31.8.2016

Submission of comments on **European Commission – Guideline on Risk proportionate approaches in clinical trials (reference)** – Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use

Comments from:

Name of organisation or individual
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1. General comments

General comment (if any)
EFPIA welcomes this document. Overall, this document is generally useful in outlining where risk-adapted approaches can be taken. It would benefit from reference to work done through the Clinical Trials Transformation Initiative on clinical quality-by-design, in which EMA has been closely engaged and Fergus Sweeney. The CTTI work includes a publication, recommendations (with EMA among the authors), and a toolkit that may have value in organisations seeking to more practically implement the concepts outlined here. (See https://www.ctti-clinicaltrials.org/projects/trial-quality). The risk-based Quality Management Section (4.1) could also be improved, to better steer organisations in applying these concepts in practice. For example, line 181-182 indicates that, "for each risk identified, an appropriate mitigation strategy (for e.g. monitoring) should be implemented or a determination that the risk can be accepted." This emphasis on accepting risks is encouraging. However, the section as a whole may be read as suggesting that if you don't accept a risk, you should add operational tasks (monitoring, training, SOPs, the list goes on) to manage the risk, rather than looking for opportunities to eliminate a risk through trial or process design. Again, reference to the CTTI work would be of benefit, including the recommendation that organisations should: "Focus effort on activities that are essential to the credibility of the study outcomes. Rigorously evaluate study design to verify that planned activities and data collection are essential. Streamline trial design wherever feasible. Similarly, deploy resources to identify and prevent or control errors that matter in the study; in other words, determine those study activities that are essential to ensure the safety of trial participants and the credibility of key study results. Consider whether nonessential activities may be eliminated from the study to simplify conduct, improve trial efficiency, and target resources to the most critical areas." It is important to make clear that this guidance refers to interventional clinical trials. Suggestion to reiterate the definition of "Clinical Trial" vs. "Clinical Study" from Regulation 536/2014 to level set and reduce possibility of misinterpretation of the scope of this guideline.
Comment 1: The judgement on the implementation of risk-proportionate approaches will always lay with the individual reviewer, for example the definition of low intervention CT's in section 3. A lot of what is described is open to subjective interpretation. We understand that the sponsor is responsible for arguing the case and justifying the classification. Specifically in case of disagreement, the regulatory reviewer should substantiate his argumentation with likewise evidence. Hierarchy of evidence could be clearly defined to ensure that benefit/risk assessments from health authorities in and outside the EU carry more weight than scientific publications. An example of this would be around the definition of low intervention CT's in section 3. A lot of what is described is open to subjective interpretation even down to the use of the phrase 'in accordance with the terms of the MA…'. That could mean following the labelling or something more in keeping with but not necessarily specified within the label. This could then be used as an example to show what types of monitoring approach might be appropriate for this trial; what type of language could be

General comment (if any)
included in the safety section of the protocol to justify a risk-adapted approach to safety reporting; what types of IMP accountability and accountability records would be appropriate; what risk proportionate approaches could be used for the content of the TMF. In general, specific practical examples will help sponsors to better understand how the guidance should be implemented.
Comment 2: As said in the scope of this "Risk proportionate approaches in clinical trials" guideline, "The present recommendations are built on the reflection paper prepared in 2013 by the EMA. There are some relevant discrepancies when referring to the Risk Assessment, as referenced in the reflection paper, which is split into Risk Identification and Risk Evaluation. Wording alignment with the reflection paper as well as with the ICH E6(R2) Integrated addendum: Good Clinical Practice would be beneficial for consistency and comprehension. The first three comments in table 2 suggest specific updates. "Monitoring strategy plan" and "monitoring plan" seems to be used interchangeably throughout the document, please use consistent terminology to avoid confusion.
Comment 3 It should be stated that there is a commitment from the beginning – i.e., from the CTA assessment – that the proposed risk identification and mitigation approach once endorsed would not be questioned at the time of any regulatory inspections unless there is a change in the benefit risk assessment (section 'Risk review', lines 226 to 233). The guidance should be clear to the inspectors. We understand that the accepted "risk identification and mitigation approach" from the CTA review is carried through for any regulatory inspection. . The guidance should be clear to the inspectors.
Comment 4: In general a factor that should be considered more in the document is whether or not a trial involves withholding, withdrawal or adjustment of another effective therapy. This would not preclude a risk-based approach to, for example, IMPD provision but such a situation should involve well monitored collection of AE, lack of efficacy and/or worsening of underlying condition. The use of a DSMB is referenced and this would be important for monitoring this situation Please add considerations in the document whether or not a trial involves withholding, withdrawal or adjustment of another effective therapy. This would not preclude a risk-based approach to, for example, IMPD provision but such a situation should involve well monitored collection of AE, lack of efficacy and/or worsening of underlying condition. Use of a DSMB would be important for monitoring this situation in a clinical trial.

