conflict of (original) record keeping regulatory requirements (Compare requirements of EU CTR 536/2014, Article 58) and is not accordable with clinical routine, especially in case of different archiving (periods). Certified copies provide no practicable solution to this point.	Do not categorise source records as part of the essential records to avoid conflicts with archieving requirements in routine clinical care
eClinical Forum	2821	2821	C.3.2	Industry has been working to establish standards for electronic trial master file (eTMF) content (C.v. CDISC TMF Reference model)	Recommend that the content of Section C.3 is revised to accommodate use of standard TMF models and the use of a distributed TMF model.
Dr. C. Wilsher	2822	2823	C. 3.2	" … are considered essential, except in justifiable and documented exceptional circumstances,…" There is no definition of "justifiable and documented exceptional circumstances". One is needed	Define "justifiable and documented exceptional circumstances"
AFI	2825	2829	C.3.3	The sentence "Table 2 lists potential trial records that when generated, would be considered essential by applying the criteria in section C.3.1 and should be retained." is not clear and could lead to different interpretation, especially regarding the terms "potential" and "when generated". It could be understood that the records listed in Table 2 are optional, meaning that they may or may not be generated on the basis of a sponsor or investigator choice.	Actually, as severals records listed in Table 2 are mandatory, such as for example insurance, the lack of these documents should represent an exception that must be justified.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA Consolidated Comments	2825	2829	C.3.3	Edit: The reference to 'nature' when discussing the presence of trial records should be reconsidered. Not sure of the intent of the phrase ' presence and nature' but perhaps 'presence and form' would be better phrasing.	their presence, format and extent is dependent on....
Ipsen	2825	2829	C.3.3	Suggestion: Move C.3.3 between Table 1 and 2 to improve readability. Since C.3.3 is specific for the use of Table 2 it may improve understanding to have the related information by closer to Table 2.	
EUCROF	2826	2828	C.3.3	"Table 2 lists potential trial records that when generated, would be considered essential by applying the criteria in section C.3.1 and should be retained." The word "potential" bears the risk that the respective records are not considered essential, although available. The rule should be very simple: if those records are available, they are essential.	Table 2 lists potential trial records that, when generated, would are be considered essential by applying the criteria in section C.3.1 and should be retained."
Sandoz AG, Switzerland	2826	2828	C.3.3.	The section explains about the "Potential essential records" and this would need further explanation. The current sentence says that these are essential when they are generated. When would such records not be generated? This is not clearly described.	"Table 2 lists potential trial records that, when generated, would be considered essential by applying the criteria in section 2828 C.3.1 and should be retained. This also means that if these records are not applicable for a clinical trial due to the specific set-up or study design, they are not considered essential. Vice versa, all documents listed in Table 1 need to be available for each trial, independent of set-up or study design."
Fergus Sweeney	2827	2827	C.3.3	the phrase "..potential trial records that when generated would be considered essential..". It is not because a record is generated that makes it essential. All sorts of records may be generated, and indeed this phrase implies that the best way to reduce filing burden is not to generate the document in the first place.	reword
Ludger Wienbrede	2828			"This is not an exhaustive list, and other trial records may also be considered essential by the sponsor or the investigator." It has been experienced in the past 20 years that auditors and inspectors have ever extended the list of essential records. This practice has highly increased the workload for handling records that are not actually relevant for showing how the relevant processes of a clinical trial were conducted. This workload reduced the capacities for handling the actually essential processes. The workload makes trials unnecessarily complex and expensive, without actually increasing patient safety and reliability of data. Therefore, the following should be added: If sponsors and investigators keep all the records in the following lists, auditors and inspectors must not require from them to keep additional records if the number of these additional records is more than 1 percent of the number of records that the sponsors and investigators already keep. Not every record that documents a process, a piece of communication, a shipment of documents is an essential record. The essentiality of a record should not be determined with the criterion that there might be circumstances whicht turn a records into an essential record. Although this could happen to any record, the approach to regard any record as essential would reduce capacities for handling relevant records and processes.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
AFI	2830	2832	C.3.3	Table 1 and 2	Compared to the previous ICH E6 (R2) revision, the R3 version lacks clarity on where the essential records listed in Tables 1 and 2 should be archived (e.g., exclusively at the site, at the sponsor, or at both). It might be helpful to add columns to the side of the documents indicating the place of archiving.
