Appendix: Detailed comments and suggested changes (with reasoning) for ICH E6 (R3) draft

1. Document Structure and Layout

The layout of Introduction, Principles and Annexes works well. However, the following modifications would help clarity:

a. **Start Annex 1 on a new page**. Sections I and II each start on a new page, 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.

b. **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).

c. **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.

d. **Add introductory text 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]).

2. Improvements to and Emphasis on the Principles

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).

a. Principles of ICH GCP (lines 35-77): 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.

Lines 60-62: The flow of the sentence is a little awkward. Suggest amend as follows:

> *"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."*

b. **Regrouping the Principles:** The 11 Principles appear in a somewhat haphazard order 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:

- **Clinical Trials are Ethical**

Principle 1 – *Rights and Well-being*

Principle 2 – *Informed, Voluntary Consent*

Principle 3 – *IRB/IEC*

- **Clinical Trials are Informative and Relevant**

  Principle 4 – *Scientifically Sound*

  Principle 9 – *Generate Reliable Results*

- **Clinical Trials are Appropriate for their Context**

  Principle 7 – *Risk Proportionate*

- **Clinical Trials are well designed and conducted, by qualified people**

  Principle 6 – *Quality*

  Principle 8 – *Protocol*

  Principle 5 – *Qualifications*

  Principle 10 – *Roles and Responsibilities*

- **Clinical Trials meet Good Manufacturing Practice (GMP) standards**

  Principle 11 - GMP

c. **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.*"

d. **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 1-265) and the applicable laws. [Note: For comparison, all FDA guidance documents currently include such a statement.]

e. **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**). This should be modified to "guideline" to be consistent with the document title ("ICH Harmonised Guideline") and encourage thoughtful implementation in line with the principles.

f. **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.)

g. **Modifications to Principles:**

Principle 1:

- **Line 79:** change "consistent with GCP" to "consistent with the Principles of GCP" to align with objectives of the guideline.
- **Point 1.3 (Lines 90-91):** 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 being given an investigational treatment or comparator).

Principle 4:

- **Line 141:** 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 flimsy 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.

Principle 5:

- **Point 5.1 (Line 159):** 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.

Principle 6:

- **Point 6.2 (Line 173):** 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.
- **Point 6.3 (Line 175):** change "compliance with GCP" to "compliance with the Principles of GCP" to align with the objectives of the guideline.
- **Point 6.3 (Line 176):** change from "to prevent recurrence" to "to address the consequences (e.g. to participant safety) and prevent recurrence"

Principle 9:

- **Point 9.2 (lines 209-213) and point 9.4 (lines 217-219)** are repetitive. One or other could be deleted with no loss of meaning.
- **Point 9.5 (lines 223-224):** 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.
- **Point 9.6 (lines 227-228):** 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.

Principle 10:

- **Lines 233-234:** 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.
- **Points 10.1 and 10.2 (lines 236-243):** 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). Hence:
- **Point 10.1 (Lines 237-238):** Delete "but they retain overall responsibility for their respective activities".
- **Point 10.2 (Lines 242-243):** Delete "resides with the sponsor or investigator, respectively" and replace with "organisation (sponsor or investigator) which has agreed to be responsible for arranging the service or activity"

Principle 11:

- **Lines 250:** 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"
- **Points 11.1-11.6 (lines 252-264):** 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.

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 5½ 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.

a. **Section 4 (lines 1813-2029):** This new section is helpful and well written. It encourages thoughtful and proportionate application to individual circumstances.

b. **Section 4 (lines 1813-2029):** 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]).

c. **Remove excessive details in Investigator and Sponsor sections:** Given the presence of this new section, much of the text on Records in the Investigator section (**Point 2.12; lines 831-911**) and Sponsor section (**lines 1590-1785**) is over-restrictive and/or lacks proportionality. Examples of such issues are shown below:
    - **Investigator section. Point 2.12.3 (lines 845-850):** "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.

- **Investigator section. Point 2.12.5 (lines 856-860):** "The investigator should review and endorse the reported data at milestones agreed upon with the sponsor (e.g. interim analysis)." Again, 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.
- **Sponsor section. Point 3.16.1.h (lines 1620-1622):** 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 <u>deleted</u> in entirety.
- **Sponsor section. Point 3.16.1.j (lines 1629-1636):** 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 *<u>(</u>*for example, central laboratory data… ePRO data*<u>) if they</u>* ~~*that are*~~ are necessary to enable investigators to make decisions…"
- **Sponsor section. Point 3.16.1.k (lines 1638-1639):** 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.