General comment (if any)
Comment 5: It is suggested that the introduction includes the following clarification: **"'Interventional' used in connection with clinical trials speaks to "intervention with usual practice". 'Interventions' are a key part of usual practice be it diagnosing or treating patients. Usual practice is regulated by the health care legislation in the individual member states. Improvement of care is part of the health care obligations and may be part of usual practice (including service evaluation, clinical audit and surveillance) or be executed as research."** *Justification: "Risk proportionate approaches" speaks to the difference in level of risk in first in man clinical trials all the way to usual practice.* *Understanding when it is experiments with medicine and when it is usual practice is key to implementing a "Risk proportionate approach".* *In the community of people working with clinical studies, the word "interventional" is generally understood as an intervention imposed on a patient. That can be a blood sample or a questionnaire. At the same time usual (clinical) practice is nothing but interventions.* *ENCEPP did in 2010 address this in a document (http://www.encepp.eu/publications/documents/4.1_NIS_TFsummary.pdf).* *Outside EU the word "experimental" is used instead of "interventional". The word "experimental" is however not much better as usual practice may include randomisation (but for medicine (http://www.hra.nhs.uk/documents/2016/06/defining-research.pdf)).* *(http://www.rdforum.nhs.uk/content/wp-content/uploads/2014/05/categorising_projects_guidance2006.pdf)*
Comment 6: • In agreement with comment no. 1: there is ambiguity around what constitutes a low-intervention clinical trial (LICT) – in general, further clarification is required to remove ambiguity around definition of LICT. • When it comes to assessing whether the use of the IMP is evidence-based in any MS and the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any MS, local differences in normal clinical practice, lack of published treatment guidelines in some MS, etc., might hamper a clear determination. Additional guidance to aid this assessment would be helpful. • Terms and definitions should be used in line with the ICH E6 addendum (revised ICH E6 anticipated 3Q16). • The distinction between guidance specific for low-interventional trials (as defined in Article 2(3) of the Regulation) and general recommendations on risk management, which can be applied to any clinical trial, are somewhat blurred within the document. We suggest a section on general recommendations applicable to all clinical trials. Aspects which apply to low-interventional trials (as defined in the Regulation) only should be

General comment (if any)
separated more clearly from general recommendations on risk management (see comment on Lines 85-88 and 156). •
Comment 7: Section 4.2 • In view of the FDA guidance document* on this topic, alignment of the wording and approach between the EU and FDA document, as far as possible, would be helpful. * FDA guidance "Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Post-approval Clinical Investigations Guidance for Industry - U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) February 2016 Clinical/Medical". • What are the expectations for Aggregate Reports: For DSURs and possibly PSURs, will there be a need to describe certain studies are subject to targeted safety data collection? Could this be clarified in the document? Please clarify what is meant by: 'risk assessment and mitigation plan that is produced in conjunction with the protocol development". Is this meant to represent the company core risk management plan? We interpret it to be a different/new document that is affixed to a protocol, but please clarify. Guidance on expectations for such a plan would be helpful. • Please clarify the expectation for: "Detailed collection and reporting of adverse events (serious and non-serious) is particularly important where data about the safety profile of an IMP from available pre-clinical and clinical trials is scarce." What exactly is needed/expected and is this any different than what we do for a high intervention study?
Comment 8: Request for a definition to be included for what constitutes an "important medical risk" (identified or potential). Most trial participants will be prepared for non-serious ADRs (headache, nausea, increased sweating, etc.) but managing blood dyscrasias, cardiac arrhythmias and the like, even in high morbidity/mortality disease states, clearly requires a proportionate approach.
Comment 9: It would be helpful to provide additional guidance on risk appropriate practices in the case of outsourcing, and the level of oversight required from a sponsor perspective, on risk based approaches in clinical trials when conducted by subcontractors.
Comment 10: It would be helpful to understand if and how the adoption of risk proportionate approaches in clinical trials will affect the acceptability of such trials in other jurisdictions. For example, with regard to studies conducted under a US IND, has there been any discussion between EU regulators and the FDA?