Catalent Pharma Solutions	2830	2830	Table 1	Please retain the "Purpose" of the essential record, and the location (Investigator/Institution & Sponsor), as they appear in ICH E6(R2) sections 8.2 to 8.4. These provide clarity.	See "Comments and rationale"
DGPharMed e. V. (Deutsche Gesellschaft für Pharmazeutische Medizin)	2830	2830	C.3 Table 1 1.10	To categorise source records as part of the essential records of the investigator/ institution causes the need for deviant archiving obligations compared to clinical routine. That causes conflict of (original) record keeping regulatory requirements (Compare requirements of EU CTR 536/2014, Article 58) and is not accordable with clinical routine, especially in case of different archiving (periods). Certified copies provide no practicable solution to this point.	Do not categorise source records as part of the essential records to avoid conflicts with archieving requirements in routine clinical care
Dr. C. Wilsher	2830	2831	C. Table 1; 1.3, 1.4	Should we consider deleting this requirement as one of the regions, party to ICH (i.e. the EU), is unable or unwilling to comply. In many sections of E6 R3 Step2, (E6 R3 line 2765, section C3.1.g; line 1051, section 3.8.2.b ; and line 2830 Table 1 items 1.3 & 1.4) there are requirements for "IRB/IEC Composition" etc, to be documented and provided in the sponsor's TMF. The European Medicines Agency position:- 9 February 2023 EMA/618888/2022 Questions and answers – Clinical Trials Information System (CTIS) and Clinical Trials Regulation (CTR) #4 :- "The CTR takes precedence over conflicting rules in guidelines, and that is applicable to GCP as well as other guidelines. Documents or data that are not described by the CTR shall not be requested or submitted based on recommendations in different guidelines. This is also applicable to the composition of the EthC. According to Article 9 of the CTR, it is up to the MS to assure the adequate composition of the EthC, and it is not required for the MS to provide the list of the EthC members involved with the assessment to the sponsor. "	
eClinical Forum	2830	2830	Table 1	This section states "data and relevant metadata (including documentation of data corrections) in the data acquisition tools" as essential documents. The section and C,3,1 raise questions on the possibilities of maintaining computerized systems in transactional state for long periods of time and on the need and practicalities if they should ever be able to be recommissioned.	Recommend revision to indicate concrete examples of the types of data/metadata that may be needed to recommission inactive computerised systems or in other similar investigations (on- and post-study audits or inspections)
EFPIA Consolidated Comments	2830	2831	Tables 1&2	We would propose to combine both tables to be examples of records which are essential. Concern regarding discussions with investigators on what records are essential. There could also be different ideas between sponsors.	Table header: Examples of records which are considered essential records based on the trial design, conduct and risk assessment.
EUCROF	2830	2831	Table 1, Table 2	It would be helpful to add which documents are kept exclusively by the investigator, e.g. signed ICF documents, by the sponsor (e.g., randomisation lists), or by both (i.e. similar to former revisions: ticklist).	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
German Pharmaceutical Industry Association (BPI)	2830		C.3	The information about the localization of the documents as given in ICH E6 R2 was very helpful and should remain	
GQMA	2830	2832	C.3.3.	In contrast to ICH E6 R2, Table 1 and Table 2 (Essential Records for all trials & potential essential records) do not contain columns anymore to specify the location of the documentation on Investigator or Sponsor side. These columns gave a clear guidance of filing location.	Re-introduce Investigator/Sponsor columns to the tables to outline the allocation of documents.
Ipsen	2830		Appendix C: Essential records	Recommendation to facilitate the reading to present the Essential Records to be filed at site or at sponsor level in the Table 1 and 2 (similiar to E2). This added level of clarity removes potential confusion at investigational sites regarding the documentation that must be maintained in the ISF.	
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	2830	2830	C.3 Table 1 - 1.4	In some countries this is not necessary as - according to national law - only IRBs/IECs that are organised and operate according to GCP are officially registered and allowed to approve/ to review a clinical trial.	Suggestion: "IRB/IEC composition, unless composition according to GCP is guaranteed/ regulated by national law."
Ollie Östlund	2830	2831	III.C.3.3 Table 1	Listing signed informed consent forms in Table 1 will cause regulators to demand that documentation of informed consent with signatures is used also in trials where signed forms are not applicable, such as "article 30" trials of the EU clinical trial regulation. Also see comments on the informed consent section.	Move signed informed consent forms to Table 2.
Quotient Sciences	2830	2832	Tables 1-2	These tables are inadequate. They are much less clear than those in Section 8 of GCP R2. We consider it essential to have absolute clarity on which documents, as a minimum, should be filed in the investigator and sponsor files and which should be filed before the trial can start. The lack of clarity will lead to different interpretations and requirements among our sponsors and queries from monitors, auditors and inspectors, increasing the burden on sponsors and investigators and increasing the likelihood of error. It may also provide scope for some sponsors to refuse to provide copies of certain documents to investigators. We need clear expectations to be set out for essential documents common to all trials, to ensure consistency and compliance. While we understand that some documents might not be relevant to all trials (e.g., unblinding procedures are not relevant to open trials), there should be clear expectations for filing of those documents for relevant trials.	Please revise Tables 1 and 2 to include columns to show which documents are expected to be filed in sponsor and investigator files and which documents must be filed before the trial can start.