- **Sponsor section. Point 3.16.1.l (lines 1641-1642):** 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.
- **Sponsor section. Point 3.16.1.m (lines 1648-1649):** Delete. Investigator endorsement of data does not necessarily add quality but definitely adds work – there are other ways to address quality as described earlier.
- **Sponsor section. Point 3.16.1.p (lines 1656-1659):** 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.
- **Sponsor section. Point 3.16.1.q (line 1665):** Data changes should not necessarily need to be authorised by the investigator (see earlier points). 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".
- **Sponsor section. Point 3.16.1.v (lines 1716-1722):** 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 requirement.
- **Sponsor section. Point 3.16.1.w.i. (line 1692):** modify to "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.
- **Sponsor section. Point 3.16.1.w.ii. (lines 1705-1707):** 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!

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.

a. **Point C.1.3 (lines 2694-2703):** 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.*"[1]

b. **Points C.1 – C3.3 (lines 2685-2829):** There is a lack of proportionality, lack of flexibility, and an undue focus on documentation rather than quality. This is in stark contrast to the recommendations of the G7 (see above).

c. As it stands **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. For example:
   - **Point C.3.1.d (line 2759)** could include focus on *important* trial procedures.
   - **Point C.3.1.f (lines 2762-2764)** could focus on documentation the *key aspects* of compliance.
   - **Point C.3.1.h (lines 2768-2770)** could require that *critical* on-trial-specific systems have been assessed.
   - **Point C.3.1.i (lines 2771-2772)** 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).
   - **Point C.3.1.n (lines 2785-2786)** suggests that it should be possible to "reconstruct" the trial – that is an 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.
   - **Point C.3.1.s (lines 2799-2801)** lacks any sense of proportionality – 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).

d. **Tables 1 – 3** are, by contrast with the preceding text, much more considered and helpful. A couple of amendments would further help encourage proportionality:
   - **Table 2 row 2.8:** Modify to "documentation of delegation of key activities…2

[1] https://www.g7uk.org/g7-discuss-100-days-mission-to-improve-readiness-for-future-pandemics/

- **Table 2 row 2.32**: Modify to "documentation of ~~relevant~~ key communications and meetings"

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 outside their control.

a. **Principle 10 (lines 233-245):** 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, but 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.

b. **Investigator Section**
   - **Point 2.3.1 (lines 457-464):** The current draft text should be reworded. 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 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.
   - **Point 2.3.2 (line 468):** change to "adequately informed about *relevant aspects of* the protocol…". 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.)
   - **Point 2.10.1 (lines 796-797):** "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.

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c. **Sponsor Section**

- **Point 3.6.2 (lines 966-967):** Change from "Agreements should be updated when necessary to reflect changes *in the activities delegated*" to "…*in the activities and responsibilities*."
- **Point 3.6.3.d (lines 984):** 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.
- **Point 3.6.6 (line 996):** 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).

6. **Other issues** – a range of corrections and clarifications that will help improve the document and the way that it is interpreted and implemented

a. Blinding & 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.

Examples where improvements could be made include:

- **Investigator section. Point 2.11 (line 826):** add after "in accordance with the protocol *since inappropriate unblinding can damage the reliability of the trial results."*
- **Sponsor section. Point 3.9.8 (lines 1095-1096):** *amend "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."*
- **Sponsor section. Point 3.6.2.e (lines 1758-1762):** 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)."

- **Data governance section. Point 4.1.3. (line 1849):** 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.)

b. 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.

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.

The guideline should emphasise that individual case reports, where there is little reason to believe the intervention caused the event, are generally uninformative when reported as single events (i.e., without a comparison of the incidence of the event in treated and untreated subjects), and they do not contribute meaningfully to the developing safety profile of an intervention.

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.

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.

The following edits to glossary definitions will aid rational and appropriate interpretation:

- **Definition of Adverse Drug Reaction (Glossary. lines 2034-2049):**
  - **Insert (between lines 2034 and 2035)** (i.e. 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*"
  - **Delete from lines 2041-2043:** "*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.

- **Definition of Suspected Unexpected Serious Adverse Reaction (SUSAR) (Glossary. lines 2057-2068):**
    - Amend "Suspected" and its definition to "Suspected reaction: There is a reasonable ~~possibility~~ probability that the drug caused the adverse ~~reaction~~ event."

c. Monitoring (Sponsor section. Point 3.11.4. Lines 1205-1228).

- **Line 1210:** 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.
- **Lines 1215-1216:** 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*."

d. **Minor improvements**

- **Line 517:** insertion "*implement appropriate measures to address the impact (e.g. on participant safety) and prevent a recurrence…"*
- **Line 562-564:** 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."*
- **Lines 1373:** insertion "*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)
- **Line 1357:** modification "*documented* ~~adequately~~ *in accordance with the sponsor requirements.*" (Note this is the same concluding text as in the point (vi) (lines 1360-1361).
- **Lines 1420-1421:** 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).

- **Lines 1448-1449:** 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)"*
- **Line 2126:** 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."
- **Line 2157:** 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.
- **Lines 2279-2280:** Addition "The RSI is included in the Investigator's Brochure or the Summary of Product Characteristics." Since some products may have a marketing authorisation already.