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 60	*Comment:* What is meant by the "status and nature of the investigational medicinal product"? Is this the administration method, the experience with the product, etc.?
Line 61	*Comment:* What is meant by the "level of difference"? Consider removing "level of"
Line 62	*Comment:* It would be helpful to define or provide a reference to explain what is meant by "normal clinical practice", as there may be differing interpretations of the term.
Line 82	*Comment*: What is meant by "more" explanations?
Line 85-88	Comment: Perhaps this passage + table would better fit in section 3 (e.g. after line 156, where the content of the CTA for low interventional CT is described)
Lines 89-90	*Comment 1:* Risk from not using/stopping another therapy should be considered. *Comment 2:* Risk can change over the life cycle of a study. For example, a vaccine study with 1-3 vaccinations at study start and a few years follow-up has a lower risk over time than a study where the study drug is dispensed throughout the whole study. The risk to subject safety in a clinical trial mainly stems from ~~two~~ **several** sources, **including**: the IMP, **not using/stopping alternate therapies**, and the trial procedures. **The risk to subject safety can change significantly over the life cycle of a study and the study type should follow this change accordingly. A phase III clinical trial normally has a reasonable high risk. When the IMP has been submitted for approval on the indication studied in the phase III trial, the risk of the continued treatment of the patients with the IMP decreases to become equal to usual practice risk when the product is approved. Extension of an**

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	interventional clinical trial could be based on secondary, usual practice data. When a study is based on secondary data from usual practice, the study type should reflect that."
Line 91	*Comment:* Mention safety reporting as well. *Proposed Change:* The Regulation provides for less stringent rules or adaptations with regards to monitoring, **safety reporting,** traceability of the IMP and content of the TMF, to those clinical trials which pose only a minimal additional risk to subject safety (as defined in Article 2(3) of the Regulation) compared to normal clinical practice.
Line 96	*Comment:* "Some risk adaptations apply in particular to low intervention clinical trials, however, depending on the circumstances, risk adaptations may be applied to any type of clinical trial" *Proposed change (if any):* "Some risk adaptations apply in particular to low intervention clinical trials, however, depending on the circumstances, risk adaptations may be applied to ~~any type of clinical trial~~ **to different stages of a clinical trial (e.g., risks may be lower during long-term follow-up stages)"**.
Lines 99-100	*Comment:* It is clear from the definition in the Regulation that the definition of low intervention only applies to products with a marketing authorisation. It is proposed to amend the wording in the EC guideline to remove any ambiguity in this regard. *Proposed change:* The determination of whether a clinical trial is low intervention or not, is ~~**largely**~~ based on the marketing authorisation status of the IMP and its intended use in the trial. **Trials with IMP which do not have a marketing authorisation cannot be considered low intervention.**
Lines 107-108	Comment; This sentence is difficult to comprehend with its three negatives. *Proposed change:*

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	Equally, if a trial is not low intervention, ~~this does not mean that~~ risk proportionate procedures can~~not~~ ~~or~~ **and** should ~~not~~ be applied.
Lines 109-127	This guideline is quite valuable especially for products which have a large safety exposure and use within the marketing authorization. However, there is a risk that the low interventional route could be used inappropriately. Therefore, it should be stressed to have a proper scientific review of these to ensure the study is being done for a valid scientific reason.
Lines 110-111	*Comment 1*: The draft guidance highlights that "some clinical trials pose only a minimal additional risk to subject safety compared to normal clinical practice and within this scenario these trials can be risk adapted". The starting premise for this statement is that the studies under discussion are by default interventional clinical trials It would be helpful to distinguish clearly in the guideline between 'low intervention clinical trials' and studies conducted in the real world setting which although inherently observational in nature, may include elements of natural randomisation (through freedom to prescribe different interventions by clinicians) and/or data gathering through use of questionnaires. Such differentiation in the guidance will avoid such observational studies being mistakenly classified as "low intervention clinical trials". *Comment 2*: This statement refers to trials that may be "risk adapted". Is this intended to mean that "risk proportionate procedures may be applied", rather than "risk adapted"? The trial itself is not risk adapted. *Proposed Change:* Some clinical trials pose only a minimal additional risk to subject safety compared to normal clinical practice and within this scenario these trials can be risk adapted. **Studies which are observational in nature, do not influence the prescribing practice of clinicians, but which may collect additional information through mechanisms such as questionnaires are non-interventional studies and hence outside the definition of low intervention clinical trial and outside the scope of the Clinical Trial Regulation. An additional requirement for a trial being considered non-interventional is also not withholding, withdrawing or adjusting an effective treatment in order for the patient to qualify for the trial.**
Lines 124-127	*Comment 1:* The list of types of published scientific evidence sources should not be a cumulative list implying all are required, rather a list of types of data that can be selected from to provide evidence. *Comment 2*: In line with OECD's recommendations, add "established medical practice" to the explanation that expands on the conditions to be fulfilled to qualify as a low intervention clinical trial.