Society for Clinical Research Sites	2830	2832	C. Table 1	We appreciate the shift from "essential documents" to "essential information" in the table. It's evident that in the current trial practices, much of this information exists electronically and is accessible to both sponsors and investigators/sites. However, it's crucial to address accountability to avoid continued duplication and excess storage of information between sponsors and investigators.	To effectively move away from excessive duplication, we suggest designating the sponsor as the main responsible party for record maintenance. Investigators could be responsible for a defined period based on local laws, unless they properly transfer custody of essential documents to the sponsor. This ensures information stays with the sponsor and prevents fragmentation across various investigator/sites, which might lack the necessary knowledge, resources, or motivation for proper record-keeping.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Swedish Monitors attending NORM meeting 2023	2830	2830	Table 1	As monitors, we miss the old table that in a clear way showed which documents should be available during the different phases of the study, and where these documents should be found. For example, the importance of informed consents ONLY being kept at site and not being sent to sponsor (ending up in the TMF) is not clear now. The new format can work if you are already familiar with the R2-revision and the excellent overview that the old table gave.	Reintroduce the old table showing which documents should be found where and during which part of the study (before site/study initiation, during, and after).
Swedish Monitors attending NORM meeting 2023	2830	2830	Table 1; 1.6	Not clear that the signed informed consents should ONLY be kept at site in the ISF, and never be sent to Sponsor (TMF).	Clarify that these documents should ONLY be found/kept on site, and never be sent to Sponsor!
Swedish Monitors attending NORM meeting 2023	2830	2830	Table 1; 1.7	Not clear that the participant identification code list should ONLY be kept at site in the ISF, and never be sent to Sponsor (TMF).	Clarify that these documents should ONLY be found/kept on site, and never be sent to Sponsor!
Swedish Monitors attending NORM meeting 2023	2830	2830	Table 1; 1.10	"Source records" - what is this? Where should it be kept? Need clarification, if by source records you mean medical records, nurse notes, printed ECGs, lablists, etc. Previously used source documents felt more intuitive, if possible to reintroduce.	Clarify what is meant by "source records". Give examples. Or maybe refer to the glossary (line 2292).
Swedish Monitors attending NORM meeting 2023	2830	2830	Table 1	New point: Source Data Location Agreement / Source Data Log. The requirement of a source data log is addressed in the EMA Q&A for GCP matters: https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp#b.-gcp-matters-section question B.3.	Add point: "Source Data Loction Agreement" / "Source Data Log".
The GCP Unit at Odense University Hospital, OPEN	2830	2830	Table 1, 1.4	This is the IRB/IEC responsibility and should not be mandatory for TMF or ISF	Delete 1.4
Catalent Pharma Solutions	2831	2831	Table 2	Please retain the "Purpose" of the essential record, and the location (Investigator/Institution & Sponsor), as they appear in ICH E6(R2) sections 8.2 to 8.4. These provide clarity.	See "Comments and rationale"
Centre for Human Drug Research	2831	2832	C.3	Wording "Potential essential documents". Suggest rephrasing to "potentially important documents". If worded as potential essential documents, it is likely that any listed document will be interpreted as being essential (taking a conservative interpretation).	Potentially important documents
EUCROF	2831	2831	Table 2	Move item 2.27 (treatment allocation and decoding documentation) after 2.24 (master randomisation list as it belongs to this category	
EUCROF	2831	2831	Table 2, 2.18	In some ICH regions in addition to the Certificate of Analysis the Certificate of Batch Release is required to confirm the compliance with GMP guidelines, thus this document should also be added to the list of clinical trial documentation that accompanies the shipment and must be filed.	
EUCROF	2831	2832	Table 2	Rename heading of Table 2 in: Table 2 - Essential Records, if generated	Table 2 - Essential Records, if generated

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
GQMA	2831	2832	C.3.3	The composition of Table 2 is prone to misunderstandings. Documents in Table 2 are defined as those which may or may not be generated depending on the type of trial. But some of the documens listed in Table 2 should be mandatory in every type of clinical trial. Example 1: There is no trial that does not collect data. Thus, a sample of the data aquisition tool (document 2.1) should always be needed. Example 2: Every trial must have a qualified investigator. Thus, proof of his qualification should always be needed (document 2.6). This list of examples is not exhaustive.	Re-evaluate the assignments of essential documents to Tables 1 and 2. Move those documents that should be essential for all trials but are currently listed in Table 2 to Table 1.