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	Proposed change: The published scientific evidence supporting the safety and efficacy of an IMP which is not used in accordance with the terms of the marketing authorisation could include evidence based treatment guidelines**,** ~~**and**~~ health technology assessment reports, ~~**and**~~ clinical trial data published in scientific peer-reviewed journals, **established medical practice** or other appropriate evidence.
4.1 Risk based quality management Lines 158-242	*Comment 1*: A diagram to reflect the cyclical nature of a quality risk management system would aid interpretation such as figure 1, EMA/269011/2013. *Comment 2:* It is not clear if the requirements refer to the submission of the Risk Management Plan (EU) or REMS (US) – currently there is no mechanism to submit this information. It is assumed that there is no specific requirement to submit this document as justification for the assessment of whether a trial is considered low interventional clinical trial, but this should be clarified. *Comment 3*: In "Risk proportionate approaches in clinical trials" please comment on the situations where pure observational studies become interventional solely due to randomisation to equipoise treatment" *Proposed change 1*: We suggest adding a reference to the "Reflection paper on risk based quality management in clinical trial" figure 1 in section 4.1 Risk based quality management. *Proposed Change 2:* "PAES which include randomisation to equipoise treatments normally have a risk similar to usual practice, and the randomisation is predominately included in the design to avoid bias/confounding. Such studies should move quickly from low-interventional to non-interventional to enable usual practice given the design of the study poses similar risk to the patients as usual practice. The obligations of providing free medicine, insurance etc. should similarly be adjusted to prevent bias/confounding."
Line 160	*Comment 1 :* Suggest this is clarified to enhance guidance; for example, programme and site site levels are missing..Addition

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	Proposed change (if any): "Risks in clinical trials should be considered **across multiple levels such as** the system, **programme,** trial **and site levels** (e.g. facilities, standard operating procedures, **clinical trial processes**, computerized systems)"
Line 166	*Comment:* Reword to reflect PV guidance *Proposed change (if any):* "..**on subject safety and well-being**, on data integrity.."
Line 171	*Comment:* Addition of risk mitigation as this seems to be missing. *Proposed change (if any):* Change to "risk control **and mitigation"**
Lines 175-177	*Comment:* Include a definition of Risk Assessment *Proposed change*: Risk **Assessment** ~~identification and evaluation~~ **Risk Assessment is the process of gathering information for Risk identification and establishing priorities for Risk evaluation.** ~~Risk identification and evaluation should be conducted, as this~~ **The systematic identification of risks and establishing which risk matter** is key to managing and mitigating risks.
Lines 181 - 182	*Comment:*

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	There seems to be a strong focus on monitoring as opposed to using new ways of risk management, like data surveillance. *Proposed change*: Would recommend adding further examples to line 181, like "(e.g. **on-site or centralized** monitoring, **medical data review, etc.**)"
Lines 183 - 188	*Comment*: As explained in section 4.2 Establishing priorities for risk evaluation (page 10/15) of the "Reflection paper on risk based quality management in clinical trials" it is "first necessary to identify the risks that really matter and to establish priorities." Line 183 says "Risks should be considered in proportion to its potential impact and the likelihood of its occurrence" Similarly, establishing a process or method for categorizing or scoring the risks should help sponsors to adequately adapt the mitigation activities and actions to the risks from a qualitative but also quantitative perspective. In addition, study feasibility is a very important risk determinant. If the study is very different from routine medical practice, this is an important risk for participants and site personnel. *Proposed change below (add to line 188)*: "To **ensure proportional mitigation activities or actions for the identified risks, sponsors might build a categorization or scoring process or system which should consider the risk potential impact, (with two objectives, determining the potential causes of that risk for mitigation purposes and determining our ability to detect the risk if it does definitively occur) for each risk."**
Line 187	
Line 189	*Comment:* The risk assessment should allow the implementation of risk mitigation / risk avoidance strategies into the protocol, and it might be too late if it would just be reviewed for potential risks briefly before protocol finalization. *Proposed change:* Recommend to change this to (changed text in italics) "The risk evaluation should commence ~~prior to the finalisation of the protocol~~ **during the protocol design phase** as the risk assessment and mitigation may influence ...".

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Line 189-191	*Comment 1:* : As part of the risk based quality management system for clinical trials proposed in section 3 Risk based quality management of the "Reflection paper on risk based quality management in clinical trials", there's an "Information gathering" process that might include incorporating already available information from previous risk assessments. Applying a knowledge management approach, risk assessments should always incorporate, if available, knowledge from previous risks assessments for trials with that same compound or pathology or from previous similar trials (similar trial design or data collection methods…etc) as well as knowledge from previous issues managements (considering these last ones can be reflective of risks which have been realized) for ensuring all potential risks are considered for each trial (including those identified for previous trials) *Comment 2*: Line 189 clarifying addition to account for both identification and evaluation. *Proposed change:* The risk **assessment** should commence prior **during the protocol design phase**l as the risk assessment and mitigation may influence the trial design and procedures, as well as the financing or funding of the clinical trial or development project. **Whenever possible, a knowledge management approach should be applied by sponsors, incorporating available knowledge from previous risks evaluations and issues managements for similar trials or those conducted for the same pathology or compound.**
Lines 192-199	*Comment:* This section refers to activities that can be considered part of "Risk control". Consider moving these lines to the "Risk Control" section (beginning line 205).
Lines 192-193	
Line 196	*Comment:* Refer to general comment in table 1. *Proposed change:* ''For example, as part of the risk ~~identification and risk~~ assessment of the safety reporting process described in the protocol.''

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Line 203-204	*Comment:* For risk assessment in multi-member state trials, we suggest a a common template is developed to ensure common criteria and understanding. It is suggested that such a template could be used for all trials to ensure that study type selected for the individual trial is consistently applied under the CT regulation. It is suggested also to include risk assessment for trials with longer duration to identify potential time points where the risk is substantially changed. This could for example be a phase III registration trial with a 10 year follow-up/extension based on secondary data.
Lines 203 – 204	*Comment* Both references seem to relate to authority related recommendations. It would be helpful to refer to additional initiatives such as CTTI or TransCelerate in the references section. *Proposed change (if any):* Consider adding references to initiatives like CTTI, TransCelerate, for example, **http://www.transceleratebiopharmainc.com/wp-content/uploads/2016/01/TransCelerate-RBM-Position-Paper-FINAL-30MAY2013.pdf.pdf http://www.transceleratebiopharmainc.com/wp-content/uploads/2013/10/2_RACT_20140411.xlsx https://www.ctti-clinicaltrials.org/projects/trial-quality**
Line 205	*Comment:* Clarify scope *Proposed change (if any):* "Risk Control **and Mitigation**"
Lines 207-208	*Comment*: To ensure the mitigations are properly managed and effectively implemented, any risk mitigation should have documented accountability even if that accountability falls outside of the organization. *Proposed change below (add to line 207-208):*

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	"The purpose of risk control is to reduce the risk to an acceptable level or determine that the risk can be accepted. The main components of risk control are risk mitigation, adaptations and risk acceptance actions**, including accountability.".**"
Line 209	*Comment:* Consider stating that a risk-based approach allows efficient assignment of the available resources efficiently, i.e., where they are most needed. If more risks are identified, more resources should be allocated. Resources would also be reallocated based on confirmation of risk.
Line 211-226	*Comment:* It would be helpful to provide clarification and examples on where and how, investigators will be part of the risk assessment/identification process. For example, investigators could be involved with the conduct of feasibility assessment.
Line 226	*Comment 1:* Risk review is based upon defining risk indicators and thresholds. *Comment 2:* "Risk review": since an ongoing reassessment of the risks should be performed, we propose that clarification is added that this could potentially lead to a re-qualification of a low-interventional trial into a non-low interventional trial. *Proposed change;* The implementation, effectiveness and need for mitigations should be periodically reviewed. **It is possible during the assessment of a substantial modification that a low-interventional clinical trial will become a non-low-interventional trial after its substantial modification.**
Lines 239-242	*Comment:*

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	The guidance indicates that implemented risk adaptations need to be reported in the clinical study report andit is unclear what is meant by "implemented risk adaptations." . The reference to ICH guidelines E3- Structure and Content of Clinical Study Reports and E6- Good Clinical Practice should be clarified, as it is unclear from these guidelines where and how risk adaptations should be described in the CSR. New RACT Risk assessment processes now in place are extensive including mitigation planning. While it is part of permanent study files, it is detailed and too much information to include in a CSR. In addition, the guidance on lines 239-242 appears to be incomplete: we would expect the entire risk documentation (i.e. risks identification, evaluation, control, review, communication & reporting) to be part of the TMF.
Line 243	*Comment:* Addition of new section Proposed change (if any): "**Risk Assessment:** **Risk Assessment provides oversight and accountability and informs decision making across the risk based quality management system"**
Lines 244-324	*Comment*: It should be stressed that reducing the adverse event reporting – should be a relatively rare exception, especially for new products. The guidance should include recommendations how to handle differences in IMP situation in different state members. We propose that if the IMP has a marketing authorisation for the indication under study in one of the Member States that it is considered "approved" for the assessment of the risk level.
Line 249-250	*Comment*: Ensure to clarify wording: to the requirements of immediate reporting from the investigator to the sponsor. i.e. what is meant by 'immediate', within 24 hour? *Proposed edits:* "... immediate reporting no later than within 24 hours...".