Quotient Sciences	2831	2832	Table 2	The purpose of Table 2 is unclear. Many of the documents in Table 2 would be generated in all trials - for example, under what circumstances would there not be informed consent material, trial-specific training records, or investigational product accountability records? There is no mention in section 2.2 of assent material or patient-facing questionnaires or diary cards.	Please merge Tables 1 and 2 into a single table. Where records might not be generated in some trials, add 'if applicable'. Please include assent material, patient-facing questionnaires and diary cards.
Society of Quality Assurance (SQA)	2831	2831	Table 2. Section 2.35	It appears that computer system validation documents that are not trial specific (e.g. platform level validation or system level validation such as one available from Cloud vendors or developed internally by sponsors) are not included as essential documents. Is that accurate? It would be advisable to obtain clarity around this through the suggested wording.	It would be advisable to obtain clarity around this. For example: "Documentation of platform-level CSV (e.g. validation report, change control, etc.) is not required to be maintained in trial records"
Swedish Monitors attending NORM meeting 2023	2831	2831	Table 2; 2.8	Delegation log/list: should absolutely be found in the Essential Records for All Trials. If you don't need to delegate personnel, the list will be short. Not having this among the essential records for all trials opens up for the thought that this is optional, even when you have to delegate personnel.	Move to Essential Records for All Trials!
Swedish Monitors attending NORM meeting 2023	2831	2831	Table 2; 2.9	Signature list: should absolutely be found in the Essential Records for All Trials. If you don't need to delegate personnel and collect their signature, the list will be short. Not having this among the essential records for all trials opens up for the thought that this is optional, even when you have to delegate personnel and need to keep track of their signatures (to verify on ICF for example).	Move to Essential Records for All Trials!
The GCP Unit at Aalborg and Aarhus University Hospital	2831	2831	Table 2	Potential Essential Records: Will that be interpreted in the same way by researchers and authorities?	
Fergus Sweeney	13120	1320	3.11.4.5.2.f	suggest separating into two concepts.	sepaarate as: f) clarifying the sponsor's protocol requirements for source records. And new g) Clarifying the site's location of source records
Medicines for Europe	-	-	Table 1, section 1.9	These documents may be not applicable to all the type of studies (e.g., short in time studies).	interim or annual reports to IRB/IEC and regulatory authority(ies), if applicable
Unicancer	201 - 202		8.3	add SMP	(e.g., statistical analysis plan, data management plan, safety management plan, monitoring plan)
Unicancer	502, 525		2.5.3. and 2.5.4	immediate hazard. How is "immediate hazard" defined?	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Unicancer	502, 525		2.5.3. and 2.5.4	2 paragraphs	§ 2.5.3 and 2.5.4 should be merged (same topic).
EFPIA Consolidated Comments			3.6.9	concern including performance metrics, as this could be a new industry	The sponsor should have access to relevant information (e.g., SOPs and update reports performance metrics) for selection and oversight of service providers.
EFPIA Consolidated Comments			3.12.2	Wording consistency with line 1163. Corrective action(s) may not be always possible. Proportionality of action is needed to ensure appropriateness of activitiy.	…corrective and/or preventive actions… The need to confirm the adequacy of those actions should be determined on a risk proportionate basis.
EFPIA Consolidated Comments			III.3.15.2(e)	in some cases modeling can be used so recommend including more flexible language to future proof the requirements for the formulation information vary across regions	If significant formulation changes are made in the investigational product(s) (including active control(s) and placebo, if applicable) during the course of clinical development, the results of any additional studies or modeling and simulation of the formulated product(s) (e.g., stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use, in accordance with applicable regulatory requirements, of the new formulation in clinical trials.
German Pharmaceutical Industry Association (BPI)				In addition, a short explanation would be helpful as to whether the previous versions of the R3 (R1,R2) are still valid at all or not.	
German Pharmaceutical Industry Association (BPI)				Based on the experience with the R2 and the Addendum, it would be helpful to supplement the topics with examples of use cases or similar. For the first few years after the R2 became valid, there was clearly visible uncertainty among the stakeholders of clinical research as to how and in what way the specifications were to be implemented in practice. They waited a long time until sufficient cases from practice became known and then began, mostly hesitantly, with their own implementation. In order to prevent this delay in the future and to eliminate uncertainty from the outset when implementing R3, appropriate examples would be useful.	