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Line 251-253	*Comment 1*: Any adverse events regardless of relatedness are required to be recorded by investigator and reported to sponsor, unless defined differently by sponsor. The current wording implies only related adverse events require reporting. There is no mention of trial procedure related SAEs in this section. Comment 2: Adverse events or laboratory abnormalities identified in the protocol as critical to the safety evaluation are reported by the investigator to the sponsor. *Comment 3*: We have reviewed Article 41 of the EU CT Regulation and cannot find a general rule involving reporting of cases which are potentially related. Article 41(1) states the following: *1. The investigator shall record and document adverse events or laboratory abnormalities identified in the protocol as critical to the safety evaluation and report them to the sponsor in accordance with the reporting requirements and within the periods specified in the protocol.* The EU CT Regulation allows the protocol to justify what should be reported to the sponsor, whereas the wording in the Commission consultation risks impeding the full potential of a risk adapted approach by implying that relatedness is the key decision point. We believe the edits below are in keeping with the spirit of the EU CT Regulation and would stimulate critical discussion on when risk adapted approaches are appropriate. *Proposed change (line 251-253):* **The investigator shall record and document adverse events or laboratory abnormalities identified in the protocol as critical to the safety evaluation associated with the IMP. ~~As a general rule, any adverse event considered by the investigator as being potentially related to the IMP, and therefore representing an adverse reaction,~~ These** should be reported to the sponsor, unless justified in the protocol and supported by the risk assessment outcome. **Relatedness to the IMP, as well as the concept of disease related events are examples of considerations for a risk adapted approach.** *Proposed change (line 255-260)* Article 41 of the Regulation refers to two possible risk adaptations to safety reporting: • selective recording and reporting of adverse events, **or laboratory abnormalities (identified in the protocol as critical to the safety evaluation)** and

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	• adaptations to ~~expedited~~ **immediate** reporting from the investigator to the sponsor, for certain serious adverse events.
Line 262 262 - 284	*Comment:* Risk adaptions to adverse event recording, collection and reporting should be detailed in the risk assessment and mitigation plan that is produced in conjunction with the protocol: *Proposed edits: replace this with* "Risk adaptions to adverse event recording, collection and reporting should be detailed in the risk assessment and mitigation plan that is produced in conjunction with the development and prior to start of the trial. **However, it should be clarified that this is not a company core risk Management Plan, EU RMP or REMS.**" **"The safety reporting rules from the investigator to the sponsor should be described in detail in the protocol. The risk assessment and mitigation plan may identify adverse events and/or laboratory abnormalities that are critical to safety evaluations and require expedited reporting from the investigator to the sponsor. These requirements should be included in the protocol."**
Lines 271 to 275 and 296 to 297	*Comment:* It is stated in lines 271 to 275 that "the protocol may select only certain (and not all) adverse events to be recorded and reported to the Sponsor". In lines 296 to 297 however, the examples are of exclusion of specific events. Active selection of AEs for collection is associated with a higher risk than specific exemptions. Please provide greater clarity on what approaches are acceptable and under what situations.
Line 277 to 283	*Comment 1*: Reduced or targeted safety data collection may be warranted by just post-marketing use. *Comment 2*: There is a significant risk of confusion and divergent EU opinions in assessing whether studies of IMP used within their marketing authorisation (MA) are interventional and subject to the EU CT Regulation or non-interventional and subject to e.g. GVP Module III (Post Authorisation Safety Studies – PASS). It is important to make clear that this guidance refers to interventional clinical trials The edits below are intended to make as clear as possible that the scope of this guidance is interventional clinical trials. *Comment 3:*

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	Does the text of the new document impose a change in expectations for protocols with aggregate reporting? What do regulators expect to see in aggregate reports? Will the EU adopt aggregate reporting or will this be driven through industry? Will it be expected that all AEs are included in reports, even though the protocol is selective? *Proposed*: *IMPs are used according to the conditions of the marketing authorisation:* ***If a study is interventional, e.g. there is an additional diagnostic or monitoring procedure or assignment of IMP is according to the protocol, ~~In this case,~~*** *a reduced or targeted safety data collection may be appropriate if supported by data from post-marketing use and if the* ***cumulative*** *number of subjects exposed during clinical development was sufficient to adequately characterize the medicinal product's safety profile (even in terms of rare adverse drug reactions), and if the occurrence of expected adverse drug reactions was similar across multiple trials in terms of seriousness and severity.*
Line 304-308	*Comment 1:* Align wording to article 41 of regulation to reflect the immediate reporting from investigator to sponsor to avoid confusion with expedited reporting to regulator. *Comment 2*: It is important to provide clarity that the serious adverse events mentioned below should still be recorded in the case report form (CRF). *Comment 3:* For trials that are focused on post marketed approvals or for long term trials such as CVOT, can sponsors report only specified AEs specific to the compound and not all AEs? *Proposed:* Article 41 of the Regulation gives the possibility for the investigator not to report certain serious adverse events to the sponsor, if provided for in the protocol. ***The investigator should still record these events in the case report form.*** In cases of blinded clinical trials carried out in high morbidity or high mortality diseases, in which efficacy or safety endpoints meet the criteria of serious adverse events, the sponsor may determine in the protocol that these outcome events are exempted from the rules of ~~expedited~~ **immediate** reporting.
Line 317-318:	Comment: Should the protocol provide a summary on how frequently the DSMB will meet? Is it not sufficient to include in the protocol a summary of what the DSMC will evaluate on a periodic basis and what will trigger their review?

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Line 320-323	*Comment*: Align wording to article 41 of regulation to reflect the immediate reporting from investigator to sponsor to avoid confusion with expedited reporting to regulator. *Proposed:* The safety reporting rules from the investigator to the sponsor should be described in detail in the protocol. The risk assessment and mitigation plan may identify adverse events and/or laboratory abnormalities that are critical to safety evaluations and require ~~expedited~~ **immediate** reporting from the investigator to the sponsor.
Line 325 - 369	*Comment:* Traceability and Accountability are 2 very different things. Traceability is about the supply chain (mainly the ability to track the origin of a drug back to manufacturer and lot information) and accountability is a term used to indicate the control and documentation of the IMP management, for demonstrating compliance with the protocol and that patients received what they should receive. In this definition, lines 327-329, it seems that traceability is only a portion of accountability. Refine wording to ensure clarity and distinction between Traceability and Accountability (especially considering there's no definitions available in the regulations) Ensure terms are distinguished through the whole section for providing clear instructions.
Line 330 - 331	*Comment: :* "information on the provisions for traceability should be contained in the application dossier" Considering this is a new requirement, some clarifications regarding what should be expected to be included and the level of detail could be really helpful for ensuring compliance with it.
339-341	Comment: "If allowed in the concerned Member State, in clinical trials where marketed products are used in accordance with the terms of the marketing authorisation, IMPs may be sourced from normal stock of the community or hospital pharmacy." It may be useful for the guidance to state whether in such circumstances, interchangeability of generic products might be acceptable and, if so, in what circumstances.
Lines 345-355	Comment: Registries capturing dispensed medicine are available in several member states. It is suggested that such a data source of medicine use is included in the text. Using information on medicine dispensed is a much better indicator of actual use compared to prescription data.
Line 359-360	*Comment 3:* Examples of appropriate justification and mitigation plan based on risk assessment would be helpful.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 363-365	*Comment 4 (line 363-365)"* "Scientific validity" – Considering this term or concept might have some subjective connotations, further details or clarifications here would be useful (as done previously in this document for the concept "scientific evidence" Lines 124-127)
Line 366 - 369	*Comment:* Consider examples for illustrative purposes. *Proposed*: Consider revising as follows: "Other risk factors, like the stability of the active ingredient, that impact the management of the IMP should also be considered in the risk assessment. **For** example, temperature monitoring **or light protection** if applicable, should be adapted depending on the outcome **of that risk assessment**."
Line 372	*Comment 1:* *We suggest including more details of what is expected to be included in the CSR for the marketing authorisation submission, such as the description of the risk management plan* and adaptations performed at the global study level. A description of the sponsor's overall RBM process in the CSR will ensure a more consistent sponsor approach to facilitate agency assessment. It should not include adaptations done at site level in trial management aspects (section 4). *Comment 2:* The extent of source data verification (SDV) versus data privacy should be addressed. In particular, it should be clearly stated that it is a consequence of a risk-based approach that data are usually not verified 100%. Adding this would avoid an inappropriate criticism of sponsors during inspections when the sponsor has used adaptive (reduced) risk-based SDV strategies and/or for isolated (insignificant) data errors which are also a consequence of risk-based approaches. In low-interventional trials the intended monitoring process can make the study a regular interventional trial. It is suggested that good

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	practice established in relation to observational studies with data extraction from "patient records" etc. is followed. In observational studies patients usually consent that specific data points are checked in their patient record. However, in observational studies it is not permitted for the monitor, auditor or inspector to read the rest of the patient records, which is normally the practice in interventional clinical trials. *Comment 3:* It would be helpful to include more details on the monitoring plan in the guidance.
Line 384	"Examples include on-site monitoring and centralised monitoring." Proposed change (if any): "Examples include on-site monitoring, **remote monitoring** and centralised monitoring."
Line 388	Comment: Suggest a reword that is more reflective of the norm. Proposed change: Consider revising as follows: "On-site monitoring remains relevant in ~~certain~~ **most** types of clinical trials,…"
Line 389	*Comment:* Minor clarification and addition Proposed change (if any): "..**for example adequacy of site facilities**, the informed consent process, .."
Line 386-390	*Comment 1*: As summarized in Article 48 of the Regulation and as reflected in section 5.18.3 of the ICH Guideline E6 – Good Clinical Practice, there are some relevant considerations for determining the extent and nature of monitoring. Risks impacting these critical aspects or other critical data for the trial should be taken into especial consideration when determining the monitoring strategy to ensure patient's safety and rights as well as data integrity.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	Comment 2: "On-site monitoring remains relevant in certain types of clinical trials, as it is instrumental for the verification of several critical aspects at the trial site, for e.g. the informed consent process, source data verification and IMP handling on site." *Comment 3*: It would seem reasonable to soften the wording since most of those activities can be performed remotely given technology. Also, SDV is no longer deemed critical; the growing body of evidence indicates a reduced value of source data verification (SDV). We would recommend focussing on Source Data Review instead as well as review of critical processes at the site. Proposed: **""**"On-site monitoring remains relevant in certain types of clinical trials, as it is instrumental for the verification of several critical aspects at the trial site, e.g. the informed consent process, ~~source data verification~~ **review of source data and of critical processes at the site such as** ~~and~~ IMP handling on site." **Identified risks impacting these critical aspects or any other trial critical data should be especially considered when determining the monitoring strategy as part of the risk proportionate approach to monitoring."**
Lines 388 - 390	Proposed change (if any):
Line 392-393	Comment: Minor clarifications suggested. Proposed change: Consider revising as follows: "The level of on-site monitoring activities may vary from frequent and/or detailed monitoring, to low**er** levels of **activity and less frequent on-site visits, to** targeted visits to certain sites only…"
Line 394	*Comment:*

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	Minor addition for clarity. Proposed change (if any): "..**in rare circumstances** no on-site visits in certain trials"
Lines 395 - 397	*Comment:* From lines 395 through 397, the document introduces mitigation by monitoring. You monitor to detect, you mitigate to prevent. Also, I would question, a monitoring strategy plan as ICH has just defined a monitoring plan.
Line 407	*Comment*: Suggested addition for clarity. *Proposed change (if any):* Change to "..procedures should be built in to **communicate**, follow-up and correct.."
Line 408 - 410	*Comment:* Recommend deleting this text since there is no requirement for a statistician or a data manager to perform central monitoring. Also can't assume the processes and actions are truly different, escalation and follow-up are basic process which can be approached in a common manner. Proposed change: ~~"Such escalation procedures will have different processes and actions when using centralised monitoring, in which the data management and/or biostatistician are involved in the identification of issues, and processes other than onsite monitoring may be used for follow-up."~~
Line 412 - 413	*Comment:* Clarifying addition

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	Proposed change (if any): " "Centralised monitoring **in particular** enables the review of reported data / information, remote contact, communication and training where relevant and can be used to set certain actions in motion when pre-determined tolerance limits for processes or data have been exceeded."
Lines 414 - 415	"Monitoring activities (whether they are on-site or done centrally) need to be sufficiently well documented to demonstrate that the monitoring plan has been followed and actions have been taken as a result of the outcome of the monitoring activities. " Proposed change (if any): "Monitoring activities (whether they are on-site or **centralized**) need to be sufficiently ~~well~~ documented to demonstrate that the monitoring plan has been followed ~~and actions have been taken as a result of the outcome of the monitoring activities~~."
Line 416	
Line 421	*Comment:* Suggested text change *Proposed change (if any):* "..A risk **proportionate** ~~adaptive~~ approach to monitoring should include utilization of one of or a combination of **adaptive** approaches listed below."
Line 426	*Comment:* Suggested clarification

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	Proposed change (if any): "..**Remote** monitoring activities.."
Line 449	*Comment*: Additional examples of how the TMF is affected are needed to specifically clarify what is meant by line 449. ''Objectives achieved by other means;''